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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 fiscal year ended December 31, 2020

OR

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

Commission file number: 001-39044

SPRINGWORKS THERAPEUTICS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**83-4066827**
(State of Other Jurisdiction of incorporation or Organization)	(I.R.S. Employer Identification No.)
100 Washington Blvd, Stamford, CT	**06902**
(Address of principal executive offices)	(Zip code)

Registrant's telephone number, including area code: (203) 883-9490

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

Title of Each Class	**Trading Symbol(s)**	**Name Of Each Exchange On Which Registered**
Common Stock, $0.0001 Par Value per Share	**SWTX**	**The Nasdaq Global Select Market**

Securities registered pursuant to Section 12(g) of the Act: None

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

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

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

Indicate by check mark whether the Registrant has submitted electronically; every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§232.0405 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 has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☒

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☒

The aggregate market value of the registrant's common stock held by non-affiliates of the registrant based on the closing price on June 30, 2020 (the last business day of the registrant's most recently completed second fiscal quarter of 2020) was $897,219,624.

The number of outstanding shares of the Registrant's Common Stock as of February 19, 2021 was 48,976,123.

Documents Incorporated by Reference

The registrant's definitive proxy statement relating to the annual meeting of shareholders will be filed with the Securities and Exchange Commission within 120 days after the close of the registrant's fiscal year ended December 31, 2020 and is incorporated by reference in Part III to the extent described herein.

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FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K, or Annual Report, contains forward-looking statements, which reflect our current views with respect to, among other things, our operations and financial performance. We make such forward-looking statements pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995 and other federal securities laws. All statements other than statements of historical facts contained in this Annual Report on Form 10-K, including statements regarding our strategy, future operations, future financial position, future revenue, projected costs, prospects, plan, objectives of management and expected market growth are forward-looking statements that involve risks and uncertainties. You can identify these forward-looking statements by the use of words such as “outlook,” “believes,” “expects,” “potential,” “continues,” “may,” “will,” “should,” “seeks,” “approximately,” “predicts,” “intends,” “plans,” “estimates,” “anticipates” or the negative version of these words or other comparable words. Accordingly, there are or will be important factors that could cause actual outcomes or results to differ materially from those indicated in these statements. We believe these factors include but are not limited to those described under “Risk Factors” and include, among other things:

- the success, cost and timing of our product development activities and clinical trials, including statements regarding the timing of our ongoing Phase 3 clinical trial of nirogacestat, the timing of our ongoing Phase 2b clinical trial of mirdametinib and the initiation and completion of any other clinical trials and related preparatory work, the expected timing of the availability of results of the clinical trials and the potentially registrational nature of the single Phase 3 clinical trial and the Phase 2b clinical trial;

- the fact that interim data from a clinical study, such as the interim data of the ReNeu clinical trial, including its interim primary efficacy, safety and tolerability data, may not be predictive of the final results of such study or the results of other ongoing or future studies;

- the potential attributes and benefits of our product candidates;

- our plans to commercialize any of our product candidates that achieve approval either alone or in partnership with others;

- our ability to obtain funding for our operations, including funding necessary to complete further development of our product candidates, and if approved, commercialization;

- the period over which we anticipate our existing cash, cash equivalents and marketable securities, will be sufficient to fund our operating expenses and capital expenditure requirements;

- the potential for our business development efforts to maximize the potential value of our portfolio;

- our ability to identify, in-license or acquire additional product candidates;

- the ability and willingness of our third-party collaborators to continue research and development activities relating to our product candidates that we are developing as combination therapies;

- our ability to obtain and maintain regulatory approval for our product candidates, and any related restrictions, limitations or warnings in the label of an approved product candidate;

- the potential benefit of Orphan Drug Designation, Fast Track Designation and Breakthrough Therapy Designation for nirogacestat, mirdametinib and any other of our product candidates that may receive one or more of these designations;

- our ability to compete with companies currently marketing or engaged in the development of treatments for desmoid tumors, NF1-PN and other oncology and rare disease indications;
- our expectations regarding our ability to obtain and maintain intellectual property protection or market exclusivity for our product candidates and the direction of such protection;
- our ability and the potential to successfully manufacture our product candidates for preclinical studies, clinical trials and, if approved, for commercial use, the capacity of our current contract manufacturing organizations, or CMOs, to support clinical supply and commercial-scale production for product candidates and our potential election to pursue additional CMOs for manufacturing supplies of drug substance and finished drug product in the future;
- the size and growth potential of the markets for our product candidates, and our ability to serve those markets, either alone or in partnership with others;
- the rate and degree of market acceptance of our product candidates, if approved;
- regulatory developments in the United States, or U.S. and foreign countries;
- our ability to contract with third-party suppliers and manufacturers and their ability to perform adequately;
- the success of competing products that are or may become available;
- risks associated with the COVID-19 pandemic, which may adversely impact our business, preclinical studies and clinical trials;
- our ability to attract and retain key scientific, medical, commercial or management personnel;
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing;
- our financial performance; and
- developments and projections relating to our competitors or our industry.

Although we believe that the expectations reflected in these forward-looking statements are reasonable, these statements relate to our strategy, future operations, future financial position, future revenue, projected costs, prospects, plans, objectives of management and expected market growth, and involve known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to be materially different from any future results, levels of activity, performance or achievements expressed or implied by these forward-looking statements. You are urged to carefully review the disclosures we make concerning these risks and other factors that may affect our business and operating results under “Item 1A. Risk Factors” in this Annual Report, as well as our other reports filed with the Securities and Exchange Commission, or the SEC. Any public statements or disclosures by us following this Annual Report that modify or impact any of the forward-looking statements contained in this Annual Report will be deemed to modify or supersede such statements in this Annual Report. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date of this document. The Company does not intend, and undertakes no obligation, to update any forward-looking information to reflect events or circumstances after the date of this document or to reflect the occurrence of unanticipated events, unless required by law to do so.

PART I

Item 1. Business

Overview

We are a clinical-stage biopharmaceutical company applying a precision medicine approach to acquiring, developing and commercializing life-changing medicines for underserved patient populations suffering from devastating rare diseases and cancer. We have a differentiated portfolio of small molecule targeted oncology product candidates and are advancing two potentially registrational clinical trials in rare tumor types, as well as several other programs addressing highly prevalent, genetically defined cancers. Our strategic approach and operational excellence in clinical development have enabled us to rapidly advance our two lead product candidates into late-stage clinical trials while simultaneously entering into multiple shared-value partnerships with industry leaders to expand our portfolio. From this foundation, we are continuing to build a differentiated global biopharmaceutical company intensely focused on understanding patients and their diseases in order to develop transformative targeted medicines.

Our most advanced product candidate, nirogacestat, is an oral, small molecule gamma secretase inhibitor, or GSI, initially in development for the treatment of desmoid tumors, a rare and often debilitating and disfiguring soft tissue tumor for which there are currently no therapies approved by the U.S. Food and Drug Administration, or FDA. We believe nirogacestat may address the significant limitations associated with existing treatment options and has the potential to become the first therapy approved by the FDA for both newly diagnosed and previously treated desmoid tumors. Since we licensed nirogacestat from Pfizer Inc., or Pfizer, in August 2017, the FDA has granted us Orphan Drug Designation, Fast Track Designation and Breakthrough Therapy Designation for this indication, and the European Commission granted Orphan Drug Designation to nirogacestat for the treatment of soft tissue sarcoma. In May 2019, we announced the initiation of the DeFi trial, a potentially registrational Phase 3 clinical trial of nirogacestat for adult patients with desmoid tumors, and in July 2020, we announced full enrollment of the DeFi trial. We expect to report topline data from this trial in the second half of 2021. In addition to the ongoing DeFi trial, a Phase 2 clinical trial was initiated in collaboration with the Children's Oncology Group, or COG, in September 2020, to evaluate nirogacestat for the treatment of pediatric patients with desmoid tumors.

Our second product candidate is mirdametinib, an oral, small molecule MEK inhibitor initially in development for the treatment of neurofibromatosis type 1-associated plexiform neurofibromas, or NF1-PN, a rare tumor of the peripheral nerve sheath that causes significant pain and disfigurement, and that most often manifests in children. We believe that mirdametinib has the potential to offer a best-in-class profile in order to enable the long-term treatment required for this patient population, as compared to other MEK inhibitors. As with nirogacestat, we licensed mirdametinib from Pfizer in August 2017; since then, the FDA has granted mirdametinib both Orphan Drug Designation and Fast Track Designation for NF1-PN, and the European Commission has granted mirdametinib Orphan Drug Designation for NF1. In October 2019, we announced the initiation of the ReNeu trial, a potentially registrational Phase 2b clinical trial of mirdametinib for pediatric and adult patients with NF1-PN. In February 2021, we reported interim clinical data from the first 20 adult patients enrolled in the Phase 2b ReNeu trial. We expect to complete enrollment of the trial in the second half of 2021.

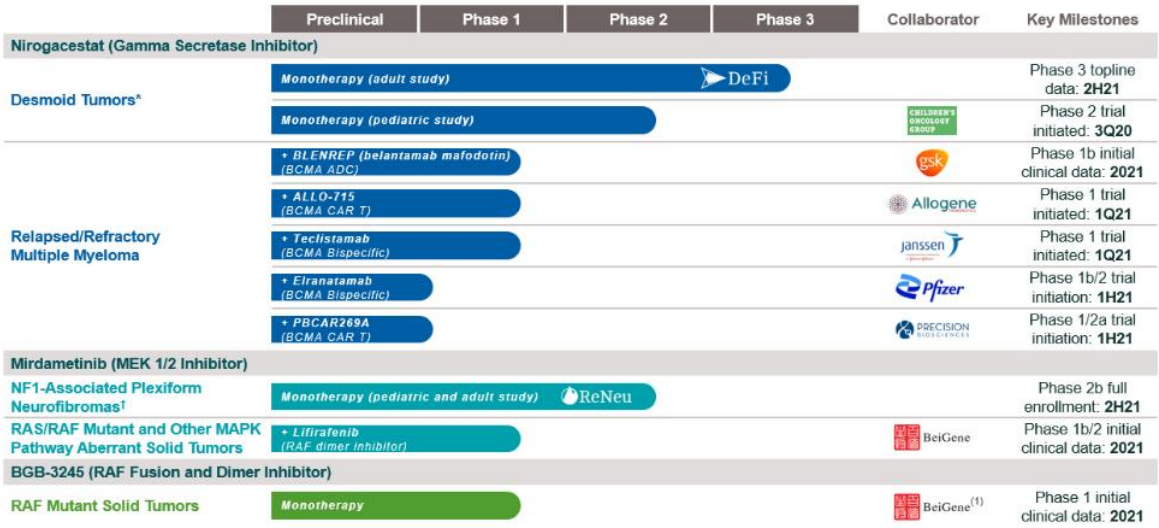
In addition to our late-stage programs in rare oncology indications, we have expanded our portfolio to develop targeted therapies for the treatment of highly prevalent hematologic malignancies and genetically defined metastatic solid tumors. To advance this strategy, we are taking a precision medicine approach in collaboration with industry leaders. In hematologic malignancies, we have announced collaborations with GlaxoSmithKline, or GSK, Janssen Biotech, Inc., or Janssen, Pfizer, Allogene Therapeutics, Inc., or Allogene, and Precision BioSciences, Inc., or Precision, to develop novel combination regimens of nirogacestat alongside our collaborators' B-cell maturation antigen, or BCMA, directed therapies for the treatment of multiple myeloma. In addition to our industry collaborations with leading BCMA therapy developers, we are working with the Fred Hutchinson Cancer Research Center, or Fred Hutch, to further explore nirogacestat's ability to potentiate BCMA-directed therapies as part of a sponsored research agreement. In genetically defined metastatic solid tumors, our current efforts center on the mitogen activated protein kinase, or MAPK, pathway. In collaboration with BeiGene, Ltd., or BeiGene, we are exploring the combination of mirdametinib with BeiGene's lifirafenib in RAS mutated and other MAPK aberrant cancers. In addition, we are exploring the use of BGB-3245 in a

distinct set of genetically defined BRAF mutated tumors via MapKure, LLC, or MapKure, an entity jointly owned by us and BeiGene.

Together, we believe that our portfolio provides multiple opportunities for value creation across three distinct categories of oncology programs, each of which has the potential to provide meaningful clinical benefit to patients suffering from severe rare diseases and cancer. In our late-stage rare oncology programs, we believe that our two potentially registrational trials with nirogacestat and mirdametinib each have best-in-class potential for the patient populations in which they are being advanced. In our malignant hematology programs, we believe that nirogacestat has the potential to become a cornerstone of BCMA combination therapy in multiple myeloma and we are seeking to achieve this goal by working with partners developing BCMA-targeted agents across modalities. In our biomarker defined metastatic solid tumor programs, we believe that our precision medicine approach to cancers harboring mutations in key MAPK pathway genes, such as RAS and BRAF, provides the opportunity for meaningful clinical benefit for biomarker defined patient populations.

Furthermore, we intend to continue to expand our portfolio by licensing additional programs with strong biological rationales and validated mechanisms of action. We also plan to continue using shared-value partnerships to maximize the potential of our therapies to serve patients. Since our founding, we have invested in building leading clinical development capabilities and have focused on structuring innovative partnerships that seek to align incentives and optimize business outcomes for each party involved. We believe that this approach will continue to allow us to expand our shared-value relationships with innovators, maximize the potential of our existing and future portfolio, and ultimately support the building of a scalable and sustainable business focused on the efficient advancement and commercialization of product candidates that hold the potential to transform the lives of patients living with severe rare diseases and cancer.

The following table summarizes our current portfolio of product candidates and anticipated key milestones:



Note: Nirogacestat = PF-03084014 and Mirdametinib = PD-0325901 (both in-licensed from Pfizer).
* Received Orphan Drug, Fast Track and Breakthrough Therapy Designations.
† Received Orphan Drug and Fast Track Designations.
(1) Being developed by MapKure, an entity that is jointly owned by us and BeiGene.

For purposes of this report, when we refer herein to a "potentially registrational trial," we are referring to a clinical trial to evaluate efficacy and safety of a product candidate to potentially support submission of a marketing application for such product candidate with the applicable regulatory authorities. Such a trial is also sometimes referred to as a Phase 2/3 or Phase 3 clinical trial or a pivotal trial.

Nirogacestat is currently in the potentially registrational Phase 3 DeFi clinical trial for the treatment of adult patients with desmoid tumors, which are rare and often debilitating and disfiguring soft tissue tumors. Desmoid tumors can aggressively invade surrounding healthy tissues and cause significant morbidities, including severe pain, internal bleeding, incapacitating loss of range of motion and, in rare cases, death. There are currently no therapies approved by the FDA for the treatment of desmoid tumors. Nirogacestat has been generally well tolerated in approximately 300 subjects and clinical activity was observed in the desmoid tumor patients enrolled in two previous clinical trials, many of whom had been heavily pre-treated. Since then, the FDA has granted nirogacestat Orphan Drug Designation, Fast Track Designation and Breakthrough Therapy Designation for the treatment of desmoid tumors. We are currently conducting the DeFi trial, a double-blind, randomized, placebo-controlled clinical trial in adults with progressing desmoid tumors. We believe that we have designed the DeFi trial such that, if nirogacestat demonstrates clinical activity consistent with that observed in desmoid tumor patients treated to date with nirogacestat, the primary endpoint of this clinical trial should be met. If the results are favorable, we plan to file for marketing approval for nirogacestat in the U.S. and select international markets. In July 2020, we announced full enrollment of the DeFi trial, and we expect to report topline data in the second half of 2021. In addition to the ongoing DeFi trial, a Phase 2 clinical trial was initiated in collaboration with COG in September 2020 to evaluate nirogacestat for the treatment of pediatric patients with desmoid tumors.

Nirogacestat + BLENREP (belantamab mafodotin-blmf) is being explored in collaboration with GSK in patients with relapsed or refractory multiple myeloma, or RRMM. GSK's BLENREP is the most clinically advanced BCMA antibody drug conjugate, or ADC, and is approved as a monotherapy in RRMM patients whose disease has progressed despite prior treatment with at least four prior therapies, including an immunomodulatory agent, proteasome inhibitor and anti-CD38 antibody. Based on data presented by GSK demonstrating synergy when combining BLENREP and nirogacestat in preclinical multiple myeloma models, we believe that the clinical activity of BLENREP may be enhanced with the addition of nirogacestat. Other than the manufacturing of nirogacestat and certain expenses related to intellectual property rights, GSK is responsible for the conduct and expenses of the collaboration, which is governed by a joint development committee with equal representation from each party. The nirogacestat combination with BLENREP is being evaluated as a cohort within GSK's DREAMM-5 platform study, which is an adaptive Phase 1b clinical trial that is currently enrolling patients. We expect initial clinical data to be reported for the combination of nirogacestat and BLENREP in 2021.

Nirogacestat + ALLO-715 is being explored in collaboration with Allogene in patients with RRMM. Allogene's ALLO-715 is a clinical-stage allogeneic BCMA chimeric antigen receptor type T, or CAR T, cell therapy. We believe that the clinical activity of allogeneic BCMA CAR T cell therapies, including ALLO-715, may be enhanced with the addition of a GSI like nirogacestat, and encouraging clinical activity has been demonstrated when combining a GSI with other BCMA CAR T cell therapies. Other than the manufacturing of nirogacestat and certain expenses related to intellectual property rights, Allogene is responsible for the conduct and expenses of the collaboration, which is governed by a joint development committee with equal representation from each party. In December 2020, Allogene announced clearance from the FDA for its Investigational New Drug application, or IND to study ALLO-715 in combination with nirogacestat. As part of their ongoing Phase 1 clinical trial for ALLO-715, Allogene initiated the cohort evaluating the combination in the first quarter of 2021.

Nirogacestat + teclistamab (JNJ-64007957) is being explored in collaboration with Janssen in patients with RRMM. Janssen's teclistamab is a clinical-stage bispecific antibody that targets BCMA and CD3 with monotherapy clinical activity having been demonstrated in RRMM patients. Based on data published by Janssen demonstrating that the activity of teclistamab was improved when combined with a GSI in preclinical multiple myeloma models, we believe that the clinical activity of teclistamab may be enhanced with the addition of nirogacestat. Other than the manufacturing of nirogacestat and certain expenses related to intellectual property rights, Janssen is responsible for the conduct and expenses of the collaboration, which is governed by a joint oversight committee with equal representation from each party. A Phase 1 clinical trial evaluating the combination was initiated in the first quarter of 2021 by Janssen.

Nirogacestat + elranatamab (PF-06863135) is being explored in collaboration with Pfizer in patients with RRMM. Pfizer's elranatamab is a clinical-stage bispecific antibody that targets BCMA and CD3 with monotherapy clinical activity having been demonstrated in RRMM patients. Based on data presented by Pfizer demonstrating that the activity of elranatamab was improved when combined with a GSI in preclinical multiple myeloma models, we believe that the clinical activity of elranatamab may be enhanced with the addition of nirogacestat. Other than the manufacturing of

nirogacestat and certain expenses related to intellectual property rights, Pfizer is responsible for the conduct and expenses of the collaboration, which is governed by a joint development committee with equal representation from each party. Pfizer is expected to initiate a Phase 1b/2 clinical trial evaluating the combination in the first half of 2021.

Nirogacestat + PBCAR269A is being explored in collaboration with Precision in patients with RRMM. Precision's PBCAR269A is a clinical-stage allogeneic BCMA CAR T cell therapy. Based on preclinical data with PBCAR269A, we believe that the clinical activity of PBCAR269A may be enhanced with the addition of nirogacestat. Other than the manufacturing of nirogacestat and certain expenses related to intellectual property rights, Precision is responsible for the conduct and expenses of the collaboration, which is governed by a joint steering committee with equal representation from each party. Precision is expected to begin evaluating the combination in the first half of 2021 by expanding its ongoing Phase 1/2a clinical trial to include a nirogacestat combination arm.

Mirdametinib is currently in the potentially registrational Phase 2b ReNeu clinical trial for the treatment of NF1-PN, which is a rare tumor of peripheral nerve sheaths that causes significant pain and disfigurement, and that most often manifests in children. In a previous Phase 2 clinical trial conducted in NF1-PN patients, mirdametinib was observed to be clinically active and generally well tolerated. Since then, the FDA has granted mirdametinib Orphan Drug Designation for the treatment of NF1 and Fast Track Designation for the treatment of NF1-PN, and the European Commission has granted mirdametinib Orphan Drug Designation for NF1. The Phase 2b ReNeu trial is an open-label, single-arm trial enrolling both pediatric and adult NF1-PN patients. Given the clinical activity and tolerability observed with mirdametinib in the previous NF1-PN clinical trial and informed by our discussions with the FDA, we designed our Phase 2b clinical trial in a manner that we believe has the potential to generate sufficient data to support approval in both pediatric and adult NF1-PN patients. In February 2021, we reported interim clinical data from the first 20 adult patients enrolled in the Phase 2b ReNeu trial. We expect to complete enrollment for the ReNeu trial in the second half of 2021. If, at the conclusion of the trial, the results are favorable, we plan to file for marketing approval for mirdametinib in the U.S. and select international markets.

Mirdametinib + lifirafenib is a combination therapy that we are evaluating in collaboration with BeiGene in a Phase 1b/2 clinical trial that is currently enrolling patients with advanced or refractory solid tumors that harbor various oncogenic driver mutations in the MAPK pathway, a signaling pathway whose constitutive activation has been reported in approximately 25% of human cancers due to mutations in genes such as RAS and RAF. Lifirafenib is a pan-RAF dimer inhibitor that was observed to be clinically active in advanced solid tumor patients with RAS and RAF mutations. Preclinical synergy has been observed with mirdametinib and lifirafenib in RAS mutant or MAPK aberrant tumors and based on these data, we believe that lifirafenib's monotherapy clinical activity can be enhanced with the addition of mirdametinib and that this combination may represent a promising therapy for cancers whose growth is reliant on MAPK pathway signaling, particularly those with mutations in RAS. In May 2019, we announced the initiation of an adaptive Phase 1b/2 clinical trial in patients with advanced or refractory solid tumors harboring relevant genetic mutations in the MAPK pathway are currently being enrolled in Australia and in the U.S. We expect to report initial clinical data from the ongoing Phase 1b/2 clinical trial in 2021.

BGB-3245 is an investigational oral, selective small molecule inhibitor of specific BRAF driver mutations and genetic fusions. BGB-3245 is being advanced via MapKure, an entity jointly owned by us and BeiGene. BGB-3245 is exclusively licensed to MapKure by BeiGene and is being initially developed as a monotherapy. Preclinical activity has been observed with BGB-3245 in a range of tumor models with BRAF mutations or BRAF fusions that are presently unaddressed with approved BRAF-directed therapies. MapKure initiated an adaptive Phase 1 dose escalation and expansion clinical trial evaluating BGB-3245 in genetically defined solid tumors in the first quarter of 2020 and patient enrollment is ongoing in Australia and in the U.S. We expect MapKure to report initial clinical data from the ongoing Phase 1 trial in 2021.

COVID-19 pandemic

In December 2019, a novel strain of coronavirus, severe acute respiratory syndrome coronavirus 2, or SARS-CoV-2, was identified in Wuhan, China. On March 11, 2020, the World Health Organization designated the outbreak of COVID-19, the disease associated with SARS-CoV2, as a global pandemic. Governments and businesses around the world have taken unprecedented actions to mitigate the spread of COVID-19, including, but not limited to, shelter- in-place orders,

quarantines, significant restrictions on travel, as well as restrictions that prohibit many employees from going to work. Since the onset of the COVID-19 pandemic, we have undertaken a number of business continuity measures to mitigate potential disruption to our operations and in order to preserve the integrity of our research and development programs. To date, we have not experienced any material disruptions to the execution of the research and development activities that we currently have underway; however, as a result of the pandemic we may experience disruptions that could impact our research and development timelines and outcomes. We will continue to evaluate the impact of the COVID-19 pandemic, along with the impact of emerging variants, on our business. While the extent to which COVID-19 impacts our future results will depend on future developments, it is possible that the global pandemic and its associated economic impacts could result in a material impact to our business, future financial condition, results of operations and cash flows.

Our strategy

Our goal is to continue building a differentiated, global biopharmaceutical company by acquiring, developing and commercializing transformative medicines for underserved patient populations. We aim to be an industry leader in rare diseases and targeted oncology.

The key elements of our strategy include:

- **Efficiently advance our lead product candidates, nirogacestat and mirdametinib, towards marketing approval in the rare oncology indications in which they are currently being developed.** We believe that our leading drug development capabilities will enable us to continue efficiently advancing our product candidates towards marketing approval, and we will make use of accelerated regulatory pathways when possible. Since our inception in August 2017, we have made rapid progress advancing two product candidates towards marketing approval. Our first product candidate, nirogacestat, was granted Orphan Drug Designation, Fast Track Designation and Breakthrough Therapy Designation by the FDA for the treatment of desmoid tumors and Orphan Drug Designation by the European Commission for the treatment of soft tissue sarcoma. Nirogacestat is currently being evaluated in the potentially registrational DeFi trial; we expect to report topline data from the Phase 3 DeFi trial in the second half of 2021. Our second product candidate, mirdametinib, was granted Orphan Drug Designation by both the FDA and the European Commission for the treatment of NF1 and Fast Track Designation by the FDA for the treatment of NF1-PN. Mirdametinib is currently being evaluated in the potentially registrational ReNeu trial; we expect to provide an update on this trial in the first quarter of 2021.

- **Establish nirogacestat as a cornerstone of BCMA-targeted therapy in multiple myeloma and deploy our precision oncology approach towards the treatment of biomarker defined subgroups of highly prevalent metastatic solid tumors.**

- **Maximize the potential of our portfolio through strategic partnerships and deploy our value-driven approach to identifying, acquiring and developing new medicines to further expand our portfolio.** We have entered into strategic partnerships to develop innovative combination therapies that leverage emerging insights into the fundamental mechanisms that drive cancer. Our strategy is to align incentives among parties by sharing development costs and downstream economics for selected partnered programs. By pursuing this strategy, we believe that we can access promising therapies being developed across the biopharmaceutical industry for which there is scientific and clinical rationale for combinations with our existing product candidates. We have announced collaborations with Allogene, BeiGene, GSK, Janssen, Pfizer and Precision and we intend to execute additional strategic partnerships in the future.

- **Commercialize our product candidates, if approved, either alone or in partnership with others, to bring new medicines to underserved patient populations using a focused and efficient approach.** We intend to market and commercialize our product candidates, if approved, in the U.S. and select international markets, either alone or in partnership with others. We expect to build our medical affairs organization and commercial infrastructure using a focused and efficient approach, initially establishing market access, sales and marketing capabilities in a targeted manner that is appropriate for the relevant product opportunity. We believe that this approach will allow us to effectively reach the patients and physicians that our product candidates have been developed for and to maximize the commercial potential of our portfolio.

- **Continue to cultivate a tightly integrated network of patient advocacy groups, key opinion leaders, research institutions and healthcare providers to inform our approach to developing therapies that can transform the lives of patients and their families.** We believe that in order to develop our portfolio in an efficient and impactful manner, it is imperative to cultivate a network of key stakeholders. Integrating the experiences and insights from these stakeholders, which include the Desmoid Tumor Research Foundation, the Children's Tumor Foundation and leading academic physicians and researchers, continues to inform our approach to developing therapies that can transform the lives of patients and their families suffering from devastating rare diseases and cancer.

- **Attract, retain and support the best talent through our deep commitment to maintaining a culture of diversity, inclusion and professional excellence.**

Our product candidates

Nirogacestat

Overview

Nirogacestat (PF-03084014), our most advanced product candidate, is an oral, selective GSI that we are developing for the treatment of certain oncology indications. Gamma secretase is a protease complex that cleaves numerous transmembrane proteins, including amyloid precursor protein, or APP, Notch, HER4, E-cadherin, N-cadherin, BCMA and CD44. Cleavage of these transmembrane proteins by gamma secretase leads to a variety of signaling events that result from the untethering of the cytoplasmic domains of these proteins. Several of gamma secretase's substrates have been implicated in a variety of diseases, including APP in Alzheimer's disease and BCMA and Notch in cancer, forming the rationale for evaluating gamma secretase as a therapeutic target. We believe there is significant potential for nirogacestat to address both newly diagnosed and previously treated desmoid tumors and has the potential to be used more broadly in cancer, either alone or in combination with other therapies.

Desmoid tumors are rare, non-metastatic soft tissue tumors that can occur in both children and adults. Depending on tumor size and location, desmoid tumors can cause severe morbidities such as pain, disfigurement, internal bleeding and incapacitating loss of range of motion. We exclusively licensed worldwide rights to nirogacestat from Pfizer in August 2017. In June 2018, the FDA granted nirogacestat Orphan Drug Designation for the treatment of desmoid tumors and in November 2018 the FDA granted nirogacestat Fast Track Designation for the treatment of adult patients with progressive, unresectable, recurrent or refractory desmoid tumors or deep fibromatosis. In August 2019, the FDA granted nirogacestat Breakthrough Therapy Designation for the treatment of adult patients with progressive, unresectable, recurrent or refractory desmoid tumors or deep fibromatosis. In addition, in September 2019, the European Commission granted nirogacestat Orphan Drug Designation for the treatment of soft tissue sarcoma.

Nirogacestat has been evaluated in nine clinical trials, excluding our ongoing Phase 3 DeFi trial and the ongoing Phase 1b combination clinical trial with GSK, and approximately 300 subjects have been exposed to treatment. Nirogacestat's clinical activity was observed in the two previous clinical trials that enrolled desmoid tumor patients, in which nirogacestat was generally well tolerated. Pfizer conducted a Phase 1 clinical trial of nirogacestat as a treatment for various types of solid tumors. Five of the seven evaluable desmoid tumor patients enrolled in this clinical trial experienced a partial response, or PR, as measured by Response Evaluation Criteria in Solid Tumors v1.0, or RECIST v1.0, yielding a 71% objective response rate, or ORR. In these seven desmoid tumor patients, median progression free survival, or PFS, had not been reached at the time of publication owing to the lack of patients progressing on therapy.

The National Cancer Institute, or NCI, then conducted a Phase 2 clinical trial evaluating nirogacestat as a treatment for desmoid tumors. Of the 17 patients enrolled in this clinical trial, 16 were evaluable for a response, five of whom had a confirmed PR and 11 of whom had stable disease, or SD, yielding a disease control rate of 100%. Furthermore, due to the lack of patients progressing on therapy, at the time of publication median PFS had not been reached.

Nirogacestat has been generally well tolerated in desmoid tumor patients as evidenced by the duration of time on therapy. In the Phase 1 clinical trial, the mean time on therapy was approximately four years. In the Phase 2 clinical trial,

59% of patients remained on therapy for at least two years, and as of January 2021, five patients are continuing to receive nirogacestat, with treatment durations exceeding 5 years for each of these patients.

Based on these encouraging results, in May 2019, we announced the initiation of the DeFi trial, a potentially registrational Phase 3, double-blind, randomized, placebo-controlled clinical trial, and in July 2020, we announced full enrollment of the trial. We believe that we have designed the DeFi trial such that if nirogacestat demonstrates clinical activity consistent with that observed in desmoid tumor patients treated to date with nirogacestat, the primary endpoint of this clinical trial, which is PFS, should be met. If the results are favorable, we plan to apply for marketing approval for nirogacestat in the U.S. and select international markets, although specific countries have not yet been finally determined.

In August 2020, we highlighted published data from investigators at the University of Minnesota and the Dana-Farber Cancer Institute demonstrating clinical benefit in four pediatric and young adult desmoid tumor patients treated with nirogacestat under our Expanded Access Program. The clinical activity of nirogacestat in these four patients yielded one complete response, two partial responses and one stable disease, with no Grade 3 or Grade 4 adverse events reported. In September 2020, a Phase 2 clinical trial was initiated in collaboration with COG to evaluate nirogacestat for the treatment of children and adolescents with progressive, surgically unresectable desmoid tumors. We are encouraged by the data in these four pediatric and young adult patients and this Phase 2 clinical trial will enable us to further evaluate the potential benefit of nirogacestat in younger desmoid tumor patients.

In addition to our development efforts in desmoid tumors, we are evaluating nirogacestat as a combination agent with BCMA-targeted therapies for the treatment of patients with multiple myeloma. GSIs have been shown to reduce cleavage of membrane-bound BCMA on multiple myeloma cells, thereby improving the activity of BCMA-targeted therapies. We are evaluating this novel combination therapy approach through clinical collaborations with several industry partners. We have entered into separate non-exclusive clinical collaborations with GSK, Allogene, Janssen, Precision and Pfizer, each of whom is developing one or more BCMA-targeted therapies. Each partner is responsible for the conduct and expenses of a clinical trial to evaluate the combination of nirogacestat with its respective BCMA agent in RRMM. In June 2020, we announced the dosing of the first patient in an adaptive Phase1b trial with GSK and we expect to initiate clinical trials with each of Allogene, Janssen, Precision and Pfizer in the first half of 2021.

Nirogacestat for treatment of desmoid tumors

Disease background

Desmoid tumors, also referred to as aggressive fibromatosis or desmoid-type fibromatosis, are rare and often debilitating and disfiguring soft tissue tumors characterized by a growth pattern that can invade surrounding healthy tissues, including joints, muscle and viscera. The morbidity of a desmoid tumor is driven by the location of the tumor and the aggressiveness of its growth pattern. Mesentery desmoid tumors, arising in the abdominal cavity, can cause potentially life-threatening abdominal vasculature and bowel obstructions. Similarly, if a desmoid tumor occurs in the head and neck region, it can result in potentially life-threatening impingement on vital structures. When desmoid tumors occur near joints, even small lesions can result in debilitating loss of range of motion, impaired mobility and severe pain. While variable in size, in rare cases, desmoid tumors have been documented to grow in excess of 30 centimeters in diameter.

Patients with desmoid tumors can experience severe impacts on their quality of life. The French desmoid tumor patient advocacy group, SOS Desmoïde, published a national survey of its members in 2015 to assess pain burden in desmoid tumor patients; out of 102 respondents, 63% noted the presence of pain associated with their disease, 38% of whom characterized their pain as permanent. During the prospective development of patient-reported outcome tools for desmoid tumors, Memorial Sloan Kettering and Quintiles evaluated the impacts of desmoid tumors in 31 patients and found that 81% reported disfigurement, 68% reported range-of-motion impairment and 65% reported a negative impact on their activities of daily living as a result of their tumors.

Desmoid tumors typically occur in patients between the ages of 15 to 60 years and are more commonly diagnosed in the third and fourth decades of life, with a two-to-three times higher prevalence in females. The yearly incidence is

estimated to be 1,000 to 1,500 new desmoid tumor patients diagnosed each year in the U.S. Most cases of desmoid tumor occur spontaneously and are associated with one of several mutations in the *CTNNB1* gene, which encodes for the β-catenin protein. There is also a subset of desmoid tumor patients whose tumors are attributable to germline mutations in the *APC* gene, which encodes for a protein involved in the degradation of β-catenin. These patients have a syndrome known as familial adenomatous polyposis, or FAP, and the incidence of desmoid tumors is 800 to 1,000 times higher in FAP patients as compared to the general population. When *APC* or *CTNNB1* mutations are present, tissue trauma, including surgery, pregnancy or soft tissue injury, can lead to the formation of desmoid tumors.

The clinical course of desmoid tumors varies across the patient population. Within any given patient, desmoid tumors can alternate between periods of rapid growth and stabilization, and spontaneous regressions have been reported in up to 20% of patients. Desmoid tumors can vary significantly in terms of their morphology and radiographic appearance but are generally routine to diagnose. Desmoid tumors are usually first noted upon physical examination or by using various imaging techniques, such as ultrasound, computed tomography, or CT, or magnetic resonance imaging, or MRI. Histologically, desmoid tumors appear with variable collagen deposition and are not clearly circumscribed. Definitive diagnosis relies upon immunohistochemical stains for nuclear localization of β-catenin. Diagnosis can also be confirmed by screening for mutations in the *CTNNB1* and *APC* genes.

Desmoid tumors, despite being highly morbid, typically have a limited impact on mortality. Due to this limited impact on overall lifespan and current poor treatment options, we believe that there is a sizable prevalent pool of desmoid tumor patients. Existing treatments for desmoid tumors often have low success rates. Up to 70% of patients undergoing surgery will relapse depending on patient age, tumor location and tumor size. Furthermore, based on feedback we have received from interviews and surveys of over 200 physicians, each of whom has treated at least five desmoid tumor patients over the preceding five years, we believe that approximately 50% of patients receiving a given systemic therapy, such as chemotherapy or a tyrosine kinase inhibitor, or a locoregional intervention such as surgery will not have a satisfactory treatment outcome and will require subsequent treatment for their desmoid tumors. Based on this market research, we believe that up to 90% or more of patients will eventually receive an active intervention, and we estimate that, in any given year over the next decade, approximately 5,500 to 7,000 desmoid tumor patients will be actively receiving treatment in the U.S.

Current treatment landscape for desmoid tumors

There are currently no therapies approved by the FDA for the treatment of desmoid tumors. Historically, desmoid tumors were treated with surgical resection, but this approach has become less favored due to an emerging body of evidence showing a post-surgical tumor recurrence rate of up to 70%, which can potentially increase disease burden and require additional intervention. In addition to the high recurrence rates, surgery itself carries risk of complications and can also be highly morbid, occasionally requiring limb amputation. Given the potential morbidities of surgery and the uncertain magnitude and durability of its benefit, physicians now typically adopt a watchful waiting approach for patients who historically may have been candidates for surgery. Despite its limitations, surgery is still used when a desmoid tumor presents significant risk of morbidity or mortality, such as tumors arising in the head and neck. Radiation therapy may also be used alone or in conjunction with surgery but is generally not preferred given the reported risk of developing secondary neoplasms.

In addition to these local treatments, systemic therapies have been used off-label with varying degrees of activity and tolerability. These therapies include chemotherapeutic agents, such as liposomal doxorubicin and vinblastine/methotrexate, non-steroidal anti-inflammatory drugs, anti-hormonal therapies and tyrosine kinase inhibitors, such as sorafenib, imatinib and pazopanib. Of these agents, only sorafenib has been studied in a randomized, double-blind, placebo-controlled clinical trial in patients with desmoid tumors; this Phase 3 clinical trial was investigator-initiated and did not have a biopharmaceutical industry sponsor. Although sorafenib demonstrated a statistically significant improvement in PFS compared to placebo, tolerability was a substantial issue; 20% of treated patients discontinued due to adverse events and an additional 22% of treated patients withdrew consent. At a median follow-up time of 27 months, 61% of the patients receiving sorafenib had discontinued treatment. Overall, we believe that the available off-label systemic therapies are poorly suited for the treatment of desmoid tumors and have not demonstrated an acceptable balance of safety and activity in this population. Therefore, we believe a significant unmet medical need exists for the treatment of desmoid tumors.

Our solution—nirogacestat for the treatment of desmoid tumors

Nirogacestat is an oral, small molecule inhibitor of gamma secretase. We believe that nirogacestat can address the significant limitations associated with existing treatment options and has the potential to become the first therapy approved by the FDA for both newly diagnosed and previously treated desmoid tumors. In May 2019, we announced the initiation of our potentially registrational Phase 3 DeFi trial evaluating nirogacestat in adult patients with progressing desmoid tumors, and in July 2020, we announced full enrollment of the trial.

Mechanism of action

Nirogacestat is an oral, potent, selective, reversible, noncompetitive small molecule inhibitor of gamma secretase, an integral protease complex that cleaves numerous functionally important transmembrane proteins, including Notch. Gamma secretase's cleavage of Notch causes the release of the Notch intracellular domain, or NICD, which shuttles into the nucleus and activates transcription of downstream target genes. Notch signaling is a regulator of cell proliferation and its dysregulation has been implicated in many forms of cancer. In desmoid tumor cell lines, nirogacestat has been observed to significantly decrease NICD release and reduce downstream activity of the Notch signaling pathway and decrease tumor cell migration, invasion and growth.

Clinical experience with nirogacestat

Approximately 300 subjects have been exposed to nirogacestat across nine clinical trials, not including ongoing clinical trials such as our Phase 3 DeFi trial in desmoid tumor patients and combination trials with BCMA-targeted therapies. Nirogacestat's clinical activity was observed in two previous clinical trials that enrolled desmoid tumor patients. The first of these was a Phase 1 dose-escalation clinical trial conducted by Pfizer in patients with solid tumors, a subset of whom had a diagnosis of desmoid tumor. Given the activity of nirogacestat in the desmoid tumor patients treated in this Phase 1 clinical trial, the NCI conducted a Phase 2 clinical trial in desmoid tumor patients, which evaluated nirogacestat at 150 mg twice daily, or BID, the same dose being used in our DeFi trial. Nirogacestat was initially intended to be developed as a potential treatment for Alzheimer's disease, but early clinical trials evaluating its pharmacokinetics and biodistribution did not demonstrate adequate brain exposure to pursue this indication. Given Notch's role in cancer, nirogacestat was subsequently investigated as a potential antitumor agent. We believe that the peripherally restricted exposure of nirogacestat, as well as the safety and tolerability profile it has demonstrated across clinical trials to date, positions it as a potentially best-in-class GSI for oncology indications.

Nirogacestat was also investigated in three Phase 1 clinical trials conducted in healthy adult subjects to assess the pharmacokinetics and pharmacodynamics of single and multiple doses. Nirogacestat was further studied in clinical trials in patients with advanced cancers either as a monotherapy or in combination with other agents. Across all clinical trials completed to date, the dose range evaluated for nirogacestat was 1 mg once daily, or QD, to 330 mg BID.

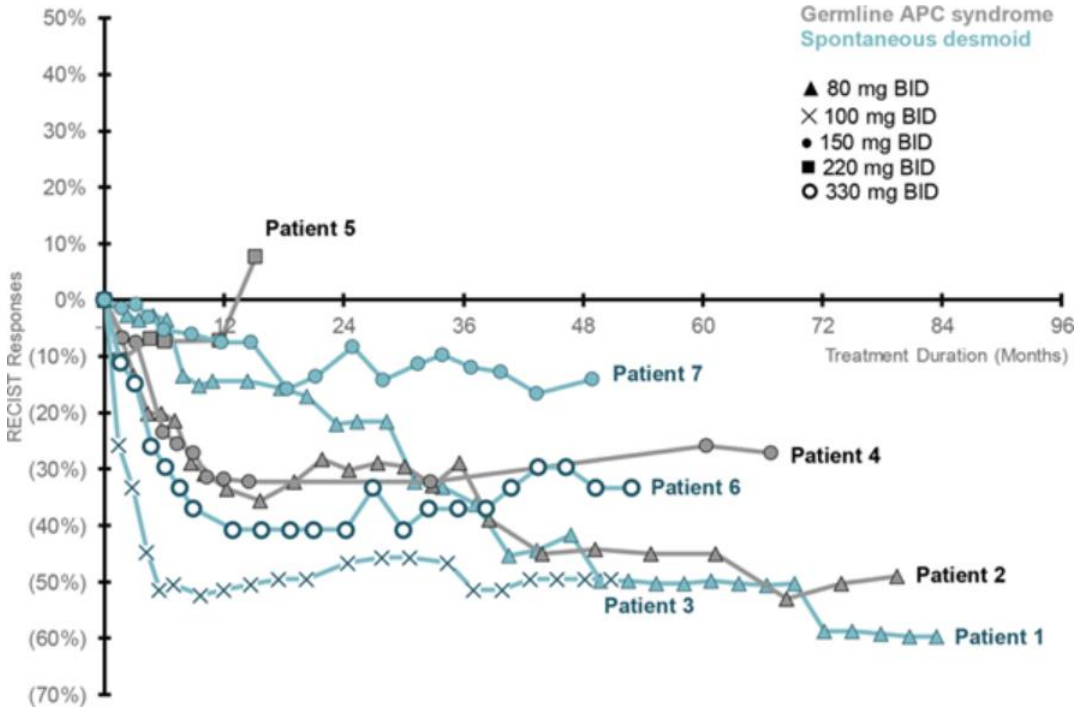
Phase 1 dose-escalation clinical trial

In June 2009, Pfizer commenced a Phase 1 dose-escalation clinical trial in patients with various solid tumors. This clinical trial was designed to determine the maximum tolerated dose, or MTD, ascertain the recommended Phase 2 dose and evaluate the safety and tolerability of nirogacestat. Sixty-four patients with solid tumors received doses of nirogacestat and the MTD was determined to be 220 mg BID. The recommended Phase 2 dose was determined to be 150 mg BID, given its comparable pharmacodynamic activity but more tolerable profile as compared to 220 mg BID.

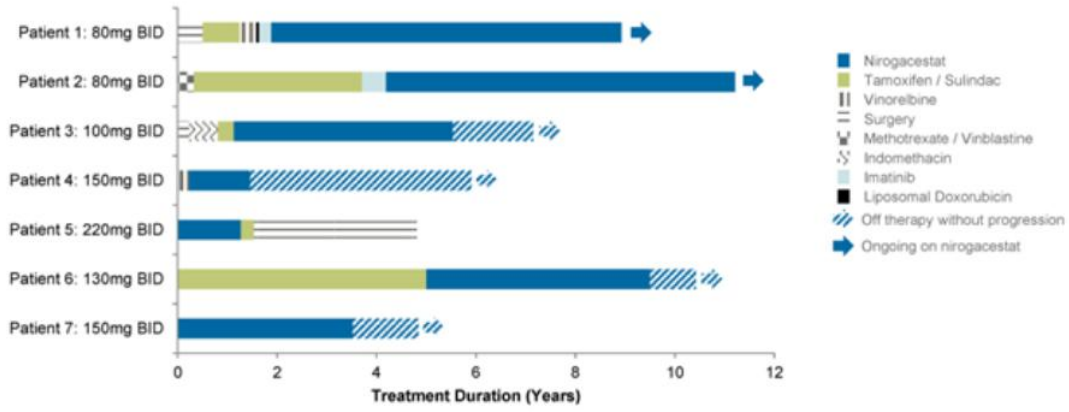
Of the 64 solid tumor patients enrolled, 46 were evaluable for response, seven of whom had desmoid tumors. Of these desmoid tumor patients, five experienced a PR (defined as at least a 30% reduction in the target lesion as measured by RECIST v1.0), yielding a 71% ORR. In the evaluable desmoid tumor patients, median PFS had not been reached at the time of publication owing to the lack of patients progressing on therapy. Patients whose desmoid tumors arose from either germline mutations in *APC* or spontaneous mutations were enrolled in this clinical trial. Patients with both of these tumor mutational characteristics experienced an objective response. Of the 39 evaluable non-desmoid tumor patients in this clinical trial, whose diagnoses included colon, breast, thyroid, non-small cell lung and pancreatic cancer, only one

patient experienced an objective response. The results of this clinical trial were reported in peer-reviewed medical journals in 2014 and 2018.

The following graph shows RECIST v1.0 responses for the seven evaluable desmoid tumor patients enrolled in this Phase 1 clinical trial:



The following chart depicts the treatment course for each of the seven evaluable desmoid tumor patients in the Phase 1 clinical trial. Each bar shows the duration of clinical benefit for all therapies received since the time of diagnosis. Arrows on the right indicate patients who were still free of a new intervention, either on nirogacestat treatment (solid) or off nirogacestat treatment (striped), at the time of publication. As shown in the table below the chart, several of these patients were refractory to a number of previous interventions. The mean treatment duration for these patients was greater than four years, suggesting favorable, long-term tolerability of nirogacestat.



Patient # / Dose	Treatment Method / Duration					
	1st Regimen	2nd Regimen	3rd Regimen	4th Regimen	5th Regimen	6th Regimen
Patient 1 80mg BID	Surgery *26 weeks*	Tamoxifen / Sulindac *39 weeks*	Vinorelbine *17 weeks*	Liposomal Doxorubicin *3 weeks*	Imatinib *13 weeks*	Nirogacestat *366 weeks*
Patient 2 80mg BID	Methotrexate / Vinblastine *17 weeks*	Tamoxifen / Sulindac *176 weeks*	Imatinib *25 weeks*	Nirogacestat *365 weeks*		
Patient 3 100mg BID	Surgery *12 weeks*	Indomethacin *30 weeks*	Tamoxifen / Sulindac *17 weeks*	Nirogacestat *229 weeks*	Off therapy w/o progression *84 weeks*	
Patient 4 150mg BID	Vinorelbine *12 weeks*	Nirogacestat *64 weeks*	Off therapy w/o progression *231 weeks*			
Patient 5 220mg BID	Nirogacestat *66 weeks*	Tamoxifen / Sulindac *14 weeks*	Surgery *170 weeks*			
Patient 6 130mg BID	Tamoxifen / Sulindac *260 weeks*	Nirogacestat *234 weeks*	Off therapy w/o progression *48 weeks*			
Patient 7 150mg BID	Nirogacestat *183 weeks*	Off therapy w/o progression *69 weeks*				

The 64 patients enrolled in the Phase 1 clinical trial received nirogacestat doses ranging from 20 mg BID to 330 BID. The most common treatment-related adverse events (recorded in greater than 10% of patients) were diarrhea (55%), nausea (38%), fatigue (30%), hypophosphatemia (27%), vomiting (23%), rash (20%) and decreased appetite (17%). The majority of adverse events were Grade 1 through 3 and dose reductions due to treatment-related adverse events were infrequent. Treatment-related adverse events that led to temporary discontinuation or dose reduction included diarrhea, hypophosphatemia, rash, nausea, vomiting and fatigue, and most of these subsequently resolved. Seven patients (11%) permanently discontinued treatment due to adverse events. Of these, four patients (6%) discontinued due to a treatment-related adverse event (one for Grade 4 anaphylactic shock, one for Grade 1 visual impairment, one for a Grade 3 drug hypersensitivity reaction and one for Grade 3 rash). The Grade 4 anaphylactic shock adverse event was considered by the trial investigator to be related to intravenous treatment with morphine for pain control, as this adverse event started 25 minutes after morphine administration. However, treatment-related causality could not be excluded because the patient had received their first dose of nirogacestat before intravenous administration of morphine.

Long-term follow-up of the seven evaluable desmoid tumor patients in the Phase 1 clinical trial confirmed that all five patients who achieved a PR continued to maintain their responses between 48 and 73+ months. As of December 2016, four patients (patients 3, 4, 6 and 7) had stopped receiving nirogacestat but continued to be followed and remain free of progression between 11 and 53+ months after cessation of therapy. In all, the mean duration of clinical benefit observed was greater than 63 months. In addition, two patients continued to receive nirogacestat under a compassionate access protocol beyond the 2017 publication date, and through December 2020, one of these patients remained on treatment, having received nirogacestat for over eleven years. We believe the duration of clinical benefit and the tolerability profile observed in this Phase 1 clinical trial supported the rationale for the NCI's subsequent clinical investigation of nirogacestat in desmoid tumor patients.

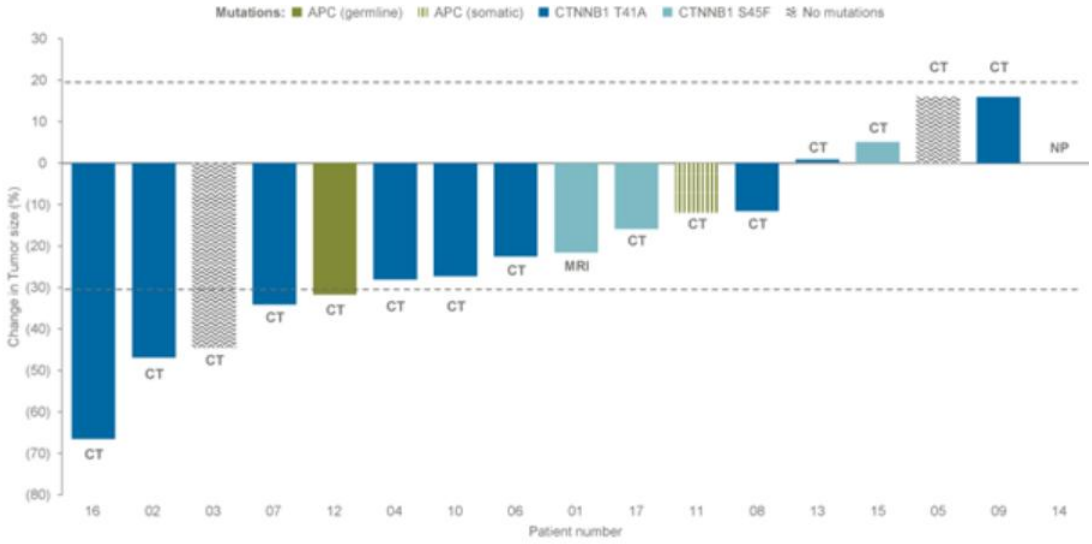
Phase 2 clinical trial

The NCI commenced a Phase 2 clinical trial in desmoid tumor patients in November 2014. This clinical trial enrolled 17 desmoid tumor patients, who received nirogacestat every day in three-week cycles at the recommended Phase 2 dose of

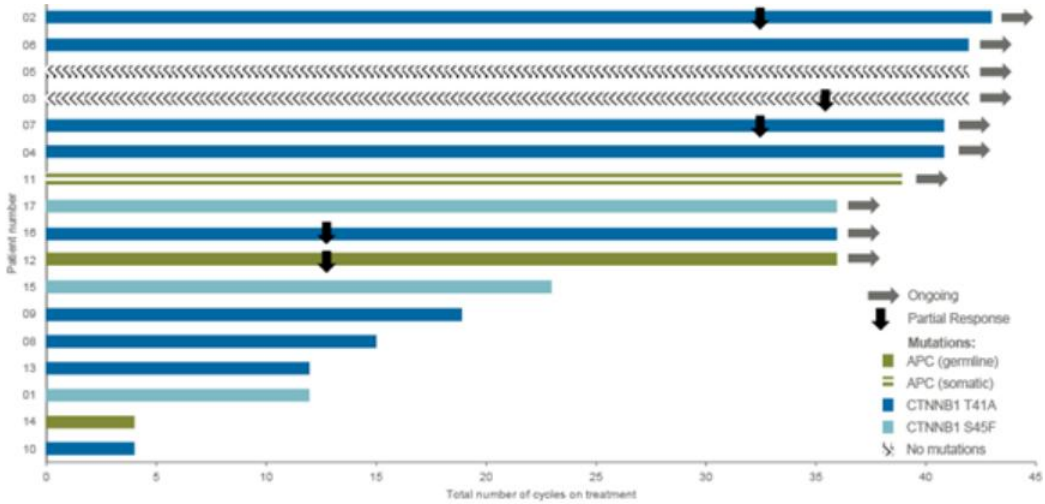
150 mg BID. Patients were enrolled irrespective of their underlying mutation, which included germline and spontaneous *APC* mutations, as well as spontaneous *CTNNB1* mutations (T41A and S45F). These patients were heavily pre-treated, having failed a median of four prior treatments (with a range of one to nine), which included various systemic therapies and local interventions, including surgery.

Sixteen patients were evaluable for a response using RECIST v1.1. Five patients had a confirmed PR and eleven patients had SD, yielding a disease control rate of 100% among the evaluable patients. Four of the five patients with a confirmed PR on nirogacestat had previously been treated with tyrosine kinase inhibitors, including sorafenib and imatinib, without a reported response. Median PFS had not been reached at the time of publication owing to the lack of patients progressing on therapy. Clinical benefit was observed independent of underlying mutation, number of previous treatments and type of previous treatments. As of January 2021, five patients are continuing to receive nirogacestat, with treatment durations exceeding 5 years for each of these patients.

Best responses in the Phase 2 clinical trial, as measured by RECIST v1.1, are shown in the following chart. Dotted lines represent cutoffs for PR (defined as a 30% reduction from baseline) and for progressive disease (defined as a 20% increase from baseline). SD is reflected between the dotted lines. Patient #01 was missing a baseline CT measurement and therefore MRI was used. Patient #14 was not evaluable for response per protocol due to not returning to the clinical trial site for the patient's first restaging evaluation and subsequently being lost to follow-up.



The following chart depicts treatment duration, clinical response and mutational status of desmoid tumor patients in the Phase 2 clinical trial. Time of PR is denoted using black arrows, and the ten patients continuing on therapy at the time of publication are denoted using gray arrows.



All patients in the Phase 2 clinical trial experienced at least one Grade 1 or Grade 2 adverse event. The most commonly reported adverse events regardless of grade and occurring in at least 30% of patients included diarrhea (76%), hypophosphatemia (76%), maculopapular rash (71%), aspartate aminotransferase increase (59%), nausea (53%), lymphocyte count decrease (53%), dry mouth (41%), alanine aminotransferase increase (35%) and anemia (35%). With the exception of hypophosphatemia, these adverse events were all reported as Grade 1 or Grade 2. The only Grade 3 adverse event occurring in at least 20% of patients was hypophosphatemia (47%), which is a known class effect of GSIs and was reversible with oral phosphate replacement therapy in the trial. Four patients required a dose reduction and one patient discontinued therapy due to Grade 2 urticaria that was not responsive to dose reduction. There were no Grade 4 adverse events reported.

DeFi trial and regulatory pathway for nirogacestat in desmoid tumors

Based upon the degree of clinical benefit for desmoid tumor patients observed in the Phase 1 and Phase 2 clinical trials, as well as our discussions with the FDA, in May 2019, we announced the initiation of our potentially registrational DeFi trial. The DeFi trial is being conducted under our open Investigational New Drug Application, or IND, for nirogacestat. As of July 2020, the trial was fully enrolled.

The DeFi trial is a Phase 3, double-blind, randomized, placebo-controlled clinical trial being conducted at clinical sites in North America and Europe. The DeFi trial is designed to evaluate the efficacy, safety and tolerability of nirogacestat compared to placebo in patients with progressing desmoid tumors. This clinical trial will consist of two phases: a double-blind phase and an optional open-label extension, or OLE, phase. This clinical trial is enrolling desmoid tumor patients whose tumors have grown by at least 20% in the last 12 months as measured by RECIST v1.1 and will include both treatment-naïve and relapsed and refractory patients. Given the treatment effect observed in previous clinical trials, patients are eligible for enrollment irrespective of the number and type of previous treatments or the specific underlying mutations in *APC* or *CTNNB1*.

Patients are being randomized in a 1:1 ratio to receive 150 mg BID of nirogacestat or placebo every day for 28 day cycles. Eligible patients with confirmed disease progression on trial may enter the optional OLE phase to receive 150 mg BID of nirogacestat. The trial was designed to enroll approximately 115 patients. The primary PFS endpoint is defined as the time from randomization until the date of assessment of progression as determined using RECIST v1.1, or death by any cause. The documented date of radiographic progression will be determined by blinded independent central

review. The FDA has stated that a PFS primary endpoint may support registration in an adequately designed trial with sufficient follow-up. We initiated the DeFi trial in May 2019, achieved complete enrollment in July 2020 and we expect topline data to be available in the second half of 2021; however, as the DeFi trial is an event-driven trial that is designed to measure the difference in PFS between patients receiving nirogacestat versus those receiving a placebo, the exact timing of the trial's topline readout could fluctuate based upon the enrollment dynamics, the rate at which tumor progression events are occurring and site data entry and verification.

The design of the DeFi trial is summarized in the schematic below:

Key secondary endpoints of the DeFi trial include safety and tolerability, ORR, duration of response and change in tumor volume. Patient-reported outcomes will also be key secondary endpoints in the DeFi trial and will be evaluated using several outcome instruments, including the Memorial Sloan Kettering/Desmoid Tumor Research Foundation Desmoid Tumor Impact and Desmoid Tumor Symptom scales, the Patient-Reported Outcomes Measurement Information System Physical Function scale, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 and the Brief Pain Inventory. These instruments were selected to measure symptoms, impact of symptoms on daily living and outcomes that are most relevant to desmoid tumor patients.

In June 2018, the FDA granted nirogacestat Orphan Drug Designation for the treatment of desmoid tumors and in November 2018, the FDA granted nirogacestat Fast Track Designation for the treatment of adult patients with progressive, unresectable, recurrent or refractory desmoid tumors or deep fibromatosis. In addition, in August 2019, the FDA granted nirogacestat Breakthrough Therapy Designation for the treatment of adult patients with progressive, unresectable, recurrent or refractory desmoid tumors or deep fibromatosis. In addition, in September 2019, the European Commission granted nirogacestat Orphan Drug Designation for the treatment of soft tissue sarcoma. If the results from the DeFi trial are favorable, we plan to file for marketing approval for nirogacestat in the U.S. and select international markets, although specific countries have not yet been finally determined.

Nirogacestat in combination with BCMA-targeted agents

BCMA is a cell surface protein universally expressed on multiple myeloma, or MM, cells, and the clinical activity of monotherapy BCMA-targeted agents have been demonstrated in this indication. GSIs have been shown to increase BCMA expression on MM cells. Activity of this combination mechanism had previously been observed in multiple preclinical models of MM using BCMA-directed therapies in combination with GSIs, and in December 2019, our collaborator GSK presented preclinical data at the American Society of Hematology Annual Meeting demonstrating the ability of nirogacestat to potentiate the efficacy of their BCMA-targeted ADC belantamab mafodotin (now approved by the FDA BLENREP) up to 3,000-fold in a panel of BCMA-expressing human cancer cell lines. We believe this combination, as compared to BCMA-directed therapies alone, may provide a meaningful clinical benefit to MM patients by improving response rates, prolonging the duration of clinical benefit or reducing the side effect profile by enabling administration at a lower dose.

In June 2019, we entered into a clinical collaboration with GSK to explore the combination of nirogacestat with their BCMA-targeted ADC, BLENREP (belantamab mafodotin-blmf), in patients with RRMM. BLENREP is the most clinically advanced BCMA-targeted ADC and is approved as a monotherapy in RRMM patients whose disease has progressed despite prior treatment with at least four prior therapies, including an immunomodulatory agent, proteasome inhibitor and anti-CD38 antibody. We believe that the clinical activity of BCMA directed therapies, including belantamab mafodotin, may be enhanced with the addition of a GSI, like nirogacestat. In June 2020, we announced the dosing of the first patient in an adaptive Phase 1b clinical trial evaluating the combination. GSK is responsible for the

conduct and expenses of the trial, which is governed by a joint development committee with equal representation from each party. We expect initial clinical data on the combination of nirogacestat plus BLENREP to be reported in 2021.

In January 2020, we entered our second collaboration evaluating nirogacestat with a BCMA-targeted agent, in this case with ALLO-715, an allogeneic BCMA-targeted CAR-T cell therapy product candidate being advanced by Allogene. In December 2020, Allogene announced clearance from the FDA for its IND to study ALLO-715 in combination with nirogacestat. As part of their ongoing Phase 1 clinical trial for ALLO-715, Allogene initiated the cohort evaluating the combination in the first quarter of 2021. Allogene is responsible for the conduct and expenses of the trial, which is governed by a joint development committee with equal representation from each party.

In September 2020, we entered our third collaboration evaluating nirogacestat with a BCMA-targeted agent, in this case with teclistamab, a clinical-stage bispecific antibody that targets BCMA and CD3 being advanced by Janssen. Teclistamab has demonstrated monotherapy clinical activity in RRMM patients. Based on data published by Janssen demonstrating that the activity of teclistamab was improved when combined with a GSI in preclinical multiple myeloma models, we believe that the clinical activity of teclistamab may be enhanced with the addition of nirogacestat. Janssen initiated a Phase 1 clinical trial evaluating the combination in the first quarter of 2021. Janssen is responsible for the conduct and expenses of the trial, which is governed by a joint oversight committee with equal representation from each party.

In September 2020, we also entered our fourth collaboration evaluating nirogacestat with a BCMA-targeted agent, in this case with PBCAR269A, an allogeneic BCMA-targeted CAR-T cell therapy being advanced by Precision. Precision is expected to begin evaluating the combination in the first half of 2021 by expanding its ongoing Phase 1/2a clinical trial to include a nirogacestat combination arm. Precision will be responsible for the conduct and expenses of the trial, which is governed by a joint steering committee with equal representation from each party.

In October 2020, we entered our fifth collaboration evaluating nirogacestat with a BCMA-targeted agent, in this case with elranatamab, a clinical-stage bispecific antibody that targets BCMA and CD3 being advanced by Pfizer. Elranatamab has demonstrated monotherapy clinical activity demonstrated in RRMM patients. Based on data presented by Pfizer demonstrating that the activity of elranatamab was improved when combined with a GSI in preclinical multiple myeloma models, we believe that the clinical activity of elranatamab may be enhanced with the addition of nirogacestat. Pfizer is expected to initiate a Phase 1b/2 clinical trial evaluating the combination in the first half of 2021. Pfizer will be responsible for the conduct and expenses of the trial, which is governed by a joint development committee with equal representation from each party.

In addition to our clinical collaborations, in September 2020, we entered into a sponsored research agreement with Fred Hutch to further explore the ability of nirogacestat to modulate BCMA and potentiate BCMA-targeting therapies in a variety of preclinical and patient-derived multiple myeloma models developed by researchers at Fred Hutch.

Disease background – multiple myeloma

MM is a plasma cell neoplasm with substantial morbidity and mortality and is the second most common hematologic malignancy in the U.S. accounting for approximately 10% of all hematologic cancers. The NCI surveillance, epidemiology and end results program estimated that in 2016 there were approximately 130,000 patients in the U.S. living with MM. Of these, approximately 27,000 have relapsed or are refractory to currently available therapies, representing a patient population with few therapeutic options and therefore a significant unmet medical need. It was estimated that approximately 13,000 individuals in the U.S. died from MM in 2020.

MM is characterized by the expansion and abnormal accumulation of malignant plasma cells in the bone marrow, which disrupts normal bone marrow function and over time can lead to anemia, hypercalcemia, thrombocytopenia, bone pain, fatigue and weight loss. As the disease progresses, it destroys the surrounding bone marrow and can lead to renal failure, increased susceptibility to infection, skeletal deterioration and neurologic disease.

Current treatment landscape for MM

Treatment of MM has advanced significantly in the past decade driven by a deeper understanding of disease processes and a sequenced or polypharmacy approach. Newly diagnosed patients with MM are treated with either with stem cell transplants or with multiple classes of therapeutic agents, either alone or in combination, to attempt to control their disease progression. These agents include proteasome inhibitors such as bortezomib, immunomodulatory drugs such as lenalidomide, monoclonal antibodies such as daratumumab, histone deacetylase inhibitors such as panobinostat, alkylating agents such as melphalan, anti-inflammatories such as dexamethasone and chemotherapeutic agents such as doxorubicin. Despite these current options, the durability of clinical response and benefit is often brief. As there are no therapies that currently are considered curative, nearly all patients who survive initial treatments are eventually deemed resistant or refractory to available therapies and their disease continues to progress. By the time these heavily pretreated patients reach this advanced state, they are often directed to clinical trials for treatment with experimental agents. Due to the advanced condition of these patients, the refractory nature of their disease and the toll prior treatments have taken on their health, responses to treatment are generally poor.

BCMA-directed agents have emerged as a potentially promising approach for the treatment of RRMM patients due to the restriction of BCMA's expression solely on the surface of plasmablasts and differentiated plasma cells. The first of these agents to receive regulatory approval was GSK's BLENREP (belantamab mafodotin-blmf), a BCMA-targeted ADC which was approved by the FDA in August 2020 as a monotherapy treatment for adults with RRMM who have received at least four prior therapies. We are aware of at least 20 distinct programs in preclinical and clinical development that target BCMA; these programs represent a variety of therapeutics modalities, including ADCs, monoclonal antibodies, bispecific antibodies, autologous chimeric antigen receptor T-cells, or CAR-T cells, and allogeneic CAR-T cells.

We are also aware of at least two efforts by others to combine a GSI and a BCMA-directed agent to treat RRMM. Juno Therapeutics, Inc., a subsidiary of Bristol-Myers Squibb Company, is currently evaluating an autologous BCMA-directed CAR T-cell therapy in combination with crenigacestat, a GSI licensed from Eli Lilly and Company in December 2017; this combination is currently in Phase 1/2 clinical testing. In December 2018, Novartis licensed the rights to another GSI, AL102, for use in combination with its autologous BCMA-directed CAR-T cell therapy; to our knowledge, this combination has not yet entered clinical testing. Both crenigacestat and AL102 have been evaluated in Phase 1 clinical trials and a challenging tolerability profile was observed for both of these agents.

Our solution – combination of nirogacestat and antibody-drug conjugate

BLENREP (belantamab mafodotin-blmf) was awarded Breakthrough Therapy Designation by the FDA in 2017 and is the first BCMA-targeted agent to receive regulatory approval from the FDA. The regulatory submission was based on the DREAMM-2 trial, an open-label, multicenter study evaluating the safety and activity of BLENREP in RRMM. In the DREAMM-2 trial, treatment of RRMM patients with BLENREP led to an objective response rate of 31% in 97 patients receiving the 2.5 mg/kg dose administered intravenously once every 3 weeks. Seventy-three percent of responders had a duration of response ≥ 6 months and the median duration of response was not reached.

Among these patients, 22% were exposed for 6 months or longer. Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received BLENREP; keratopathy (2.1%) was the most frequent adverse reaction resulting in permanent discontinuation. Serious adverse reactions occurred in 40% of patients who received BLENREP. Serious adverse reactions in >3% of patients included pneumonia (7%), pyrexia (6%), renal impairment (4.2%), sepsis (4.2%), hypercalcemia (4.2%), and infusion-related reactions (3.2%). Fatal adverse reactions occurred in 3.2% of patients, including sepsis (1%), cardiac arrest (1%), and lung infection (1%). Dosage interruptions due to an adverse reaction occurred in 54% of patients who received BLENREP. Adverse reactions which required a dosage interruption in >3% of patients included keratopathy (47%), blurred vision (5%), dry eye (3.2%), and pneumonia (3.2%). Dose reductions due to an adverse reaction occurred in 29% of patients. Adverse reactions which required a dose reduction in >3% of patients included keratopathy (23%) and thrombocytopenia (5%). The most common adverse reactions (≥20%) were keratopathy, decreased visual acuity, nausea, blurred vision, pyrexia, infusion-related reactions, and fatigue.

We believe that the ongoing Phase 1b clinical trial of the combination of nirogacestat and BLENREP, which was initiated pursuant to our collaboration agreement with GSK, is the first clinical trial testing the combination of a GSI with a BCMA-targeted ADC for patients with RRMM. We believe that nirogacestat, by maintaining a high level of surface expression of BCMA on MM cells and by reducing peripheral antigen sink resulting from shed soluble BCMA extracellular domain, or ECD, can improve clinical outcomes over belantamab mafodotin alone. In particular, as compared to BLENREP alone, we believe this combination may improve response rates, prolong the duration of clinical benefit or reduce the side effect profile by enabling administration of BLENREP at a lower dose.

Our solution – combination of nirogacestat and allogeneic CAR-T cell therapies

ALLO-715 is a BCMA-targeted allogeneic CAR-T cell therapy product candidate in clinical testing for the treatment of RRMM and is delivered to patients via one-time infusion. The ALLO-715 Phase 1 monotherapy trial is currently ongoing and following the FDA clearance in December 2020 of an IND submitted by Allogene to study ALLO-715 in combination with nirogacestat, Allogene initiated a new combination cohort as part of their ongoing Phase 1 clinical trial in the first quarter of 2021.

PBCAR269A is a BCMA-targeted allogeneic CAR-T cell therapy product candidate in clinical testing for the treatment of RRMM and is delivered to patients via one-time infusion. Precision is expected to begin evaluating the combination of nirogacestat and PBCAR269A in the first half of 2021 by expanding its ongoing Phase 1/2a clinical trial studying PBCAR269A to include a nirogacestat combination arm, pursuant to our collaboration agreement with Precision.

We believe that the ongoing and planned combination clinical trials of nirogacestat with ALLO-715 and PBCAR269A will be the first clinical trials testing the combination of a GSI with an allogeneic BCMA CAR-T cell therapy product candidate. Autologous BCMA-targeted CAR-T cell therapy products have been associated with high response rates in clinical trials. We believe that nirogacestat, by maintaining a high level of surface expression of BCMA on MM cells and by reducing peripheral antigen sink resulting from shed soluble BCMA ECD may improve clinical outcomes over monotherapy CAR-T cell therapy. In particular, we believe this combination may improve response rates, prolong the duration of clinical benefit or reduce the side effect profile by enabling administration of a lower dose of CAR-T cells.

Our solution – combination of nirogacestat and bispecific antibodies

Teclistamab is a bispecific antibody targeting BCMA and CD3 in clinical testing for the treatment of RRMM. The teclistamab Phase 2 monotherapy trial is ongoing and pending discussions with regulators, we expect Janssen to initiate the Phase 1 clinical trial to evaluate the combination of nirogacestat and teclistamab in early 2021, pursuant to our collaboration agreement with Janssen.

Elranatamab is a bispecific antibody targeting BCMA and CD3 in clinical testing for the treatment of RRMM. A Phase 1 trial evaluating elranatamab as a single agent and in combination with lenalidomide or a PD-1 inhibitor is ongoing. Pending discussions with regulators, we expect Pfizer to initiate a Phase 1b/2 clinical trial to evaluate the combination of nirogacestat and elranatamab in the first half of 2021, pursuant to our collaboration agreement with Pfizer. We believe that the planned combination clinical trials of nirogacestat with teclistamab and elranatamab will be the first clinical trials testing the combination of a GSI and a BCMAxCD3 bispecific antibody. We believe that nirogacestat, by maintaining a high level of surface expression of BCMA on MM cells and by reducing peripheral antigen sink resulting from shed soluble BCMA ECD may improve clinical outcomes over monotherapy bispecific antibody treatment. In particular, we believe this combination strategy may improve response rates, prolong the duration of clinical benefit or reduce the side effect profile by enabling administration at a lower dose.

Our differentiation – combination of nirogacestat and BCMA-targeted therapies

We believe that BCMA-targeted therapies will play an important role in the future treatment paradigm of MM, with each of our collaboration partners possessing particular advantages among the modalities being investigated to therapeutically target BCMA. ADCs and bispecific antibodies possess several attractive features, including conventional infusion schedules and standard pharmaceutical manufacturing, storage and administration processes. In addition, dosing of ADCs and bispecific antibodies can be readily modified throughout the course of treatment. Allogeneic CAR-T cell

therapies have the benefit of potentially yielding profound clinical benefit using a one-time infusion of an ‘off-the-shelf’ cell therapy product. Physician and patient preference for a given BCMA-targeted therapy modality may depend upon the treatment setting in which a patient is receiving care, the clinical characteristics of a given patient and the efficacy and tolerability profile of the therapy.

Given our clinical experience with nirogacestat as well as its tolerability profile at doses we believe will be active in combination with BCMA-targeted therapies based upon preclinical MM models, we believe that nirogacestat could be a compelling and differentiated GSI for use in combination with a BCMA-directed therapy in MM.

Combination mechanism of action

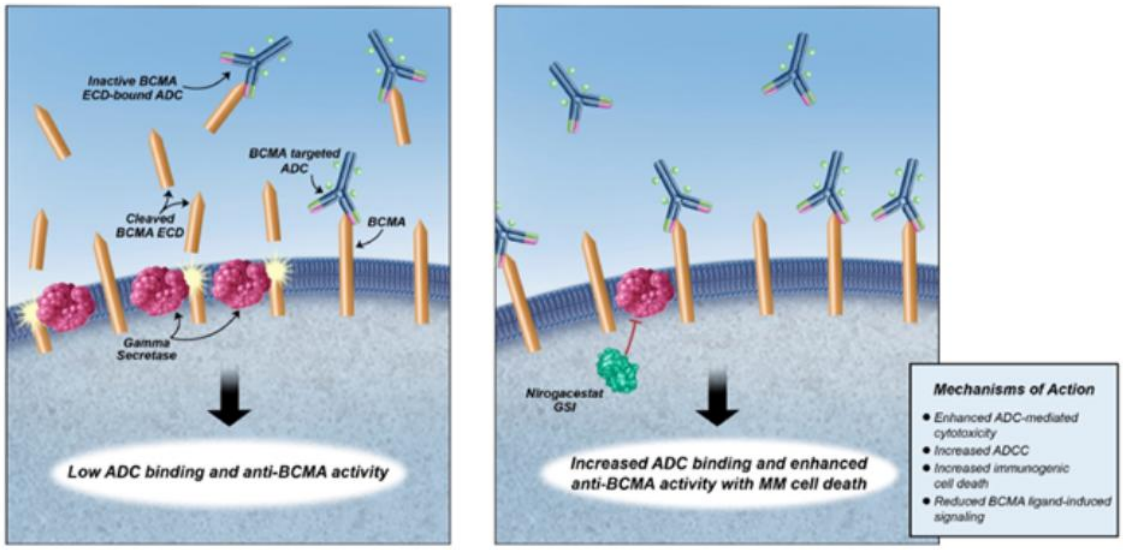
Gamma secretase has been shown to directly cleave membrane-bound BCMA, resulting in the release of the BCMA ECD from the cell surface. By inhibiting gamma secretase, membrane-bound BCMA can be preserved, increasing target density while reducing levels of soluble BCMA ECD, which may serve as decoy receptors. Nirogacestat’s ability to enhance the activity of BCMA-directed therapies has been observed in multiple preclinical models of MM, which was first presented in December 2019 at the 61st Annual American Society of Hematology meeting by our collaborator GSK in combination with belantamab mafodotin.

BLENREP’s activity against BCMA-expressing MM cells is attributable to four potential mechanisms: (1) targeted delivery of its cytotoxic payload, (2) antibody-dependent cellular cytotoxicity, (3) BCMA receptor signaling inhibition due to blocking of ligand binding and (4) immunogenic cell death. BLENREP is a humanized IgG1 monoclonal antibody targeting BCMA, which is conjugated to a monomethyl auristatin F, or MMAF, payload. Auristatin based cytotoxics have been employed in a variety of investigational ADCs, as well as in the approved agent brentuximab vedotin, a CD30 targeting molecule indicated in several hematologic malignancies.

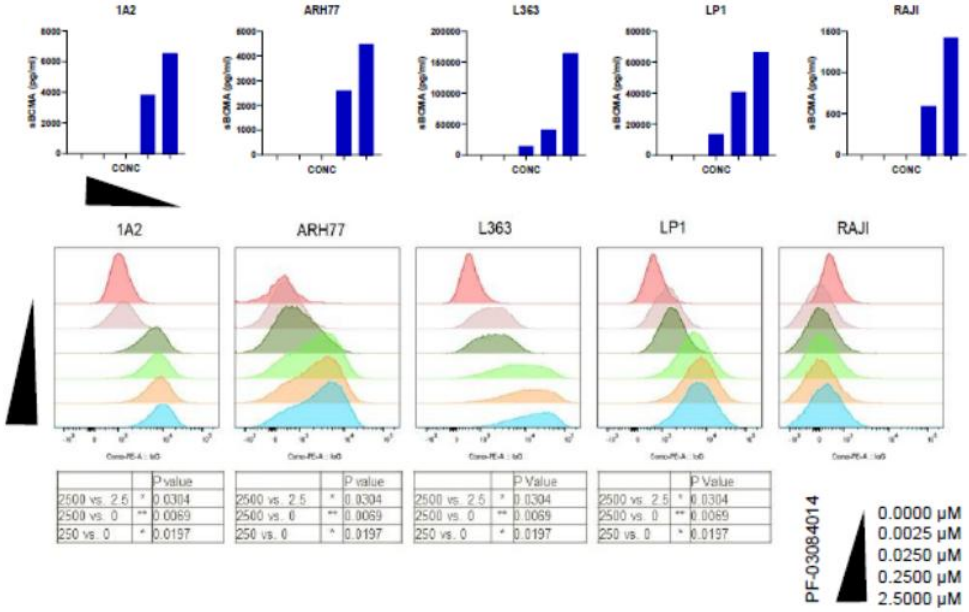
The activity of allogeneic CAR-T cell therapies, such as ALLO-715 and PBCAR269A, against BCMA-expressing MM cells is driven by direct T-cell mediated killing of BCMA expressing MM cells.

The activity of BCMAxCD3 bispecific antibodies, such as teclistamab and elranatamab, is driven by the recruitment and activation of T cells to kill BCMA-expressing MM cells.

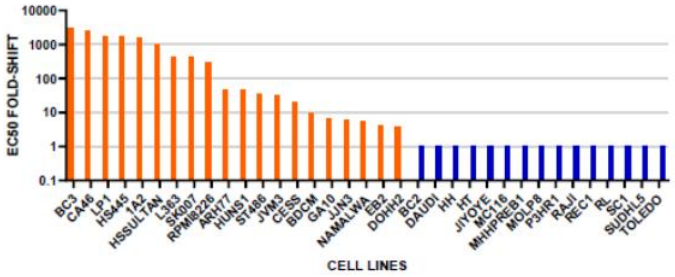
The following graphic illustrates the effect of GSI (shown in combination with a BCMA directed ADC) on decreasing gamma secretase-mediated cleavage of BCMA, leading to increased density of target (BCMA) on cancer cells and reduced levels of decoy receptors (soluble BCMA ECD).



The data demonstrated that treatment of BCMA-expressing cancer cell lines with nirogacestat led to significantly increased levels of cell surface expression of BCMA and corresponding decreases in shedding of BCMA, as measured by levels of soluble BCMA. We believe each of these mechanisms is important for potentiating the activity of BCMA-directed therapies.



A 3-day proliferation assay on a panel of multiple myeloma and lymphoma cell lines with varying levels of BCMA expression was conducted. Results showed that adding nirogacestat enhanced multiple myeloma cell killing activity of belantamab mafodotin up to 3,000-fold and enabled sensitivity in belantamab mafodotin resistant cell lines outside of multiple myeloma.



Therefore, we believe that by increasing surface expression of BCMA and reducing the shedding of soluble BCMA, nirogacestat may enhance the ability of BCMA therapies to target disease-causing MM cells and improve clinical activity or tolerability in patients.

Planned combination therapies future clinical trials

In addition to the ongoing adaptive Phase 1b trial evaluating the combination of nirogacestat and BLENREP in patients with RRMM that is being conducted by GSK, the ongoing Phase 1 trial evaluating the combination of nirogacestat and ALLO-715 in patients with RRMM that is being conducted by Allogene and the ongoing Phase 1 trial evaluating the combination of nirogacestat and teclistamab in patients with RRMM that is being conducted by Janssen, we expect two additional clinical trials for nirogacestat in combination with each of our collaborators' BCMA-targeted therapies to initiate in the first half of 2021.

We and Pfizer have designed a clinical trial to evaluate the combination of nirogacestat and elranatamab in patients with RRMM. Pending discussions with regulators, we expect Pfizer to initiate this Phase 1b/2 combination clinical trial in the first half of 2021.

Precision is expected to begin evaluating the combination of nirogacestat and PBCAR269A in the first half of 2021 by expanding its ongoing Phase 1/2a clinical trial to include a nirogacestat combination arm.

Mirdametinib

Overview

Mirdametinib (PD-0325901) is an oral, small molecule inhibitor of MEK1 and MEK2. MEK proteins occupy a pivotal position in the MAPK pathway, a key signaling network that regulates cell growth and survival, and that plays a central role in multiple oncology and rare disease indications.

We are initially investigating mirdametinib as a monotherapy for the treatment of patients with NF1-PN, a rare disorder characterized by mutations in the MAPK pathway that lead to the growth of peripheral nerve sheath tumors, which cause significant pain, disfigurement and morbidity. NF1-PN are most often diagnosed in the first two decades of life and are characterized by aggressive tumor growth, which is typically more rapid during childhood. In August 2017, we licensed exclusive worldwide rights to mirdametinib from Pfizer. In October 2018 and July 2019, the FDA and European

Commission, respectively, granted mirdametinib Orphan Drug Designation for the treatment of NF1, and in May 2019, the FDA granted mirdametinib Fast Track Designation for the treatment of NF1-PN.

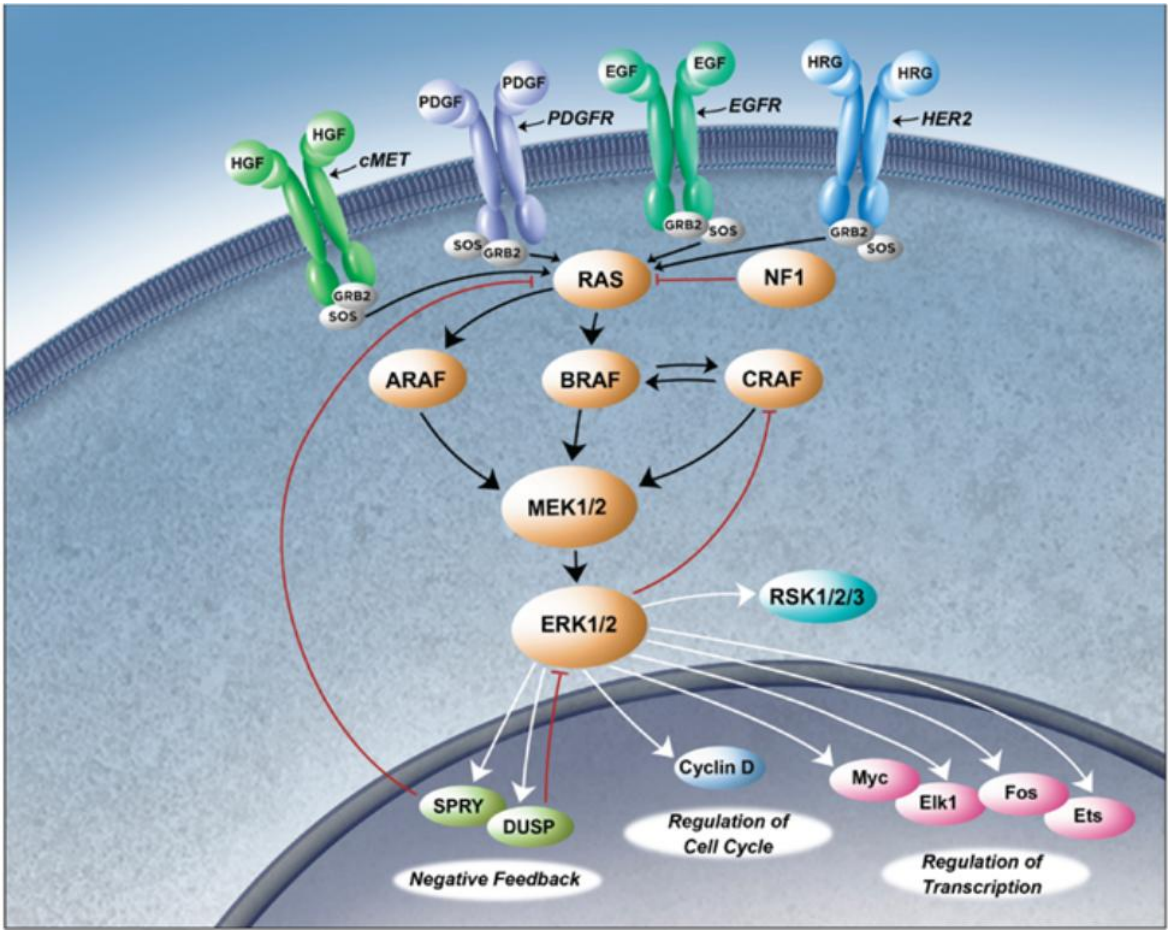
Mirdametinib has been evaluated in eight Phase 1 and 2 clinical trials, with over 200 subjects having been exposed to treatment. A Phase 2 clinical trial was conducted by the Neurofibromatosis Clinical Trial Consortium, which evaluated mirdametinib in 19 NF1-PN patients. In this clinical trial, 42% of patients experienced an objective response (defined as at least a 20% volumetric reduction in their target PN tumor) by 12 months of treatment. Based on the strength of these data and our interactions with the FDA, we initiated our potentially registrational single-arm, open-label Phase 2b ReNeu clinical trial of mirdametinib in NF1-PN patients in October 2019. The primary endpoint for the ReNeu trial is ORR, with an objective response defined as at least a 20% reduction in tumor volume from baseline as determined by volumetric MRI assessment. If the results of this clinical trial are favorable, we plan to file for marketing approval for mirdametinib in the U.S. and select international markets, although specific countries have not yet been finally determined.

In addition to our monotherapy program in NF1-PN, we believe that mirdametinib holds promise for use in multiple targeted combination therapies in oncology. Our first such effort is evaluating mirdametinib in combination with BeiGene's RAF dimer inhibitor, lifirafenib (BGB-283). In May 2019, we announced the initiation of an adaptive Phase 1b/2 clinical trial of this combination that is being conducted by BeiGene. This trial is currently enrolling patients in the U.S. and Australia with advanced or refractory solid tumors harboring relevant genetic mutations in the MAPK pathway.

Overview of the MAPK pathway

The MAPK pathway, which relies upon the RAS-RAF-MEK-ERK signaling cascade, represents a central biological pathway in all human cells that is responsible for helping to regulate cellular transcription, proliferation and survival. The general structure of the pathway consists of RAS, a small GTPase, and three downstream protein kinases, RAF, MEK and ERK. In addition, at the level of RAS, the pathway is negatively regulated by several proteins, including neurofibromin, the protein encoded by the *NF1* gene. Given its direct regulation of ERK, which directly controls downstream signaling through the MAPK pathway, MEK occupies a pivotal position in this signaling cascade and represents a rational therapeutic target for addressing indications where overactivation of the MAPK pathway contributes significantly to disease onset and/or progression.

Constitutive activation of the MAPK pathway has been reported in approximately 25% of human cancers, including colon, lung, breast, pancreatic, ovarian and renal tumors. The cause of pathway activation is varied and tissue-specific, but is driven by one or more of the following mechanisms, each of which is depicted in the illustration below: (i) upstream activation of one or more receptor tyrosine kinases, such as EGFR, (ii) mutations in a *RAS* isoform, such as *KRAS* and (iii) other mutations or aberrations within the pathway, such as in *BRAF* and *NF1*.



Mirdametinib for treatment of NF1-PN

Disease background

NF1 is a rare, autosomal dominant tumor predisposition disorder that arises from mutations in the *NF1* gene, which encodes for neurofibromin, a key negative regulator of the MAPK pathway. NF1 is the most common form of neurofibromatosis, with an estimated global birth incidence of approximately 1 in 3,000 individuals. We estimate that there are approximately 100,000 patients living with NF1 in the U.S. NF1 is clinically heterogeneous and manifests in a variety of symptoms across numerous organ systems, including abnormal pigmentation, skeletal deformities, tumor growth and neurological complications, such as cognitive impairment. Patients with NF1 have a 15-year mean reduction in their life expectancy compared to the general population.

NF1 patients have an approximately 30% to 50% lifetime risk of developing plexiform neurofibromas, or PN, which are tumors that grow in an infiltrative pattern along the peripheral nerve sheath and that can cause severe disfigurement, pain

and functional impairment; in rare cases, NF1-PN may be fatal. NF1-PN are most often diagnosed in the first two decades of life and can be confirmed using routine imaging techniques. These tumors are characterized by aggressive growth, which is typically more rapid during childhood. NF1-PN typically do not spontaneously regress. In a study published in 2012 examining the natural growth dynamics of NF1-PN, 95 NF1-PN patients had the volumes of individual PN lesions monitored over time. Of these 95 patients, 69 were older than 16 years of age at the time of the initial assessment; these 69 patients had a total of 146 NF1-PN lesions monitored. At an average follow-up time of 2.4 years (range 1.05 to 4.10 years), six lesions (4.1%) were documented to have had a volumetric decrease of at least 20%.

While NF1-PN are benign, these tumors can undergo malignant transformation, leading to malignant peripheral nerve sheath tumors, or MPNST. NF1 patients have an 8% to 15% lifetime risk of developing MPNST, a diagnosis that carries with it a 12-month survival rate of under 50%. In addition to MPNST, NF1 patients are at an increased risk of developing other malignancies, including breast cancer and gliomas.

Current treatment landscape for NF1-PN

A MEK inhibitor, Koselugo (selumetinib), was approved by the FDA in April 2020 for the treatment of pediatric patients two years of age and older with NF1 who have symptomatic, inoperable PN. While surgical resection is another treatment option for NF1-PN patients, wide margins are required to resect the tumors, and this is an outcome that can rarely be achieved in NF1-PN patients. This is because NF1-PN arise from nerve cells and grow in an infiltrative pattern, making it challenging to successfully resect tumors without severe comorbidities, such as permanent nerve damage and disfigurement. Patients that are ineligible for surgery or those who have had a recurrence post-surgery are often treated with a variety of off-label therapies. Among these off-label therapies are various systemic treatments, such as chemotherapy and immunotherapy, which have not been shown to consistently confer a clinical benefit.

The inadequacy of surgery highlights the need for improved systemic therapies. Given that NF1-PN is driven by overactivation of the MAPK pathway, MEK inhibitors have emerged as a class of therapies that hold significant promise for the treatment of NF1-PN, and we believe that MEK inhibitors have the potential to become the standard of care.

In addition to Koselugo, we are aware of at least two other MEK inhibitors in Phase 2 clinical trials for this indication, including a MEK inhibitor approved for other oncology indications that is sometimes used off-label in NF1-PN patients. Given the lifelong and devastating nature of NF1-PN, as well as the need to begin treating patients at a young age, we believe that the optimal MEK inhibitor is one that will have a tolerability profile suitable for long-term dosing while simultaneously arresting or reversing tumor growth.

Our solution — mirdametinib for the treatment of NF1-PN

Mirdametinib is an oral, small molecule inhibitor of MEK1 and MEK2, which we are developing as a monotherapy in NF1-PN. Based on results from prior clinical trials, we believe that mirdametinib, using the dose and schedule from the NF1-PN Phase 2 clinical trial, has the potential to offer a potentially best-in-class profile in order to enable the long-term treatment required for this patient population, as compared to other MEK inhibitors. Given the clinical activity and tolerability profile observed with mirdametinib in the previous NF1-PN clinical trial, and following our discussions with the FDA, we designed our ongoing potentially registrational Phase 2b clinical trial, or the ReNeu trial, in a manner that we believe has the potential to generate sufficient data to support approval in both pediatric and adult NF1-PN patients. If the results of the ReNeu trial are favorable, we plan to file for marketing approval for mirdametinib in the U.S. and select international markets, although specific countries have not yet been finally determined.

Mechanism of action

Neurofibromin is a critical repressor of RAS signaling and is impaired in patients with a mutated *NF1* gene, resulting in constitutive activation of the MAPK pathway. MEK inhibitors can reduce MAPK pathway activity and therefore arrest or reverse NF1-PN growth, which has been observed clinically with several MEK inhibitors, including mirdametinib.

Clinical experience with mirdametinib

Over 200 subjects have been exposed to mirdametinib across eight clinical trials, not including our ongoing ReNeu trial in NF1-PN patients and the ongoing Phase 1b/2 combination clinical trial with BeiGene. Mirdametinib has shown clinical activity in a previous Phase 2 clinical trial conducted by the Neurofibromatosis Clinical Trial Consortium that enrolled adolescent and adult NF1-PN patients, and data from this clinical trial was published in the Journal of Clinical Oncology in 2021. Given the activity and tolerability of mirdametinib in this clinical trial, we are utilizing the same dose and schedule in our potentially registrational Phase 2b ReNeu trial. Furthermore, based on discussions with the FDA, we will be enrolling pediatric NF1-PN patients, in addition to adolescent and adult patients.

Mirdametinib has been tested in monotherapy clinical trials across a broad dose range (from 1 mg QD to 30 mg BID), with the initial MTD determined to be 15 mg BID and the recommended Phase 2 dose determined to be 10 mg BID administered on a five days-on, two days-off schedule.

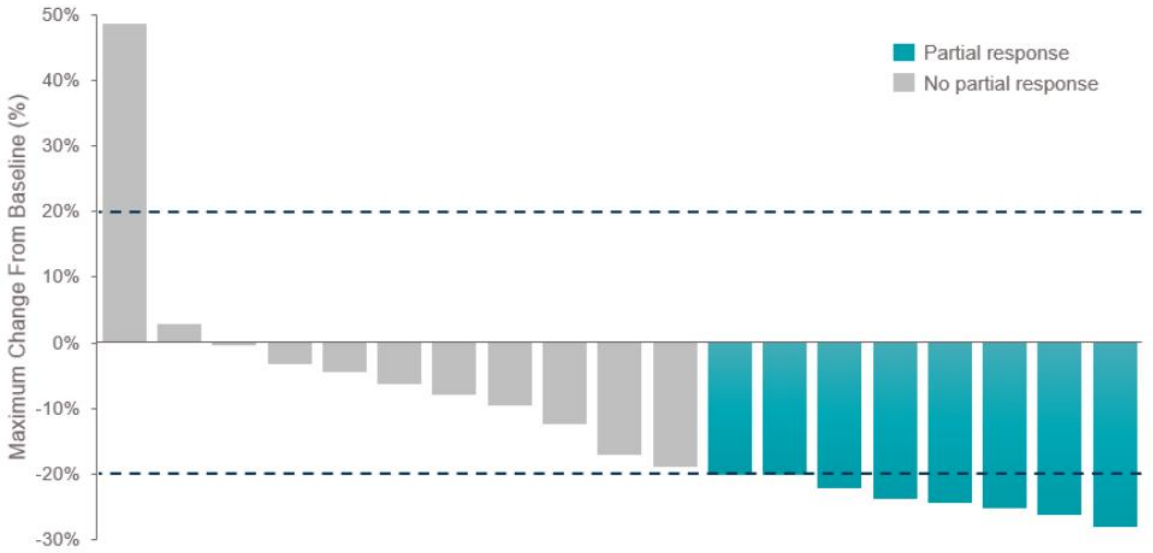
Post-treatment biopsies taken in a Phase 1 monotherapy clinical trial in solid tumors showed a pharmacodynamic effect at doses as low as 1 mg QD, as measured by a greater than 90% decrease in levels of phosphorylated ERK from baseline, demonstrating inhibition of the MAPK pathway. Furthermore, in the Phase 2 clinical trial in NF1-PN patients, clinical activity was observed at doses of 4 mg BID and below. These pharmacodynamic and clinical activity data at doses below the MTD formed the rationale for continuing to advance mirdametinib in NF1-PN and in genetically defined solid tumors, either alone or in combination.

To date, the safety profile of monotherapy mirdametinib in patients with advanced cancers at doses lower than 10 mg BID using an intermittent schedule has been characterized by mostly manageable and reversible toxicities, and mirdametinib is observed to be generally well tolerated. The most frequently reported of these adverse events have been rash, nausea, vomiting, diarrhea and fatigue.

Other adverse events have been reported at a lower frequency, though these adverse events primarily occurred in patients who received doses above 10 mg and up to 30 mg BID, a range that is significantly higher than the maximum allowable dose of 4 mg BID being used in our ongoing Phase 2b ReNeu trial. These adverse events included ocular disorders (visual disturbances, blurred vision and retinal vein occlusion), nervous system disorders (confusion, slowed ideation, slurred speech and hallucinations), musculoskeletal and connective tissue disorders (general weakness and neck muscle weakness associated with mild and moderate elevations in creatine kinase) and cardiac disorders (decreased left ventricular ejection fraction and congestive heart failure).

Phase 2 clinical trial in NF1-PN

The Phase 2 clinical trial evaluating mirdametinib in adolescents and adults with NF1-PN enrolled 19 patients between 16 and 39 years of age. This clinical trial commenced in June 2014 and data was published in the Journal of Clinical Oncology in 2021. Patients received an oral dose of 2 mg/m^2 BID with a maximum dose of 4 mg BID (without regard to food) on a four-week cycle of three weeks-on, one week-off. Eight patients (42%) achieved an objective response by cycle 12, prospectively defined as a volumetric reduction in their target PN of at least 20%, and 10 patients (53%) had stable disease. The following chart shows maximum tumor volume change from baseline for each patient.



The protocol specified that patients were to be removed from the clinical trial if they did not achieve at least a 15% volumetric reduction in their target PN by cycle eight of treatment, corresponding to approximately eight months on therapy. Patients achieving at least a 15% reduction in their target PN by cycle eight of treatment, but who did not achieve at least a 20% reduction in their target PN by cycle 12 of treatment, were also removed from the trial. Importantly, it has been observed in subsequent clinical trials of other MEK inhibitors that some NF1-PN patients achieved their first objective response to therapy 12 months or more following the start of treatment. Therefore, we believe that the design of this clinical trial was not optimized to demonstrate the full potential of mirdametinib's antitumor activity in the NF1-PN patients that were enrolled, a consideration that we have aimed to address in our ongoing potentially registrational Phase 2b ReNeu trial by allowing patients to remain on treatment for up to 24 months.

Patients completed the following patient-reported outcome (PRO) measures as part of the trial protocol: (i) the Numerical Rating Scale-11, which is a measure of pain intensity, (ii) the Brief Pain Inventory Pain Interference subscale, which is a measure of the impact of pain on daily functioning and (iii) the Pediatric Quality of Life (QoL) Inventory NF1 module, which is a measure of disease-specific health-related QoL impact across 16 domains. These PRO measures showed statistically significant improvement with mirdametinib in multiple areas, including tumor pain intensity reduction from baseline by cycle 4 in the total sample, cognitive function improvement from baseline at cycle 8 in the total sample and QoL improvement by cycle 8 for patients who achieved a partial response.

Mirdametinib was generally well tolerated in this trial. There were no Grade 4 or Grade 5 adverse events reported. Two treatment-related Grade 3 events, occurring in the same patient, were reported. The most common adverse events of any grade were acneiform rash (95%), fatigue (58%), and nausea (53%). Five patients (26%) had dose reductions due to adverse events, including one patient for Grade 3 abdominal and/or back pain, one patient for Grade 2 nausea, one patient for Grade 2 fatigue and two patients for Grade 1 rash. No patients discontinued treatment due to dose limiting toxicity. Five patients discontinued mirdametinib treatment: four due to low-grade rash that was perceived to be intolerable and one due to noncompliance with the trial protocol.

Mirdametinib ReNeu trial in NF1-PN and regulatory pathway

Given the degree of clinical benefit observed in patients with NF1-PN in the previous Phase 2 clinical trial of mirdametinib, and informed by our discussions with the FDA, we initiated the potentially registrational ReNeu clinical trial in the fourth quarter of 2019. The ReNeu trial is a Phase 2b, longitudinal, open-label clinical trial designed to evaluate the efficacy, safety and tolerability of mirdametinib in patients at least two years of age with an inoperable NF1-PN that is causing significant morbidity or major deformity. The ReNeu trial is being conducted at clinical sites in

North America. As in the previous Phase 2 clinical trial in NF1-PN patients, mirdametinib is being administered orally at a 2 mg/m^2 BID dose with a maximum dose of 4 mg BID (without regard to food). Dosing is occurring on a four-week cycle with a three weeks-on, one week-off schedule. The intervention period will last for up to 24 cycles. In contrast to the previous Phase 2 clinical trial, we have designed our ReNeu trial with an intervention period that we believe is optimized to demonstrate the full antitumor activity of mirdametinib in NF1-PN patients.

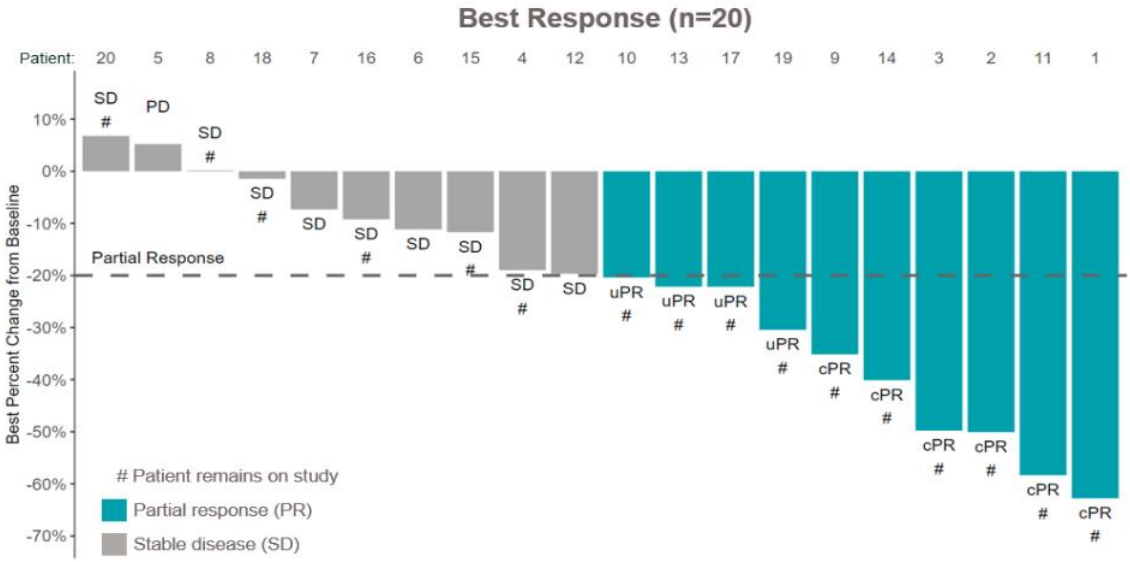
We anticipate enrolling approximately 100 patients in the Phase 2b ReNeu trial, roughly half of whom will be pediatric patients. As of February 2021, the ReNeu trial has reached approximately 70% of its final enrollment target, and we expect to complete enrollment in the second half of 2021. The primary endpoint is ORR measured using three-dimensional MRI volumetric analysis and assessed by blinded independent central review, or BICR. As in the previous Phase 2 clinical trial, an objective response is defined as a decrease of at least 20% in tumor volume in the target NF1-PN by BICR. Key secondary endpoints include the duration of response and health-related quality-of-life measurements.

Interim clinical data

In February 2021, we reported interim clinical data from the first 20 adult patients enrolled in the Phase 2b ReNeu trial. Demographics and baseline characteristics are shown in the table below.

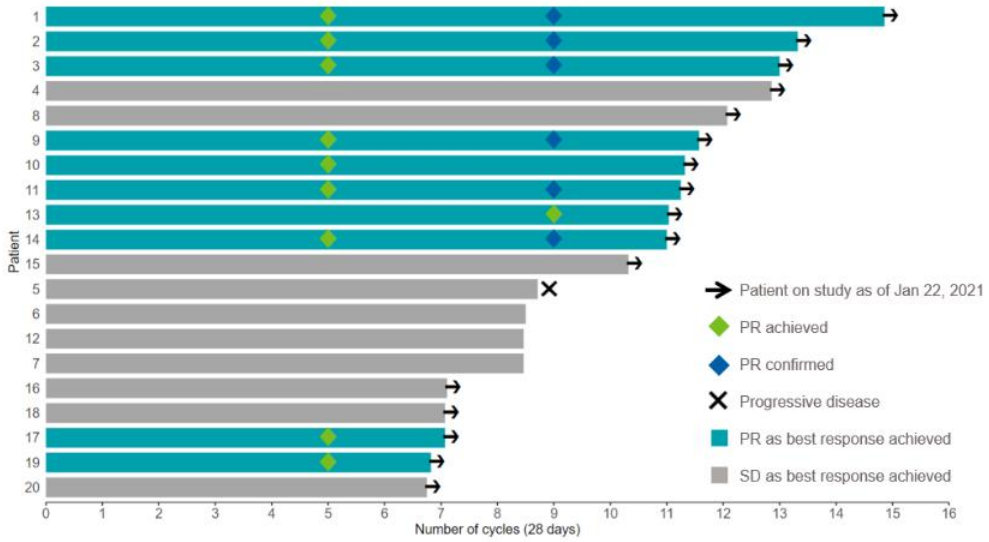
Characteristic	n (%)
Patients enrolled	20
Median age at enrollment [range] - years	33.5 [19 – 69]
Sex	
Male	4 (20)
Female	16 (80)
Location of target neurofibroma	
Head and Neck	9 (45)
Lower Extremities	6 (30)
Chest Wall	1 (5)
Paraspinal	1 (5)
Upper Extremities	1 (5)
Other	2 (10)
Type of neurofibroma-related complication	
Pain	20 (100)
Major Deformity	10 (50)
Motor Dysfunction/Weakness	10 (50)
Lower Extremity	7 (35)
Upper Extremity	3 (15)
Progression of PN at Entry	6 (30)
Optic Glioma	2 (10)
Airway Dysfunction	1 (5)
Other	3 (15)

As of the data cutoff date of January 22, 2021, 10 of these 20 patients (50%) had achieved an objective response, as assessed by a reduction of at least 20% in tumor volume by BICR. The following chart shows the best percent change in tumor volume from baseline in these first 20 adult patients. For seven of the 10 patients who achieved an initial objective response, subsequent scheduled scans were available, and six of these seven patients had confirmed responses, with the remaining patient showing stable disease.



PD: progressive disease; PR: partial response (defined as a ≥20% reduction in tumor volume); cPR: confirmed partial response; uPR: unconfirmed partial response; SD: stable disease

The duration of treatment for the 20 patients evaluated is shown in the chart below. As of the January 22, 2021 data cut-off, 16 patients (80%) remained on therapy and four patients discontinued treatment with one due to disease progression, one due to an adverse event of Grade 1 diarrhea, one participant decision and one patient being unable to undergo the required MRI imaging due to a titanium rod implant from non-treatment related worsening of scoliosis. At the time of data cut-off, the median time on treatment for these 20 patients was 10.1 cycles (approximately 10 months) and all 10 patients who had achieved an objective response remained on therapy.



PR: partial response (defined as a ≥20% reduction in tumor volume); SD: stable disease

As of the January 22, 2021 data cut-off, mirdametinib continued to be generally well tolerated. The majority of treatment-related adverse events, or TRAEs, were Grade 1 or 2 with only one Grade 3 TRAE of rash reported; no Grade 4 or 5 adverse events have been reported. One patient required a dose reduction due to a Grade 3 rash. The following table shows the most common treatment-emergent adverse events, or TEAEs, occurring in ≥15% of the 20 patients evaluated as well as Grade 3 TEAEs and TRAEs.

	Treatment-Emergent AEs (≥15% of patients)			Treatment-Related AEs	
Adverse Event	**All Grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
At least 1 AE	20 (100)	3 (15)	-	1 (5)	-
Dermatitis acneiform/Rash/ Rash maculopapular	18 (90)	1 (5)	-	1 (5)	-
Nausea	10 (50)	-	-	-	-
Diarrhea	9 (45)	-	-	-	-
Vomiting	5 (25)	-	-	-	-
Abdominal Pain	5 (25)	-	-	-	-
Fatigue	5 (25)	-	-	-	-
Dry skin	4 (20)	-	-	-	-
Ejection fraction decreased	4 (20)	-	-	-	-
Dyspnea	3 (15)	1 (5)	-	-	-
Hypertension	3 (15)	-	-	-	-
Coronavirus infection	-	1 (5)	-	-	-
Coronavirus test positive	-	1 (5)	-	-	-
Headache	-	1 (5)	-	-	-
Non-cardiac chest pain	-	1 (5)	-	-	-
Scoliosis	-	1 (5)	-	-	-

Regulatory pathway

In October 2018, the FDA granted mirdametinib Orphan Drug Designation for the treatment of NF1, in May 2019, the FDA granted mirdametinib Fast Track Designation for the treatment of patients at least two years of age with NF1-associated inoperable PN that are progressing or causing significant morbidity and in July 2019, the European Commission granted mirdametinib Orphan Drug Designation for the treatment of NF1. If the results of the Phase 2b clinical trial are favorable, we plan to file for marketing approval for mirdametinib in the U.S. and select international markets.

Mirdametinib in combination with a RAF dimer inhibitor (lifirafenib)

Overview

In September 2018, we entered into a global clinical collaboration with BeiGene to evaluate the combination of mirdametinib with BeiGene's RAF dimer inhibitor, lifirafenib, in patients with advanced or refractory solid tumors harboring *RAS* mutations, *RAF* mutations or other MAPK pathway aberrations. Lifirafenib has been observed to potently inhibit BRAF, CRAF and ARAF across all homodimeric and heterodimeric conformations of these proteins that have been evaluated. Furthermore, monotherapy lifirafenib has shown activity in tumors harboring *RAS* and *RAF* mutations in a multicenter, open-label Phase 1 clinical trial conducted by BeiGene. We believe that lifirafenib's clinical activity can be enhanced with the addition of a potent and selective MEK inhibitor like mirdametinib and provide a potentially promising combination therapy for cancers whose growth is reliant on MAPK pathway signaling, such as those with mutations in *RAS* or *RAF*. In May 2019, we announced the initiation of an adaptive Phase 1b/2 clinical trial being

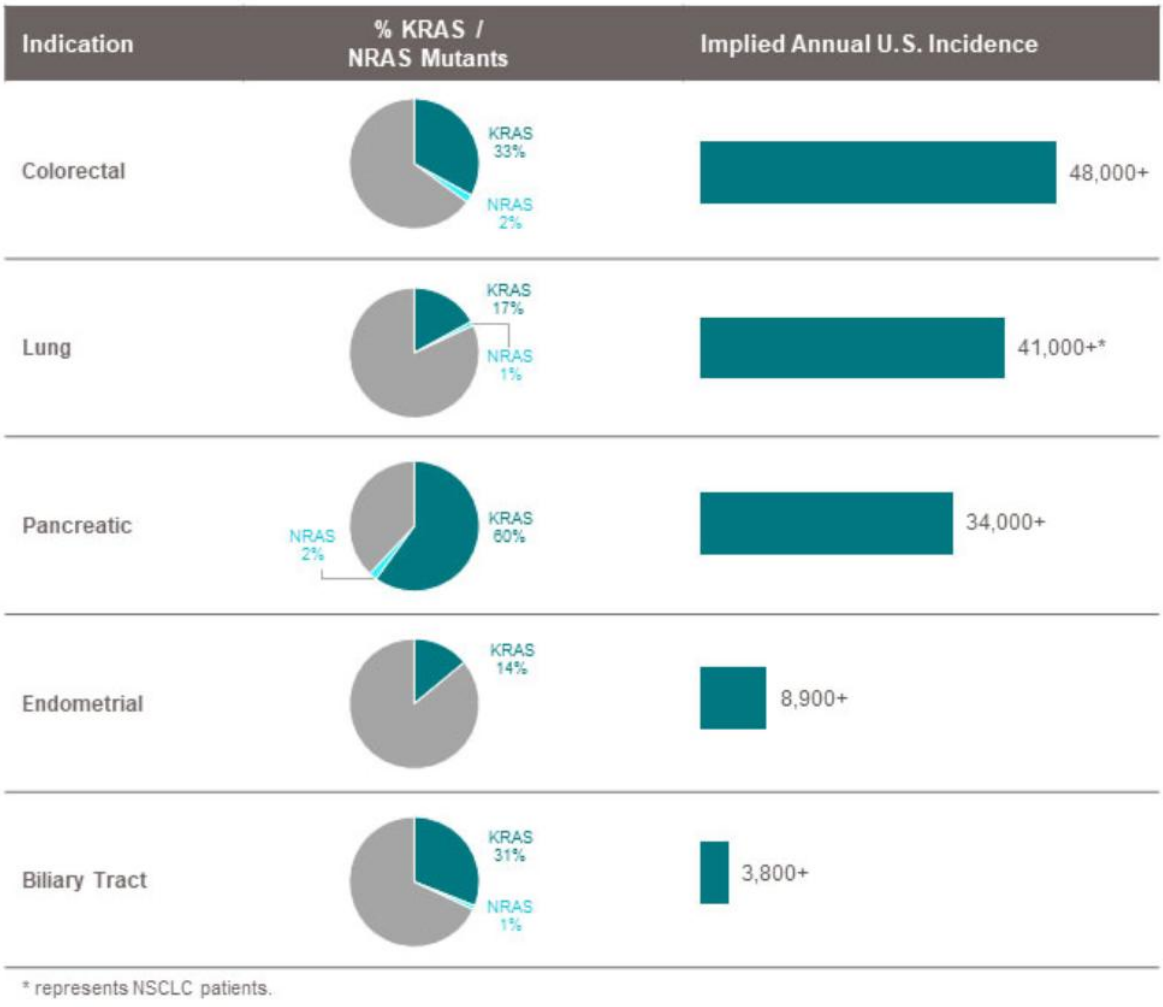
conducted by BeiGene that is currently enrolling patients in the U.S. and Australia with advanced or refractory solid tumors harboring relevant genetic mutations in the MAPK pathway.

Disease background

RAS mutations

RAS mutations are one of the most common genetic aberrations found in human cancers and these driver mutations are found in approximately 25% of all solid tumors, representing over 200,000 new patients diagnosed in the U.S. each year. RAS proteins, which are comprised of the KRAS, HRAS and NRAS isoforms, are central to the transduction of receptor tyrosine kinase signaling and lead to downstream activation of the canonical RAF-MEK-ERK signaling cascade of the MAPK pathway.

The following table illustrates the reported prevalence of *KRAS* and *NRAS* mutations in selected types of solid tumors.



We believe that effective therapies for patients harboring *RAS* mutations represent a significant clinical need. To date, MEK or RAF inhibitors used as monotherapies have generally demonstrated only limited clinical activity in patients whose tumors harbor *RAS* mutations. These tumors are generally poorly responsive to targeted therapies and *RAS* mutations typically confer poor prognosis, although outcomes can vary across different cancer types with *RAS* mutations.

RAF mutations

RAF mutations have been reported in up to 7% of all solid tumors, with the most widely described being the *BRAF* V600 mutations, commonly found in patients with metastatic melanoma. While there are approved MEK-RAF targeted combination therapies for patients with *BRAF* V600 mutations, patients eventually progress on these therapies representing a significant unmet clinical need.

In addition, there have been numerous non-V600 *BRAF* mutations described, which are not responsive to the currently approved therapies, and the use of the existing therapies has been shown to paradoxically increase the ability of tumor cells with these non-V600 *BRAF* mutations to proliferate.

Other MAPK aberrations

Patients with mutations and aberrations in the MAPK pathway aside from *RAS* and *RAF* mutations also represent a substantial unmet clinical need owing to a lack of approved therapies. Such tumors include malignant cancers driven by *NF1* mutations, such as MPNST.

Current treatment landscape

We are not aware of any therapies currently approved by the FDA specifically for the treatment of cancers harboring *RAS* mutations. There are several approved therapies in indications where *RAS* mutations are frequent, though these therapies are not specifically designed to address *RAS* mutations. There are multiple programs in clinical development today for *RAS*-mutant solid tumors that are evaluating various mechanisms of action.

For *RAF* mutations, we are not aware of any therapies currently approved by the FDA for treatment of patients harboring non-V600 *BRAF* mutations. There are several approved therapies in indications where *RAF* mutations are frequent, though none are designed to address *RAF* mutations aside from those therapies targeting *BRAF* V600 mutations, and even for these an unmet medical need exists because patients eventually progress on these therapies.

For patients whose tumors harbor other MAPK aberrations, we are not aware of any therapies currently approved by the FDA. There are several approved therapies in indications where we believe such MAPK pathway aberrations are frequent, though these therapies are not specifically designed to address these aberrations.

Our solution—combination of mirdametinib and lifirafenib

We believe that the biological rationale and the differentiated pharmacological properties of mirdametinib in combination with lifirafenib support the potential to provide significant clinical benefit in these large genetically defined tumor populations with significant unmet medical need. Our ongoing Phase 1b/2 clinical trial of the novel combination of mirdametinib and lifirafenib is among the first clinical trials evaluating vertical inhibition of the MAPK pathway using a RAF dimer inhibitor and a MEK inhibitor. We believe this combination has the potential to provide meaningful clinical benefit in patients with solid tumors harboring *RAS* mutations, *RAF* mutations and other MAPK pathway aberrations.

Preclinical data with the combination of mirdametinib and lifirafenib demonstrating antitumor activity in *RAS* mutant cancer models were presented at the 2015 American Association for Cancer Research, or AACR, Conferences. A variety of MEK inhibitors were evaluated in combination with lifirafenib in this preclinical study, and mirdametinib was observed to be among the MEK inhibitors with the highest synergy and the most potent antitumor activity in combination. Additional preclinical data from studies of mirdametinib in combination with lifirafenib presented at the

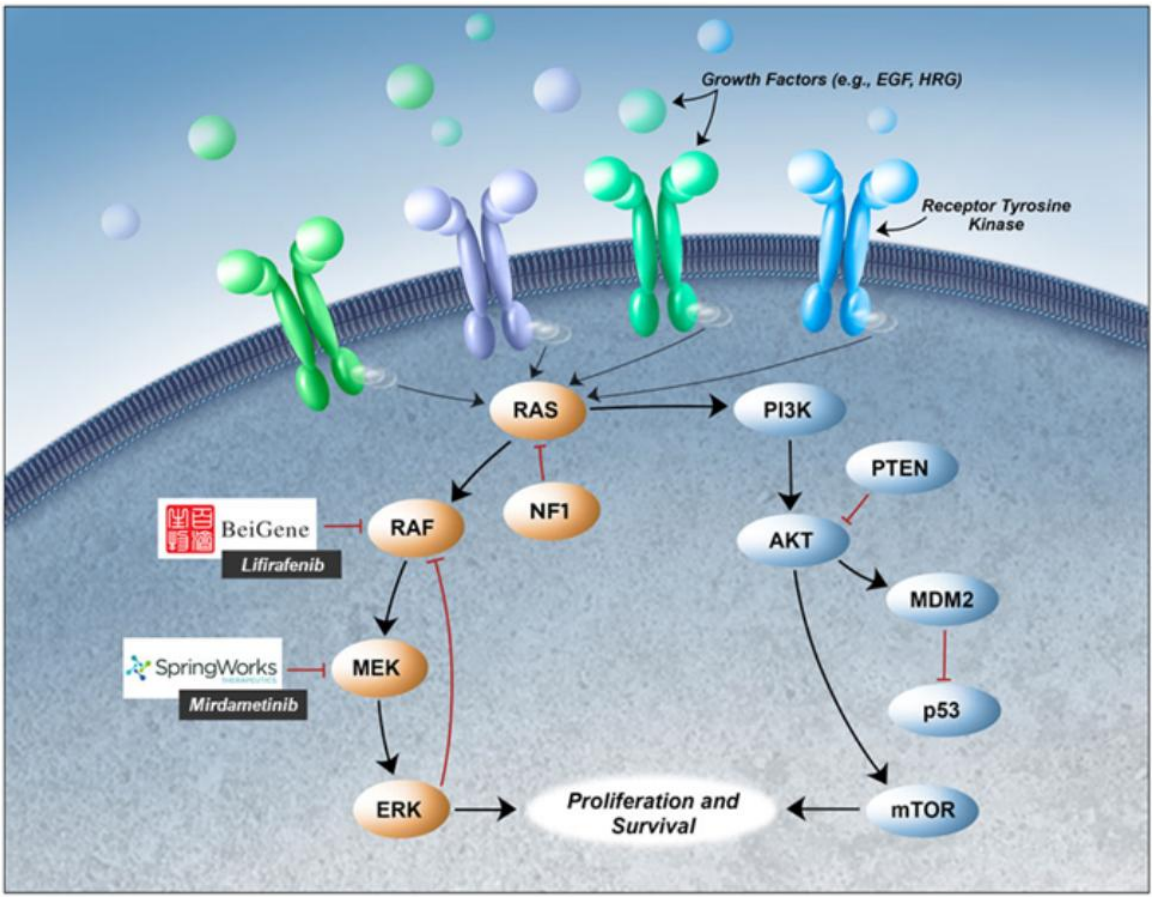
2020 AACR Virtual Annual Meeting II demonstrated potent and synergistic activity in vitro and in vivo across a panel of cancer models harboring a variety of *RAS* mutations. BeiGene's lifirafenib has demonstrated antitumor activity as a monotherapy in a completed Phase 1 clinical trial in patients with *RAS* and *RAF* mutated solid tumors and was observed to be generally well tolerated.

Combination mechanism of action

Given lifirafenib's activity profile, we believe that it is among the most promising RAF inhibitors. In particular, lifirafenib has been observed to inhibit both dimeric and monomeric forms of RAF, which we believe should overcome the paradoxical MAPK pathway activation seen with several other RAF inhibitors. Furthermore, lifirafenib has shown potent inhibition in preclinical studies across all RAF isoforms tested. We believe these two attributes are primarily responsible for the monotherapy activity data observed with this compound in its Phase 1 clinical trial.

Currently approved RAF inhibitors were designed to address tumors whose growth is reliant upon signaling via monomeric forms of BRAF, such as those with *BRAF* V600 mutations, a subset of MAPK aberrations commonly found in metastatic melanoma. In this setting, the addition of a MEK inhibitor to a BRAF V600 inhibitor showed significant clinical activity beyond monotherapy BRAF inhibition. By targeting both monomeric and dimeric forms of RAF, RAF dimer inhibitors, such as lifirafenib, are designed to work in tumors beyond just those harboring *BRAF* V600 mutations and therefore have the potential to address a much broader range of genetically defined patient populations. This includes *RAS*-mutant cancers, which predominantly signal through hetero- and homodimeric RAF; both of these conformations are potentially addressed by lifirafenib.

The following illustration depicts how the combination of mirdametinib and lifirafenib is intended to vertically inhibit the MAPK pathway to prevent the proliferation and survival of cancer cells reliant upon this pathway.



We believe that by vertically inhibiting two key, adjacent constituents of the MAPK pathway, the combination of mirdametinib and lifirafenib can potentially address the resistance mechanisms and feedback loops that have prevented development of therapies for many devastating cancers harboring MAPK pathway gene mutations, such as those in *RAS*, *RAF* and *NF1*. In particular we believe that the Phase 1 clinical data demonstrated lifirafenib's activity across both monomeric and dimeric forms of RAF, as well as mirdametinib's observed clinical pharmacodynamic activity at low doses, provide the opportunity for a leading combination therapy to address tumors with aberrant MAPK signaling.

Combination of mirdametinib and lifirafenib clinical trial

In May 2019, we announced the initiation of an adaptive Phase 1b/2 clinical trial evaluating the combination of mirdametinib and lifirafenib. This clinical trial is enrolling patients with advanced or refractory solid tumors harboring relevant genetic mutations in the MAPK pathway. This clinical trial is being conducted by BeiGene in collaboration with us in both the U.S. and Australia. The clinical trial is comprised of two stages. In the first stage, we intend to determine the MTD and recommended Phase 2 dose of the combination therapy. In the second stage, the trial is expected to enroll expansion cohorts comprised of patients with tumor types and mutational backgrounds of interest, which may include non-small cell lung cancer and endometrial cancer with *KRAS* mutations, to assess antitumor efficacy, safety and tolerability of the combination therapy at the recommended Phase 2 dose. We expect to report initial clinical data from the ongoing Phase 1b/2 trial in 2021.

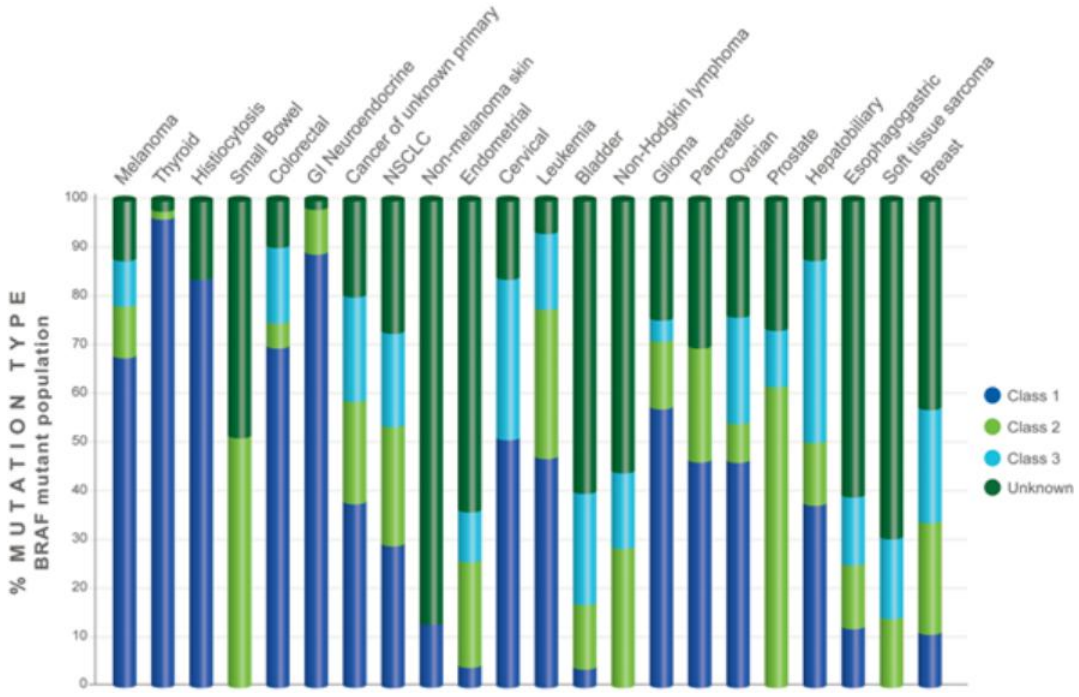
BGB-3245 in genetically defined BRAF-mutant solid tumors

In June 2019, we announced the formation of MapKure, which is jointly owned by us and BeiGene. BeiGene licensed to MapKure exclusive rights to BGB-3245, a novel, oral, selective small molecule inhibitor of monomeric and dimeric forms of activating *BRAF* mutations, including V600 *BRAF* mutations, non-V600 BRAF mutations and RAF fusions. MapKure is advancing BGB-3245 through clinical development for solid tumor patients harboring *BRAF* driver mutations and *BRAF* fusions that were observed to be sensitive to the compound in preclinical studies. In February 2020 MapKure, BeiGene and SpringWorks announced the initiation of a Phase 1 dose-escalation and expansion clinical trial evaluating BGB-3245 in adult patients with advanced or refractory solid tumors harboring specific genetic mutations that based on preclinical results are predicted to be sensitive to treatment with BGB-3245. We expect to report initial clinical data from the ongoing trial in 2021.

In addition to our significant, but non-controlling equity ownership in MapKure, we have one seat on each of MapKure's joint steering committee and its board of directors. We are also contributing to the clinical development of BGB-3245 and other operational activities through a service agreement with MapKure.

Based on preclinical data, we believe that BGB-3245 may be unique in its BRAF binding and disassociation properties, potentially enabling differentiated antitumor activity as compared to other known RAF inhibitors. We believe this may better position BGB-3245 for clinical development as a monotherapy in certain biomarker defined patient populations. These biomarkers include de novo Class 2 *BRAF* mutations, de novo *BRAF* fusions and *BRAF* resistance mutations following treatment with BRAF V600 inhibitors.

To date, approximately 200 unique mutant *BRAF* alleles have been identified in human tumors. Activating *BRAF* mutations have been categorized into three classes: Class 1 mutants, comprised of constitutively active monomers, such as V600E mutations, Class 2 mutants, comprised of constitutively active dimers, and Class 3 mutants, which are kinase-impaired or kinase-dead. Today, only Class 1 BRAF mutations have any approved targeted therapeutic options, such as vemurafenib, dabrafenib and encorafenib for the treatment of BRAF V600E/K-mutant metastatic melanoma. The following table summarizes the distribution of BRAF mutations that have been described in the scientific literature as of 2017.



Despite the clinical activity of approved BRAF inhibitors in patients with Class 1 *BRAF* mutations, emerging evidence suggests that resistance commonly develops via mutations that enable ligand independent signaling by dimerization of the protein, such as p61 *BRAF* V600E and *BRAF* V600E/L514V, which represent an area of unmet medical need. BGB-3245 has demonstrated preclinical activity against these mutations.

Furthermore, BRAF fusion proteins have recently been described as drivers of cancer cell growth, and patients can now be screened for such fusions in the clinical setting. Recent literature suggests that these mutations may account for 0.3% of all human cancers, with 20 novel BRAF fusions now identified across 12 distinct tumor types, with enrichment in specific cancers. We believe that BGB-3245 may also address patients with these BRAF fusions.

License and collaboration agreements

Pfizer license agreements

We were originally conceived by Pfizer as an innovative way to advance investigational therapies that may hold significant promise for underserved patients, and Freda Lewis-Hall, M.D., DFAPA, the former Executive Vice President and Chief Medical Officer of Pfizer, is a member of our board of directors. Pfizer initially made an equity investment and also contributed royalty- and milestone-bearing product licenses, including for our two lead product candidates, nirogacestat and mirdametinib.

A description of each of our license agreements with Pfizer is set forth below:

Nirogacestat license agreement

In August 2017, we entered into a license agreement, or the Nirogacestat License Agreement, with Pfizer pursuant to which we acquired exclusive (including as to Pfizer) worldwide sublicensable rights to research, develop and manufacture nirogacestat for the treatment, diagnosis and prevention of all diseases and commercialize nirogacestat for the treatment, diagnosis and prevention of all diseases other than Alzheimer's disease, breast cancer and prostate cancer. Additionally, Pfizer agreed that, for ten years, it would not conduct a clinical trial of a gamma secretase inhibitor for desmoid tumors. Pfizer retained rights to commercialize nirogacestat for the treatment of Alzheimer's disease, breast cancer and prostate cancer. We subsequently amended the Nirogacestat License Agreement in July 2019 with regard to certain provisions relating to intellectual property.

Pursuant to the Nirogacestat License Agreement, as amended, we are obligated to use commercially reasonable efforts to develop and seek regulatory approval for at least one product in the U.S. and if regulatory approval is obtained, to commercialize such product in the U.S. If, following regulatory approval in the U.S., we reasonably anticipate that the product will receive a certain level of reimbursement in certain countries, then we are obligated to use commercially reasonable efforts to develop and seek regulatory approval for the product in such country and if regulatory approval is obtained, to commercialize such product in such country.

We are required to pay Pfizer up to an aggregate of $232.5 million upon achievement of certain commercial milestone events.

We will pay Pfizer tiered royalties on sales of nirogacestat at percentages ranging from the mid-single digits to the low 20s, that may be subject to deductions for expiration of valid claims, amounts due under third-party licenses and generic competition.

Unless earlier terminated, the Nirogacestat License Agreement will expire upon the expiration of all royalty obligations. The royalty period will expire on a country-by-country basis upon the later of (i) ten years from the first commercial sale, (ii) the expiration of all regulatory or data exclusivity and (iii) the expiration of the last-to-expire valid patent claim. Following expiration of the applicable royalty period for a country, we will continue to have a perpetual, fully paid-up, non-exclusive license to all IP licensed during the royalty period for such country. We have the right to terminate the Nirogacestat License Agreement for convenience upon thirty (30) days' prior written notice. Pfizer may not terminate the agreement for convenience. Either we or Pfizer may terminate the Nirogacestat License Agreement if the other party

is in material breach and such breach is not cured within the specified cure period. In addition, either we or Pfizer may terminate the Nirogacestat License Agreement in the event of specified insolvency events involving the other party. If Pfizer terminates the agreement as a result of our uncured material breach or our insolvency, Pfizer retains its license with respect to targets for which it has exercised an option (unless Pfizer elects otherwise), subject to reduced payment obligations.

Mirdametinib license agreement

In August 2017, we entered into a license agreement, or the Mirdametinib License Agreement with Pfizer pursuant to which we acquired exclusive (including as to Pfizer) worldwide sublicensable rights to research, develop, manufacture and commercialize mirdametinib for the treatment of all diseases. Additionally, Pfizer agreed, that for ten years, it will not conduct a clinical trial with a MEK inhibitor for NF1, but excluding a MEK inhibitor owned or controlled by a third party that acquires, or is acquired by, Pfizer. We subsequently amended the Mirdametinib License Agreement in August 2019 with regard to certain provisions relating to intellectual property.

Pursuant to the Mirdametinib License Agreement, as amended, we are obligated to use commercially reasonable efforts to develop and seek regulatory approval for at least one product in the U.S. and if regulatory approval is obtained, to commercialize such product in the U.S. If, following regulatory approval in the U.S., we reasonably anticipate that the product will receive a certain level of reimbursement in certain countries, then we will use commercially reasonable efforts to develop and seek regulatory approval for the product in such country and if regulatory approval is obtained, to commercialize such product in such country.

We are required to pay Pfizer up to an aggregate of $229.8 million upon achievement of certain commercial milestone events.

We will pay Pfizer tiered royalties on sales of mirdametinib at percentages ranging from the mid-single digits to the low 20s, that may be subject to deductions for expiration of valid claims, amounts due under third party licenses and generic competition.

Unless earlier terminated, the Mirdametinib License Agreement will expire upon the expiration of all royalty obligations. The royalty period will expire on a country-by-country basis upon the later of (i) ten years from the first commercial sale, (ii) the expiration of all regulatory or data exclusivity and (iii) the expiration of the last-to-expire valid patent claim. Following expiration of the applicable royalty period for a country, we will continue to have a perpetual, fully paid-up, non-exclusive license to all IP licensed during the royalty period for such country. We have the right to terminate the Mirdametinib License Agreement for convenience upon thirty (30) days' prior written notice. Pfizer may not terminate the agreement for convenience. Either we or Pfizer may terminate the Mirdametinib License Agreement if the other party is in material breach and such breach is not cured within the specified cure period. In addition, either we or Pfizer may terminate the Mirdametinib License Agreement in the event of specified insolvency events involving the other party. If Pfizer terminates the agreement as a result of our uncured material breach or our insolvency, Pfizer retains its license with respect to targets for which it has exercised an option (unless Pfizer elects otherwise), subject to reduced payment obligations.

BeiGene clinical collaboration agreement

In August 2018, we entered into a clinical collaboration agreement with BeiGene, the BeiGene Collaboration Agreement, to evaluate the safety, tolerability and preliminary efficacy of combining BeiGene's investigational RAF dimer inhibitor, lifirafenib (BGB-283), and mirdametinib, in a Phase 1b clinical trial for patients with advanced or refractory solid tumors.

We and BeiGene are obligated to use commercially reasonable efforts to complete our respective activities for the clinical trial. BeiGene is responsible for administering the clinical trial and we are responsible for performing the fixed dose formulation activities at our cost. Each party will be solely responsible for its costs associated with manufacturing and supply of its compound for the clinical trial. Upon completion of the clinical trial, if the parties agree that certain pre-defined criteria have been satisfied, the parties will negotiate in good faith a definitive agreement to provide for the

expansion of the clinical collaboration and a commercial relationship based on specified principles, provided that neither party is obligated to enter into such definitive agreement.

We will share with BeiGene equally the costs associated with the clinical trial. The collaboration is managed by a joint steering committee of equal representation from us and BeiGene.

During a specified exclusivity period, neither party will develop or commercialize the other party's compound. Further, for a certain period following the effective date of the agreement, neither party will clinically develop (or prepare to clinically develop) or commercialize the combination of certain inhibitors in any form, or any products containing any such combination, except as permitted by the BeiGene Collaboration Agreement.

Unless earlier terminated, the BeiGene Collaboration Agreement will expire on the one-year anniversary of the date that BeiGene provides the final clinical trial report for the clinical trial to us. Either party may terminate the BeiGene Collaboration Agreement as follows: (i) either party entirely ceases all development of its compound, (ii) either party reasonably concludes that there is a patient safety issue or (iii) if a regulatory authority withdraws approval for either party's compound or the clinical trial. Either party may also terminate the BeiGene Collaboration Agreement if the other party is in material breach and such breach is not cured within the specified cure period.

GlaxoSmithKline clinical collaboration agreement

In June 2019, we entered into a clinical trial collaboration and supply agreement with GSK, the GSK Collaboration Agreement, to evaluate nirogacestat in combination with BLENREP (belantamab mafodotin-blmf), GSK's BCMA ADC, which was approved by the FDA in August 2020 as a monotherapy treatment for adults with relapsed refractory multiple myeloma (RRMM), with such combination trial also in patients with RRMM in an adaptive Phase 1b clinical trial.

GSK is responsible for administering the clinical trial and is responsible for all costs associated with the direct conduct of the clinical trial, other than the manufacture and supply of nirogacestat and certain expenses related to intellectual property rights. The collaboration is managed by a joint development committee of equal representation by us and GSK. Following completion of the clinical trial, within a specified period of time, either party may propose new agreements for the purpose of performing one or more additional clinical trials of the combination therapy for the treatment of relapsed and refractory multiple myeloma. If a party proposes to conduct an additional clinical trial, the parties will negotiate in good faith, without obligation, the details of a definitive agreement to provide for the expansion of the clinical collaboration. If the parties do not reach an agreement, and only one party wishes to proceed with an additional clinical trial, it may do so if the other party does not object to the protocol based on safety concerns.

Unless earlier terminated, the GSK Collaboration Agreement will expire upon completion of the analyses contemplated by the clinical trial. Either party may terminate the GSK Collaboration Agreement as follows: (i) if either party commits a material breach of the GSK Collaboration Agreement that is not cured within a certain time period, (ii) either party files a petition in bankruptcy, insolvency or similar proceedings and such proceedings are not dismissed within a certain time period, (iii) due to regulatory action that prevents a party from supplying its compound or if a party, in its own discretion, determined to discontinue the manufacture or development of its compound for medical, scientific or legal reasons, (iv) either party concludes in good faith that there is a Material Safety Issue, as defined in the GSK Collaboration Agreement, or (v) if a clinical hold with respect to either party's compound arises during the term of the GSK Collaboration Agreement.

Allogene clinical collaboration agreement

In January 2020, we entered into a clinical trial collaboration and supply agreement with Allogene, the Allogene Collaboration Agreement, to evaluate nirogacestat in combination with ALLO-715, Allogene's investigational allogeneic BCMA-targeted CAR-T cell product, in patients with relapsed or refractory multiple myeloma.

Allogene is responsible for administering the Phase 1 clinical trial and is responsible for all costs associated with the direct conduct of the clinical trial, other than the manufacture and supply of nirogacestat and certain expenses related to

intellectual property rights. The collaboration is managed by a joint development committee of equal representation by us and Allogene.

Unless earlier terminated, the Allogene Collaboration Agreement will expire upon completion of the analyses contemplated by the clinical trial. Either party may terminate the Allogene Collaboration Agreement as follows: (i) if either party commits a material breach of the Allogene Collaboration Agreement that is not cured within a certain time period, (ii) either party files a petition in bankruptcy, insolvency or similar proceedings and such proceedings are not dismissed within a certain time period, (iii) due to regulatory action that prevents a party from supplying its compound or if a party, in its own discretion, determined to discontinue the manufacture or development of its compound for medical, scientific or legal reasons, (iv) either party concludes in good faith that there is a Material Safety Issue, as defined in the Allogene Collaboration Agreement, or (v) if a clinical hold with respect to either party's compound arises during the term of the Allogene Collaboration Agreement.

Janssen clinical collaboration agreement

In September 2020, we entered into a clinical collaboration and supply agreement with Janssen, the Janssen Collaboration Agreement, to evaluate our investigational gamma secretase inhibitor, or GSI, nirogacestat, in combination with Janssen's bispecific antibody targeting B-cell maturation antigen, or BCMA, and CD3, teclistamab, in patients with relapsed or refractory multiple myeloma.

Janssen is responsible for administering the Phase 1 clinical trial and is responsible for all costs associated with the direct conduct of the clinical trial, other than the manufacture and supply of nirogacestat and certain expenses related to intellectual property rights. The collaboration is managed by a joint oversight committee of equal representation by us and Janssen.

Unless earlier terminated, the Janssen Collaboration Agreement will expire upon completion of the analyses contemplated by the clinical trial. Either we or Janssen may terminate the Janssen Collaboration Agreement as follows: (i) if either party commits a material breach of the Janssen Collaboration Agreement that is not cured within a certain time period, (ii) if either party concludes in good faith that the study may unreasonably affect patient safety and safety issues are unable to be addressed by amendment to the protocol, or (iii) due to regulatory action that prevents a party from supplying its compound or if a party, in its own discretion, determined to discontinue the manufacture or development of its compound for medical, scientific or legal reasons. Janssen may terminate the Janssen Collaboration Agreement for any reason so long as it provides advance written notice to us as specified in such agreement. We may terminate the Janssen Collaboration Agreement and supply of nirogacestat if we reasonably and in good faith believe nirogacestat is not used by Janssen as described in the protocol.

Precision clinical collaboration agreement

In September 2020, we entered into a clinical trial collaboration agreement with Precision, the Precision Collaboration Agreement, to evaluate nirogacestat in combination with PBCAR269A, an investigational allogeneic chimeric antigen receptor, or CAR, T cell therapy candidate targeting BCMA, in patients with relapsed or refractory multiple myeloma.

Precision is responsible for administering the Phase 1/2a clinical trial and is responsible for all costs associated with the direct conduct of the clinical trial, other than the manufacture and supply of nirogacestat and certain expenses related to intellectual property rights. The collaboration is managed by a joint steering committee of equal representation by us and Precision. Following completion of the clinical trial, within a specified period of time, either party may propose new agreements for the purpose of performing one or more additional clinical trials of the combination therapy. If a party proposes to conduct an additional clinical trial, the parties will negotiate in good faith, without obligation, the details of a definitive agreement to provide for the expansion of the clinical collaboration.

Unless earlier terminated, the Precision Collaboration Agreement will expire upon completion of the analyses contemplated by the clinical trial. Either party may terminate the Precision Collaboration Agreement as follows: (i) if either party commits a material breach of the Precision Collaboration Agreement that is not cured within a certain time period, (ii) either party files a petition in bankruptcy, insolvency or similar proceedings and such proceedings are not

dismissed within a certain time period, (iii) due to regulatory action that prevents a party from supplying its compound or if a party, in its own discretion, determined to discontinue the manufacture or development of its compound for medical, scientific or legal reasons, (iv) either party concludes in good faith that there is a Material Safety Issue, as defined in the Precision Collaboration Agreement, or (v) if a clinical hold with respect to either party's compound arises during the term of the Precision Collaboration Agreement. In addition, Precision may terminate the Precision Collaboration Agreement if it determines, following a review of available data, that further development or commercialization of the combination therapy is not commercially reasonable.

Pfizer clinical collaboration agreement

In October 2020, we entered into a clinical trial collaboration and supply agreement with Pfizer, the Pfizer Collaboration Agreement, to evaluate nirogacestat in combination with Pfizer's bispecific antibody targeting BCMA and CD3, elranatamab, in patients with relapsed or refractory multiple myeloma.

Pfizer is responsible for administering the Phase 1b/2 clinical trial and is responsible for all costs associated with the direct conduct of the clinical trial, other than the manufacture and supply of nirogacestat and certain expenses related to intellectual property rights. The collaboration is managed by a joint development committee of equal representation by us and Pfizer.

Unless earlier terminated, the Pfizer Collaboration Agreement will expire upon completion of the analyses contemplated by the clinical trial. Either we or Pfizer may terminate the Pfizer Collaboration Agreement: (i) if either party commits a material breach of the Pfizer Collaboration Agreement that is not cured within a certain time period, (ii) if either party concludes in good faith that the study may unreasonably affect patient safety and safety issues are unable to be addressed by amendment to the protocol, or (iii) due to regulatory action that prevents a party from supplying its compound or if a party, in its own discretion, determined to discontinue the manufacture or development of its compound for medical, scientific or legal reasons. SpringWorks may terminate the Pfizer Collaboration Agreement and supply if SpringWorks reasonably and in good faith believes nirogacestat is being used in an unsafe manner and Pfizer fails to reasonably and in good faith address such issue.

Jazz Pharmaceuticals asset purchase and exclusive license agreement

In October 2020, we announced an asset purchase and exclusive license agreement with Jazz Pharmaceuticals Ireland Limited, or Jazz, the Jazz Agreement, pursuant to which Jazz acquired our fatty acid amide hydrolase, or FAAH, inhibitor program including PF-04457845. Jazz made an upfront payment of $35 million to us with potential future payments of up to $375 million based upon the achievement of certain clinical development, regulatory, and commercial milestones. In addition, Jazz is obligated to pay us sales-based royalties on future net sales of PF-04457845.

Pursuant to the Jazz Agreement, Jazz is obligated to use commercially reasonable efforts to develop and seek regulatory approval for at least one product in the U.S. and if regulatory approval is obtained, to commercialize such product in the U.S.

Unless earlier terminated, the Jazz Agreement shall remain in effect on a product-by-product and country-by-country basis until the expiration of the royalty term for such product in such country, as defined in the Jazz Agreement. Either party may terminate the Jazz Agreement if either party commits a material breach of the Jazz Agreement that is not cured within a certain time period. Jazz may terminate the Jazz Agreement for any reason so long as it provides advance written notice to us as specified in such agreement.

Manufacturing

We rely on third parties to manufacture nirogacestat and mirdametinib. We have entered into agreements with contract manufacturing organizations, or CMOs, to produce drug substance for the nirogacestat and mirdametinib programs.

We require all of our CMOs to conduct manufacturing activities in compliance with current good manufacturing practice, or cGMP, requirements. We currently rely solely on these CMOs for scale-up and process development work

and to produce sufficient quantities of our product candidates for use in preclinical studies and clinical trials. We anticipate that these CMOs will have the capacity to support both clinical supply and commercial-scale production, but we do not have any formal agreements at this time to cover commercial production. We may also elect to enter into agreements with other CMOs to manufacture supplies of drug substance and finished drug product.

Sales and marketing

If any of our product candidates are approved, we intend to market and commercialize them in the U.S. and select international markets, either alone or in partnership with others.

Many desmoid tumor and NF1-PN patients are managed by specialist physicians, including oncologists, medical geneticists and neurologists, and therefore we believe can be reached with a targeted sales force.

For our product candidates being explored in combination with other agents or in highly prevalent diseases, we intend to establish commercialization strategies for each in collaboration with our partner as we approach potential marketing approval, and will share responsibilities in a manner that takes into account our respective commercial infrastructures, competencies and country-specific expertise.

Educational and patient initiatives

We actively collaborate with desmoid tumor and NF1-PN constituents through a number of initiatives, including participation in patient meetings and educational initiatives. Examples of such constituents include the Desmoid Tumor Research Foundation, COG and Children's Tumor Foundation. We undertake these activities in order to better understand the burdens and unmet needs these patients face so that we can more effectively facilitate their access to our product candidates, if approved. In each of these disease areas we will support disease awareness and diagnosis and subsequent treatment of identified patients, by providing information, increasing physician awareness and creating more efficient referral pathways.

Competition

The pharmaceutical industry is characterized by rapid evolution of technologies and intense competition. While we believe that our product candidates, technology, knowledge, experience and scientific resources provide us with competitive advantages, we face competition from major pharmaceutical and biotechnology companies, academic institutions, governmental agencies and public and private research institutions, among others.

Any product candidates that we successfully develop and commercialize will compete with approved treatment options, including off-label therapies, and new therapies that may become available in the future. Key considerations that would impact our ability to effectively compete with other therapies include the efficacy, safety, method of administration, cost, level of promotional activity and intellectual property protection of our products. Many of the companies against which we may compete have significantly greater financial resources and expertise than we do in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products.

For our program in desmoid tumors, where there are no therapies currently approved by the FDA, we are aware that other companies are, or may be, developing products for this indication, including Ayala Pharmaceuticals, Inc., Bayer Corporation, Cellestia Biotech AG and Iterion Therapeutics, Inc. We are also aware of several therapies, some of which are generic, that are used off-label for the treatment of desmoid tumors. These therapies include chemotherapeutic agents, such as liposomal doxorubicin and vinblastine/methotrexate, non-steroidal anti-inflammatory drugs, anti-hormonal therapies and tyrosine kinase inhibitors, such as sorafenib, imatinib and pazopanib.

For the treatment of NF1-PN, AstraZeneca's Koselugo is currently the only therapy approved by the FDA. We are aware that other companies are, or may be, developing products for this indication, including Array BioPharma Inc. (a subsidiary of Pfizer), Daiichi Sankyo Co., Ltd., Exelixis, Inc., F. Hoffmann-La Roche Ltd, Infixion Bioscience, Inc., NFlection Therapeutics, Inc., Novartis International AG and Teton Therapeutics LLC. We are also aware of several

therapies, some of which are generic, that are used off-label for the treatment of NF1-PN. These therapies include radiotherapy and various systemic treatments, such as chemotherapy and immunotherapy.

For our targeted oncology portfolio, we are aware that other oncology focused companies are or may be developing products for the treatment of solid tumors with *RAS* mutations, *RAF* mutations and other MAPK aberrations, including Amgen Inc., AstraZeneca PLC, Basilea Pharmaceutica Ltd., Black Diamond Therapeutics, Inc., Boehringer Ingelheim International GmbH, Chugai Pharmaceutical Co Ltd, Daiichi Sankyo Co., Ltd., Day One Biopharmaceuticals, Inc., Eli Lilly and Company, F. Hoffmann-La Roche Ltd., Hanmi Pharmaceutical Co., Ltd., Kinnate Biopharma Inc., Merck & Co., Inc., Mirati Therapeutics, Inc., Moderna Inc., Novartis International AG, Pfizer, Revolution Medicines, Inc., TheRas, Inc. and Wellspring Biosciences, Inc. There may be additional companies with programs suitable for addressing these patient populations that could be competitive with our efforts but that have not yet disclosed specific clinical development plans. In addition we are aware that other oncology focused companies are or may be developing products targeting BCMA for the treatment of multiple myeloma patients, including AbbVie Inc., Amgen Inc, AstraZeneca PLC, Autolus Therapeutics plc, bluebird bio, Inc., Bristol-Myers Squibb, Cartesian Therapeutics, Inc., CRISPR Therapeutics AG, Heidelberg Pharma GmbH, Legend Biotech Corporation, Novartis International AG, Poseida Therapeutics, Inc., Regeneron Pharmaceuticals and Seagen.

Smaller or early-stage companies, including oncology-focused therapeutics companies, may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These companies may also compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites, enrolling patients in clinical trials and acquiring technologies complementary to, or necessary for, our programs.

The availability of reimbursement from government and private payors will also significantly impact the pricing and competitiveness of our products. Our competitors may obtain FDA or other regulatory approvals for their products more rapidly than we may obtain approvals for our product candidates, which could result in our competitors establishing a strong market position before we are able to commercialize our product candidates.

Intellectual property

Our success depends in part on our ability to obtain and maintain proprietary protection for our product candidates, manufacturing and process discoveries and other know-how, to operate without infringing the proprietary rights of others, and to prevent others from infringing our proprietary rights. We plan to protect our proprietary position using a variety of methods, which include pursuit of U.S. and foreign patent applications related to proprietary technology, inventions and improvements, such as compositions of matter and methods-of-use, that we determine are important to the development and implementation of our business. For example, we, our licensors, or our collaborators currently have, or are pursuing, patents covering the composition of matter for our product candidates and we plan to generally pursue patent protection covering methods-of-use for one or more clinical programs. We also rely on trade secrets, trademarks, know-how, continuing technological innovation and potential in-licensing opportunities to develop and maintain our proprietary position.

Patents

At the time we were formed in August 2017, we entered into license agreements with Pfizer for our lead product candidates, pursuant to which we acquired exclusive worldwide rights under Pfizer patents and know-how to develop, manufacture and commercialize our lead product candidates.

We have exclusive licenses under the Nirogacestat License Agreement to patent rights in the U.S. and numerous foreign jurisdictions relating to nirogacestat. The patent rights in-licensed under the Nirogacestat License Agreement include five granted patents in the U.S. (with the agreement originally covering three such patents, and two additional patents having been subsequently granted based on work conducted by us and with Pfizer’s consent) and more than 25 patents granted in foreign jurisdictions including Australia, Canada, China, France, Germany, Spain, United Kingdom and Japan. A U.S. patent covering nirogacestat as a composition of matter has a statutory expiration date in 2025 and a U.S. composition of matter patent that covers the polymorphic form of nirogacestat that is currently in clinical development

expires in 2039, in each case, not including patent term adjustment or any patent term extension, and relevant foreign counterparts are expected to expire in 2025, in each case, not including any patent term extensions. In addition, a Notice of Allowance from the United States Patent and Trademark Office has been received for a patent application with composition of matter claims covering several polymorphic forms of nirogacestat, including the polymorphic form that is currently in clinical development and which is also covered by the above referenced U.S. patent. The patent issuing from this application will also expire in 2039. If we are successful in obtaining regulatory approval of nirogacestat for the treatment of desmoid tumors, we expect to rely on orphan drug exclusivity, which generally grants seven years of marketing exclusivity in the U.S. and 10 years of marketing exclusivity in Europe. See "License and collaboration agreements—Pfizer license agreements" above for additional information on our rights under the Nirogacestat License Agreement. Nirogacestat received Orphan Drug Designation in the U.S. for the treatment of desmoid tumors.

We have exclusive licenses under the Mirdametinib License Agreement to patent rights in the U.S. and numerous foreign jurisdictions relating to mirdametinib. The patent rights in-licensed under the Mirdametinib License Agreement include two granted patents in the U.S. and more than 45 patents granted in foreign jurisdictions including Australia, Canada, China, France, Germany, Spain, United Kingdom and Japan. A U.S. patent covering mirdametinib as a composition of matter has a statutory expiration date in 2021, not including patent term adjustment or patent term extension, and relevant foreign counterparts are expected to expire in 2021, in each case, not including any patent term extensions. With patent term adjustments, the U.S. patent expires in 2022. If we are successful in obtaining regulatory approval of mirdametinib for the treatment of NF1, we expect to rely on orphan drug exclusivity, which generally grants seven years of marketing exclusivity in the U.S. and 10 years of marketing exclusivity in Europe. See "License and collaboration agreements—Pfizer license agreements" above for additional information on our rights under the Mirdametinib License Agreement. The FDA has granted mirdametinib Orphan Drug Designation for NF1-PN, and the European Commission has granted mirdametinib Orphan Drug Designation for NF1.

For combination therapeutics involving nirogacestat or mirdametinib, there may be opportunities to enhance our patent estate, which we will explore. There can be no assurance that patents will issue from any of these efforts.

Trade secrets

In addition to patents, we rely on trade secrets and know-how to develop and maintain our competitive position. We typically rely on trade secrets to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection. We protect trade secrets and know-how by establishing confidentiality agreements and invention assignment agreements with our employees, consultants, scientific advisors, contractors and partners. These agreements generally provide that all confidential information developed or made known during the course of an individual or entity's relationship with us must be kept confidential during and after the relationship. These agreements also generally provide that all inventions resulting from work performed for us or relating to our business and conceived or completed during the period of employment or assignment, as applicable, shall be our exclusive property. In addition, we take other appropriate precautions, such as physical and technological security measures, to guard against misappropriation of our proprietary information by third parties.

Coverage, pricing and reimbursement

Successful commercialization of new drug products depends in part on the extent to which reimbursement for those drug products will be available from government health administration authorities, private health insurers and other organizations. Government authorities and other third-party payors, such as private health insurers and health maintenance organizations, decide which drug products they will pay for and establish reimbursement levels. The availability and extent of reimbursement by governmental and private payors is essential for most patients to be able to afford a drug product. Sales of drug products depend substantially, both domestically and abroad, on the extent to which the costs of drug products are paid for by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or reimbursed by government health administration authorities, private health coverage insurers and other third-party payors.

A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and other third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular

drug products. In many countries, the prices of drug products are subject to varying price control mechanisms as part of national health systems. In general, the prices of drug products under such systems are substantially lower than in the U.S. Other countries allow companies to fix their own prices for drug products, but monitor and control company profits. Accordingly, in markets outside the U.S., the reimbursement for drug products may be reduced compared with the U.S. In the U.S., the principal decisions about reimbursement for new drug products are typically made by the Centers for Medicare & Medicaid Services, or CMS, an agency within the Department of Health and Human Services, or HHS. CMS decides whether and to what extent a new drug product will be covered and reimbursed under certain federal governmental healthcare programs, such as Medicare, and private payors tend to follow CMS to a substantial degree. However, no uniform policy of coverage and reimbursement for drug products exists among third-party payors and coverage and reimbursement levels for drug products can differ significantly from payor to payor. In the U.S., the process for determining whether a third-party payor will provide coverage for a biological product typically is separate from the process for setting the price of such product or for establishing the reimbursement rate that the payor will pay for the product once coverage is approved. With respect to biologics, 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 FDA-approved products for a particular indication, or place products at certain formulary levels that result in lower reimbursement levels and higher cost sharing obligation imposed on patients. A decision by a third-party payor not to cover our product candidates could reduce physician utilization of a product. Moreover, a third-party payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Adequate third-party reimbursement may not be available to enable a manufacturer to maintain price levels sufficient to realize an appropriate return on its investment in product development. Additionally, coverage and reimbursement for products can differ significantly from payor to payor. One third-party payor's decision to cover a particular medical product does not ensure that other payors will also provide coverage for the medical product, or will provide coverage at an adequate reimbursement rate. As a result, the coverage determination process usually requires manufacturers to provide scientific and clinical support for the use of their products to each payor separately and is a time-consuming process.

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 we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future. Third-party payors are increasingly challenging the prices charged for medical products and services, examining the medical necessity and reviewing the cost-effectiveness of pharmaceutical products, in addition to questioning safety and efficacy. If third-party payors do not consider a product to be cost-effective compared to other available therapies, they may not cover that product after FDA approval or, if they do, the level of payment may not be sufficient to allow a manufacturer to sell its product at a profit.

In addition, in many foreign countries, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing and reimbursement vary widely from country to country. In the European Union, or EU, governments influence the price of products through their pricing and reimbursement rules and control of national healthcare systems that fund a large part of the cost of those products to consumers. Some jurisdictions operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed to by the government. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical trials that compare the cost effectiveness of a particular product to currently available therapies. Other member states allow companies to fix their own prices for medicines, but monitor and control company profits. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our products. The downward pressure on healthcare costs in general, particularly prescription products, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross border imports from low-priced markets exert a commercial pressure on pricing within a country.

Government regulation

Government authorities in the U.S. 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, labeling, packaging, storage, record-keeping, promotion, advertising, distribution, post-approval monitoring and reporting, marketing and export and import of drug products, such as nirogacestat, mirdametinib and our other product candidates. Generally, before a new drug can be marketed, considerable data demonstrating its quality, safety

and efficacy must be obtained, organized into a format specific for each regulatory authority and submitted for review and approved by the regulatory authority.

Clinical trials

The clinical stage of development involves the administration of the investigational product to healthy volunteers or patients under the supervision of qualified investigators, generally physicians not employed by, or under control of, the trial sponsor, in accordance with Good Clinical Practices, or GCPs, which include the requirement that all research subjects provide their informed consent for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, the objectives of the clinical trial, dosing procedures, subject selection and exclusion criteria and the parameters to be used to monitor subject safety and assess efficacy. Each protocol, and any subsequent amendments to the protocol, must be submitted to the FDA as part of the IND. Furthermore, each clinical trial must be reviewed and approved by an Institutional Review Board, or IRB, for each institution at which the clinical trial will be conducted to ensure that the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the informed consent form that must be provided to each clinical trial subject or his or her legal representative, and must monitor the clinical trial until completed. There also are requirements governing the reporting of ongoing clinical trials and completed clinical trial results to public registries. Information about most clinical trials must be submitted within specific timeframes for publication on the www.clinicaltrials.gov website. Information related to the product, patient population, phase of investigation, trial sites and investigators and other aspects of the clinical trial is made public as part of the registration of the clinical trial. Sponsors are also obligated to discuss the results of their clinical trials after completion. Disclosure of the results of these trials can be delayed in some cases for up to two years after the date of completion of the trial. Competitors may use this publicly available information to gain knowledge regarding the progress of development programs. Human clinical trials are typically conducted in three sequential phases, which may overlap or be combined:

- Phase 1 clinical trials generally involve a small number of healthy volunteers or disease-affected patients who are initially exposed to a single dose and then multiple doses of the product candidate. The primary purpose of these clinical trials is to assess the metabolism, pharmacologic action, side effect tolerability and safety of the drug.

- Phase 2 clinical trials involve studies in disease-affected patients to determine the dose required to produce the desired benefits. At the same time, safety and further pharmacokinetic and pharmacodynamic information is collected, possible adverse effects and safety risks are identified, and a preliminary evaluation of efficacy is conducted.

- Phase 3 clinical trials generally involve a larger number of patients at multiple sites and are designed to provide the data necessary to demonstrate the effectiveness of the product for its intended use, its safety in use and to establish the overall benefit/risk relationship of the product and provide an adequate basis for product approval. These trials may include comparisons with placebo and/or other comparator treatments. The duration of treatment is often extended to mimic the actual use of a product during marketing.

A registrational trial is a clinical trial that adequately meets regulatory agency requirements for the evaluation of a drug candidate’s efficacy and safety such that it can be used to justify the approval of the drug. Generally, registrational trials are Phase 3 trials but may be Phase 2 trials if the trial design provides a reliable assessment of clinical benefit, particularly in situations where there is an unmet medical need.

Post-approval trials, sometimes referred to as Phase 4 clinical trials, may be conducted after initial marketing approval. These trials are used to gain additional experience from the treatment of patients in the intended therapeutic indication, particularly for long-term safety follow up. In certain instances, the FDA may mandate the performance of Phase 4 clinical trials as a condition of approval of a Biologics License Application, or BLA.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. The FDA or the sponsor may suspend or terminate a clinical trial at any time, or the FDA may impose other sanctions on various grounds, including a finding that the research patients are being

exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the requirements of the IRB or if the drug has been associated with unexpected serious harm to patients. There are also requirements related to registration and reporting of certain clinical trials and completed clinical trial results to public registries.

U.S.—FDA regulation

Approval process

In the U.S., pharmaceutical products are subject to extensive regulation by the FDA. The Federal Food, Drug, and Cosmetic Act, or the FDC Act, and other federal and state statutes and regulations, govern, among other things, the research, development, testing, manufacture, storage, recordkeeping, approval, labeling, promotion and marketing, distribution, post-approval monitoring and reporting, sampling, and import and export of pharmaceutical products. Failure to comply with applicable U.S. requirements may subject a company to a variety of administrative or judicial sanctions, such as FDA refusal to approve pending New Drug Applications, or NDAs, warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, civil penalties and criminal prosecution.

Pharmaceutical product development for a new product or certain changes to an approved product in the U.S. typically involves preclinical laboratory and animal tests, the submission to the FDA of an IND, which must become effective before clinical testing may commence, and adequate and well-controlled clinical trials to establish the safety and effectiveness of the drug for each indication for which FDA approval is sought. 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 or disease.

Preclinical tests include laboratory evaluation of product chemistry, formulation and toxicity, as well as animal trials to assess the characteristics and potential safety and efficacy of the product. The conduct of the preclinical tests must comply with federal regulations and requirements, including good laboratory practices. The results of preclinical testing are submitted to the FDA as part of an IND along with other information, including information about product chemistry, manufacturing and controls and a proposed clinical trial protocol. Long term preclinical tests, such as animal tests of reproductive toxicity and carcinogenicity, may continue after the IND is submitted.

A 30-day waiting period after the submission of each IND is required prior to the commencement of clinical testing in humans. 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.

Clinical trials involve the administration of the investigational new drug to healthy volunteers or patients under the supervision of a qualified investigator. Clinical trials must be conducted: (i) in compliance with federal regulations; (ii) in compliance with GCP, an international standard meant to protect the rights and health of patients and to define the roles of clinical trial sponsors, administrators, and monitors; as well as (iii) under protocols detailing the objectives of the trial, the parameters to be used in monitoring safety, and the effectiveness criteria to be evaluated. Each protocol involving testing on U.S. patients and subsequent protocol amendments must be submitted to the FDA as part of the IND.

The FDA may order the temporary, or permanent, discontinuation of a clinical trial at any time, or impose other sanctions, if it believes that the clinical trial either is not being conducted in accordance with FDA requirements or presents an unacceptable risk to the clinical trial patients. The trial protocol and informed consent information for patients in clinical trials must also be submitted to an IRB for approval. An IRB may also require the clinical trial at the site to be halted, either temporarily or permanently, for failure to comply with the IRB’s requirements, or may impose other conditions. Clinical trials to support NDAs for marketing approval are typically conducted in three sequential phases, but the phases may overlap. In Phase 1, the initial introduction of the drug into healthy human subjects or patients, the drug is tested to assess metabolism, pharmacokinetics, pharmacological actions, side effects associated with increasing doses, and, if possible, early evidence on effectiveness. Phase 2 usually involves trials in a limited patient population to determine the effectiveness of the drug for a particular indication, dosage tolerance and optimum dosage,

and to identify common adverse effects and safety risks. If a compound demonstrates evidence of effectiveness and an acceptable safety profile in Phase 2 evaluations, Phase 3 trials are undertaken to obtain the additional information about clinical efficacy and safety in a larger number of patients, typically at geographically dispersed clinical trial sites, to permit FDA to evaluate the overall benefit-risk relationship of the drug and to provide adequate information for the labeling of the drug. In most cases FDA requires two adequate and well-controlled Phase 3 clinical trials to demonstrate the efficacy of the drug. A single Phase 3 trial with other confirmatory evidence may be sufficient in rare instances where the trial is a large multi-center trial demonstrating internal consistency and a statistically very persuasive finding of a clinically meaningful effect on mortality, irreversible morbidity or prevention of a disease with a potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible.

Pursuant to the 21st Century Cures Act, which was enacted on December 13, 2016, the manufacturer of an investigational drug for a serious or life-threatening disease is required to make available, such as by posting on its website, its policy on evaluating and responding to requests for expanded access. This requirement applies on the later of 60 days after the date of enactment or the first initiation of a Phase 2 or Phase 3 trial of the investigational drug. After completion of the required clinical testing, an NDA is prepared and submitted to the FDA. FDA approval of the NDA is required before marketing of the product may begin in the U.S. The NDA must include the results of all preclinical, clinical and other testing and a compilation of data relating to the product's pharmacology, chemistry, manufacture and controls. The cost of preparing and submitting an NDA is substantial. The submission of most NDAs is additionally subject to a substantial application user fee, currently $2,875,842 for Fiscal Year 2021, and the manufacturer and/or sponsor under an approved NDA are also subject to annual program fees for eligible products, which are currently $336,432 for Fiscal Year 2021.

The FDA has 60 days from its receipt of an NDA to determine whether the application will be accepted for filing based on the agency's threshold determination that it is sufficiently complete to permit substantive review. Once the submission is accepted for filing, the FDA begins an in-depth review. The FDA has agreed to certain performance goals in the review of new drug applications. Most such applications for standard review drug products are reviewed within ten to twelve months; most applications for priority review drugs are reviewed in six to eight months. Priority review can be applied to drugs that the FDA determines offer major advances in treatment or provide a treatment where no adequate therapy exists. The review process for both standard and priority review may be extended by FDA for three additional months to consider certain late-submitted information, or information intended to clarify information already provided in the submission.

The FDA may also refer applications for novel drug products, or drug products that present difficult questions of safety or efficacy, to an advisory committee—typically a panel that includes clinicians and other experts—for review, evaluation and a recommendation as to whether the application should be approved. The FDA is not bound by the recommendation of an advisory committee, but it generally follows such recommendations. Before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP. Additionally, the FDA will inspect the facility or the facilities at which the drug is manufactured. FDA will not approve the product unless compliance with cGMP is satisfactory and the NDA contains data that provide substantial evidence that the drug is safe and effective in the indication studied.

After the FDA evaluates the NDA and the manufacturing facilities, it issues either an approval letter or a complete response letter. 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, or when, those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included.

An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. As a condition of NDA approval, the FDA may require a risk evaluation and mitigation strategy, or REMS, to help ensure that the benefits of the drug outweigh the potential risks. REMS can include medication guides, communication plans for healthcare professionals and elements to assure safe use, or ETASU. ETASU can 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 requirement for a REMS can materially affect the

potential market and profitability of the drug. Moreover, product approval may require substantial post-approval testing and surveillance to monitor the drug's safety or efficacy. Once granted, product approvals may be withdrawn if compliance with regulatory standards is not maintained or problems are identified following initial marketing.

Changes to some of the conditions established in an approved application, including changes in indications, labeling or manufacturing processes or facilities, require submission and FDA approval of a new NDA or NDA supplement before the change can be implemented. An NDA supplement for a new indication typically requires clinical data similar to that in the original application, and the FDA uses the same procedures and actions in reviewing NDA supplements as it does in reviewing NDAs.

Exclusivity

Upon NDA approval of a new chemical entity, or NCE, which is a drug that contains no active moiety that has been approved by FDA in any other NDA, that drug receives five years of marketing exclusivity during which FDA cannot receive any Abbreviated New Drug Application, or ANDA, seeking approval of a generic version of that drug. Certain changes to a drug, such as the addition of a new indication to the package insert, are associated with a three-year period of exclusivity during which FDA cannot approve an ANDA for a generic drug that includes the change.

An ANDA may be submitted one year before NCE exclusivity expires if a Paragraph IV certification is filed. If there is no listed patent in the Orange Book, there may not be a Paragraph IV certification, and, thus, no ANDA may be filed before the expiration of the exclusivity period.

Patent term extension

After NDA approval, owners of relevant drug patents may apply for up to a five-year patent extension for one patent. The allowable patent term extension is calculated as half of the drug's testing phase—the time between IND and NDA submission—and all of the review phase—the time between NDA submission and approval up to a maximum of five years. The time can be shortened if FDA determines that the applicant did not pursue approval with due diligence. The total patent term after the extension may not exceed 14 years from approval.

For patents that might expire during the application phase, the patent owner may request an interim patent extension. An interim patent extension increases the patent term by one year and may be renewed up to four times. For each interim patent extension granted, the post-approval patent extension is reduced by one year. The director of the U.S. Patent and Trademark Office must determine that approval of the drug covered by the patent for which a patent extension is being sought is likely. Interim patent extensions are not available for a drug for which an NDA has not been submitted.

Orphan drugs

Under the Orphan Drug Act, the FDA may grant Orphan Drug Designation to drugs or biologics intended to treat a rare disease or condition—generally a disease or condition that affects fewer than 200,000 individuals in the U.S. or affects more than 200,000 individuals in the U.S. where there is no reasonable expectation that the cost of developing the drug or therapeutic biologic will be recovered from sales in the U.S. Orphan Drug Designation must be requested before submitting an NDA. Among the other benefits of Orphan Drug Designation are tax credits for certain research and a waiver of the NDA application user fee. After the FDA grants Orphan Drug Designation, the generic identity of the drug and its potential orphan use are disclosed publicly by the FDA. Orphan Drug Designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. The first NDA applicant to receive FDA approval for a particular active ingredient to treat a particular disease with FDA Orphan Drug Designation is entitled to a seven-year exclusive marketing period in the U.S. for that product, for that indication. During the seven-year exclusivity period, the FDA may not approve any other applications to market the same drug for the same disease, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity or if the FDA finds that the holder of the orphan exclusivity has not shown that it can assure the availability of sufficient quantities of the orphan product to meet the needs of patients with the disease or condition for which the drug was designated. Orphan drug exclusivity does not prevent the FDA from approving a different drug for the same disease or condition, or the same drug for a different disease or condition. Such a designation, may also be revoked by the FDA in

certain circumstances, such as if the agency finds that the applicant's request for designation request omitted material information required under the Orphan Drug Act and its implementing regulations.

Fast Track Designation and accelerated approval

The FDA is required to facilitate the development, and expedite the review, of drugs that are intended for the treatment of a serious or life-threatening disease or condition for which there is no effective treatment, and which demonstrate the potential to address unmet medical needs for the condition. Under the Fast Track program, the sponsor of a new drug candidate may request that the FDA designate the drug candidate for a specific indication as a Fast Track drug concurrent with, or after, the filing of the IND for the drug candidate. The FDA must determine if the drug candidate qualifies for Fast Track Designation within 60 days of receipt of the sponsor's request.

Under the Fast Track program and the FDA's accelerated approval regulations, the FDA may approve a drug for a serious or life-threatening illness that provides meaningful therapeutic benefit to patients over existing treatments based upon a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, 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.

In clinical trials, a surrogate endpoint is a measurement of laboratory or clinical signs of a disease or condition that substitutes for a direct measurement of how a patient feels, functions or survives. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. 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, will allow the FDA to withdraw the drug from the market on an expedited basis. All promotional materials for product candidates approved under accelerated regulations are subject to prior review by the FDA.

In addition to other benefits such as the ability to use surrogate endpoints and engage in more frequent interactions with the FDA, the FDA may initiate review of sections of a Fast Track drug's NDA before the application is complete. This rolling review is available if the applicant provides, and the FDA approves, a schedule for the submission of the remaining information and the applicant pays applicable user fees. However, the FDA's time period goal for reviewing an application does not begin until the last section of the NDA is submitted. Additionally, 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.

Breakthrough therapy designation

Breakthrough Therapy Designation by the FDA provides more extensive development consultation opportunities with FDA senior staff, allows for the rolling review of the drug's application for approval and indicates that the product could be eligible for priority review if supported by clinical data at the time of application submission for drugs that are intended to treat a serious or life-threatening disease or condition where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. Under the breakthrough therapy program, the sponsor of a new drug candidate may request that the FDA designate the drug candidate for a specific indication as a breakthrough therapy concurrent with, or after, the filing of the IND for the drug candidate. The FDA must determine if the drug candidate qualifies for Breakthrough Therapy Designation within 60 days of receipt of the sponsor's request.

Disclosure of clinical trial information

Sponsors of clinical trials of FDA regulated products, including drugs, are required to register and disclose certain clinical trial information. Information related to the product, patient population, phase of investigation, trial sites and investigators and other aspects of the clinical trial is then made public as part of the registration. Sponsors are also obligated to discuss the results of their clinical trials after completion. Disclosure of the results of these trials can be

delayed in certain circumstances for up to two years after the date of completion of the trial. Competitors may use this publicly available information to gain knowledge regarding the progress of development programs.

EU regulation

In the EU, our product candidates also may be subject to extensive regulatory requirements. As in the U.S., medicinal products can be marketed only if a marketing authorization from the competent regulatory agencies has been obtained.

Similar to the U.S., the various phases of preclinical and clinical research in the EU are subject to significant regulatory controls.

The Clinical Trials Directive 2001/20/EC, the Directive 2005/28/EC on GCP, and the related national implementing provisions of the individual EU Member States govern the system for the approval of clinical trials in the EU. Under this system, an applicant must obtain prior approval from the competent national authority of the EU Member States in which the clinical trial is to be conducted. Furthermore, the applicant may only start a clinical trial at a specific trial site after the competent ethics committee has issued a favorable opinion. The clinical trial application must be accompanied by, among other documents, an IMPD, or the Common Technical Document, with supporting information prescribed by Directive 2001/20/EC, Directive 2005/28/EC, where relevant the implementing national provisions of the individual EU Member States and further detailed in applicable guidance documents. All suspected unexpected serious adverse reactions to the investigated drug that occur during the clinical trial have to be reported to the competent national authority and the Ethics Committee of the Member State where they occurred.

In April 2014, the new Clinical Trials Regulation, (EU) No 536/2014 was adopted. Currently, the regulation is anticipated not to come into effect before December 2021. The Clinical Trials Regulation will be directly applicable in all the EU Member States, repealing the current Clinical Trials Directive 2001/20/EC. Conduct of all clinical trials performed in the EU will continue to be bound by currently applicable provisions until the new Clinical Trials Regulation becomes applicable. The extent to which ongoing clinical trials will be governed by the Clinical Trials Regulation will depend on when the Clinical Trials Regulation becomes applicable and on the duration of the individual clinical trial. If a clinical trial continues for more than three years from the day on which the Clinical Trials Regulation becomes applicable the Clinical Trials Regulation will at that time begin to apply to the clinical trial.

The new Clinical Trials Regulation aims to simplify and streamline the approval of clinical trials 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 for clinical trial sponsors; and a harmonized procedure for the assessment of applications for clinical trials, which is divided in two parts. Part I is assessed by the competent authorities of all EU Member States in which an application for authorization of a clinical trial has been submitted (Member States concerned). Part II is assessed separately by each Member State concerned. Strict deadlines have been established for the assessment of clinical trial applications. The role of the relevant ethics committees in the assessment procedure will continue to be governed by the national law of the concerned EU Member State. However, overall related timelines will be defined by the Clinical Trials Regulation.

To obtain a marketing authorization of a drug in the EU, we may submit Marketing Authorization Applications, or MAA, either under the so-called centralized or national authorization procedures.

Centralized procedure

The centralized procedure provides for the grant of a single marketing authorization following a favorable opinion by the European Medicines Agency, or EMA, that is valid in all EU Member States, as well as Iceland, Liechtenstein and Norway. The centralized procedure is compulsory for medicines produced by specified biotechnological processes, products designated as orphan medicinal products, advanced therapy medicines (such as gene-therapy, somatic cell-therapy or tissue-engineered medicines) and products with a new active substance indicated for the treatment of specified diseases, such as HIV/AIDS, cancer, diabetes, neurodegenerative disorders or autoimmune diseases and other immune dysfunctions and viral diseases. The centralized procedure is optional for products that represent a significant therapeutic, scientific or technical innovation, or whose authorization would be in the interest of public health. Under the

centralized procedure the maximum timeframe for the evaluation of an MAA by the EMA is 210 days, excluding clock stops, when additional written or oral information is to be provided by the applicant in response to questions asked by the Committee of Medicinal Products for Human Use, or the CHMP. Accelerated assessment might be granted by the CHMP in exceptional cases, when a medicinal product is expected to be of a major public health interest, particularly from the point of view of therapeutic innovation. The timeframe for the evaluation of an MAA under the accelerated assessment procedure is of 150 days, excluding stop-clocks.

National authorization procedures

There are also two other possible routes to authorize medicinal products in several EU countries, which are available for investigational medicinal products that fall outside the scope of the centralized procedure:

- Decentralized procedure. Using the decentralized procedure, an applicant may apply for simultaneous authorization in more than one EU country of medicinal products that have not yet been authorized in any EU country and that do not fall within the mandatory scope of the centralized procedure.

- Mutual recognition procedure. In the mutual recognition procedure, a medicine is first authorized in one EU Member State, in accordance with the national procedures of that country. Following this, further marketing authorizations can be sought from other EU countries in a procedure whereby the countries concerned agree to recognize the validity of the original, national marketing authorization.

Under the above described procedures, before granting an MAA, the EMA or the competent authorities of the Member States of the European Economic Area, or EEA, make an assessment of the risk-benefit balance of the product on the basis of scientific criteria concerning its quality, safety and efficacy.

EU regulatory exclusivity

In the EU, new products authorized for marketing (i.e., reference products) qualify for eight years of data exclusivity and an additional two years of market exclusivity upon marketing authorization. The data exclusivity period prevents generic applicants from relying on the preclinical and clinical trial data contained in the dossier of the reference product when applying for a generic marketing authorization in the EU during a period of eight years from the date on which the reference product was first authorized in the EU. The market exclusivity period prevents a successful generic applicant from commercializing its product in the EU until ten years have elapsed from the initial authorization of the reference product in the EU. The ten-year market exclusivity period can be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies.

EU orphan designation and exclusivity

The criteria for designating an orphan medicinal product in the EU, are similar in principle to those in the U.S. Under Article 3 of Regulation (EC) 141/2000, a medicinal product may be designated as orphan if (i) it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition; (ii) either (a) such condition affects no more than five in 10,000 persons in the EU when the application is made, or (b) the product, without the benefits derived from orphan status, would not generate sufficient return in the EU to justify investment; and (iii) there exists no satisfactory method of diagnosis, prevention or treatment of such condition authorized for marketing in the EU, or if such a method exists, the product will be of significant benefit to those affected by the condition, as defined in Regulation (EC) 847/2000. Orphan medicinal products are eligible for financial incentives such as reduction of fees or fee waivers and are, upon grant of a marketing authorization, entitled to ten years of market exclusivity for the approved therapeutic indication. The application for orphan designation must be submitted before the application for marketing authorization. The applicant will receive a fee reduction for the marketing authorization application if the orphan designation has been granted, but not if the designation is still pending at the time the marketing authorization is submitted. Orphan designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

The ten-year market exclusivity in the EU may 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 designation, for example, if the product is sufficiently profitable not to justify maintenance of market exclusivity. Additionally, marketing authorization may be granted to a similar product for the same indication at any time if:

- the second applicant can establish that its product, although similar, is safer, more effective or otherwise clinically superior;
- the applicant consents to a second orphan medicinal product application; or
- the applicant cannot supply enough orphan medicinal product.

Other regulations – rest of the world

For other countries outside of the EU and the U.S., such as countries in Eastern Europe, Latin America or Asia, the requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from jurisdiction to jurisdiction. Additionally, the clinical trials must be conducted in accordance with cGCP requirements and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

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

Other healthcare laws

Manufacturing, sales, promotion and other activities following product approval are also subject to regulation by numerous regulatory authorities in the U.S. in addition to the FDA, including CMS, the HHS Office of Inspector General and HHS Office for Civil Rights, other divisions of the HHS and the Department of Justice.

Healthcare providers, physicians, and third-party payors will play a primary role in the recommendation and prescription of any products for which we obtain marketing approval. Our current and future arrangements with third-party payors, healthcare providers and physicians may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute any drugs for which we obtain marketing approval. In the U.S., these laws include, without limitation, state and federal anti-kickback, false claims, physician transparency, and patient data privacy and security laws and regulations, including but not limited to those described below.

The U.S. federal Anti-Kickback Statute, or AKS, prohibits, among other things, any person or entity from knowingly and willfully offering, paying, soliciting, receiving or providing any remuneration, directly or indirectly, overtly or covertly, to induce or in return for purchasing, leasing, ordering or arranging for or recommending the purchase, lease or order of any good, facility, item or service reimbursable, in whole or in part, under Medicare, Medicaid or other federal healthcare programs. The term “remuneration” has been broadly interpreted to include anything of value. The AKS has been interpreted to apply to arrangements between pharmaceutical and medical device manufacturers on the one hand and prescribers, purchasers, formulary managers and beneficiaries on the other hand. Although there are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution, the exceptions and safe harbors are drawn narrowly. Failure to meet all of the requirements of a particular applicable statutory exception or regulatory safe harbor does not make the conduct per se illegal under the AKS. Instead, the legality of the arrangement will be evaluated on a case-by-case basis based on a cumulative review of all its facts and circumstances. Several courts have interpreted the statute’s intent requirement to mean that if any one purpose of an arrangement involving remuneration is to induce referrals of federal healthcare covered business, the statute has been violated. In addition, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. Moreover, a claim including items or services resulting from a violation of the AKS constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act. On November 20, 2020, the Office of Inspector General, or OIG finalized further modifications to the AKS. Under the final rule, OIG added safe harbor

protections under the AKS for certain coordinated care and value-based arrangements among clinicians, providers, and others. The final rule (with some exceptions) became effective January 19, 2021. We continue to evaluate what effect, if any, this rule will have on our business.

Although we would not submit claims directly to payors, drug manufacturers can be held liable under the federal False Claims Act, which imposes civil penalties, including through civil whistleblower or qui tam actions, against individuals or entities (including manufacturers) for, among other things, knowingly presenting, or causing to be presented to federal programs (including Medicare and Medicaid) claims for items or services, including drugs, that are false or fraudulent, claims for items or services not provided as claimed, or claims for medically unnecessary items or services. The government may deem manufacturers to have "caused" the submission of false or fraudulent claims by, for example, providing inaccurate billing or coding information to customers or promoting a product off-label. Several biopharmaceutical, medical device and other healthcare companies have been prosecuted under federal false claims and civil monetary penalty laws for, among other things, allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. Other companies have been prosecuted for causing false claims to be submitted because of the companies' marketing of products for unapproved (e.g., or off-label), and thus non-covered, uses. In addition, the civil monetary penalties statute imposes penalties against any person who is determined to have presented or caused to be presented a claim to a federal health program that the person knows or should know is for an item or service that was not provided as claimed or is false or fraudulent.

Our future marketing and activities relating to the reporting of wholesaler or estimated retail prices for our products, if approved, the reporting of prices used to calculate Medicaid rebate information and other information affecting federal, state and third-party reimbursement for our products, and the sale and marketing of our product candidates, are subject to scrutiny under these laws.

The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, created additional federal criminal statutes that prohibit, among other actions, knowingly and willfully executing, or attempting to execute, a scheme to defraud or to obtain, by means of false or fraudulent pretenses, representations or promises, any money or property owned by, or under the control or custody of, any healthcare benefit program, including private third-party payors, knowingly and willfully embezzling or stealing from a healthcare benefit program, willfully obstructing a criminal investigation of a healthcare offense and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. Similar to the AKS, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation.

In addition, there has been a recent trend of increased federal and state regulation of payments made to physicians and certain other healthcare providers. The Affordable Care Act, or the ACA, imposed, among other things, new annual reporting requirements through the Physician Payments Sunshine Act for covered manufacturers for certain payments and "transfers of value" provided to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Effective January 1, 2022, these reporting obligations will extend to include transfers of value made to certain non-physician providers such as physician assistants and nurse practitioners. Failure to submit timely, accurately and completely the required information for all payments, transfers of value and ownership or investment interests may result in civil monetary penalties. Covered manufacturers must submit reports by the 90th day of each subsequent calendar year and the reported information is publicly made available on a searchable website.

We may also be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and their respective implementing regulations, including the Final HIPAA Omnibus Rule published on January 25, 2013, impose specified requirements relating to the privacy, security and transmission of individually identifiable health information held by covered entities and their business associates. Among other things, HITECH made HIPAA's security standards directly applicable to "business associates," defined as independent contractors or agents of covered entities that create, receive, maintain or transmit protected health information in connection with providing a service for or on behalf of a covered entity, although it is unclear that we would be considered a "business associate" in the normal course of our business. HITECH also increased the civil and criminal penalties that may be

imposed against covered entities, business associates and possibly other persons, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same requirements, thus complicating compliance efforts. See "European data collection" below for a discussion of data privacy and security enactments of the EU.

For example, California's Consumer Privacy Act, or CCPA, went into effect in January 2020, and the California Attorney General has since promulgated final regulations. The law provides broad rights to California consumers with respect to the collection and use of their personal information and imposes data protection obligations on certain businesses. While the CCPA does not apply to protected health information that is subject to HIPAA or personal information collected, used or disclosed in research, as defined by federal law, the CCPA may still affect our business activities. Moreover, on November 3, 2020, California voters passed the California Privacy Rights Act, or CPRA, under a ballot initiative. The CPRA amends the existing CCPA to include new consumer rights and additional data protection obligations. The new data protection requirements under the CPRA apply to information collected on or after January 1, 2022. With the promulgation of final regulations, the California State Attorney General has commenced enforcement actions against CCPA violators. The uncertainty surrounding the implementation of CCPA and the amendments under the CPRA exemplifies the vulnerability of our business to the evolving regulatory environment related to personal data and protected health information. The California law further expands the need for privacy and process enhancements and commitment of resources in support of compliance. Moreover, more than ten states have proposed bills in the last year with provisions similar to the CCPA and CPRA. It is likely that other states will pass laws similar to the CCPA and the CPRA in the near future and a federal data protection law may also be on the horizon.

Similar state and foreign fraud and abuse laws and regulations, such as state anti-kickback and false claims laws, may apply to sales or marketing arrangements and claims involving healthcare items or services. Such laws are generally broad and are enforced by various state agencies and private actions. Also, many states have similar fraud and abuse statutes or regulations that may be broader in scope and may apply regardless of payor, in addition to items and services reimbursed under Medicaid and other state programs. Some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant federal government compliance guidance, and require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers, marketing expenditures or drug pricing.

In order to distribute products commercially, we must comply with state laws that require the registration of manufacturers and wholesale distributors of drug and biological products in a state, including, in certain states, manufacturers and distributors who ship products into the state even if such manufacturers or distributors have no place of business within the state. Some states also impose requirements on manufacturers and distributors to establish the pedigree of product in the chain of distribution, including some states that require manufacturers and others to adopt new technology capable of tracking and tracing product as it moves through the distribution chain. Several states have enacted legislation requiring pharmaceutical and biotechnology companies to establish marketing compliance programs, file periodic reports with the state, make periodic public disclosures on sales, marketing, pricing, clinical trials and other activities, and/or register their sales representatives, as well as to prohibit pharmacies and other healthcare entities from providing certain physician prescribing data to pharmaceutical and biotechnology companies for use in sales and marketing, and to prohibit certain other sales and marketing practices. All of our activities are potentially subject to federal and state consumer protection and unfair competition laws.

The scope and enforcement of each of these laws is uncertain and subject to rapid change in the current environment of healthcare reform, especially in light of the lack of applicable precedent and regulations. Federal and state enforcement bodies have recently increased their scrutiny of interactions between healthcare companies and healthcare providers, which has led to a number of investigations, prosecutions, convictions and settlements in the healthcare industry. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, disgorgement, contractual damages, reputational harm, diminished profits and future earnings, imprisonment, exclusion of drugs from government

funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations, as well as additional reporting obligations and oversight if we become subject to a corporate integrity agreement or other agreement to resolve allegations of non-compliance with these laws, any of which could adversely affect our ability to operate our business and our financial results. If any of the physicians or other healthcare providers or entities with whom we expect to do business is found to be not in compliance with applicable laws, they may be subject to significant criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs. Ensuring business arrangements comply with applicable healthcare laws, as well as responding to possible investigations by government authorities, can be time- and resource consuming and can divert a company's attention from the business.

European data collection

The collection and use of personal health data in or arising from the EU are governed by the provisions of the Data Protection Directive, and the General Data Protection Regulation, or GDPR. This directive imposes several requirements relating to the consent of the individuals to whom the personal data relates, the information provided to the individuals, notification of data processing obligations to the competent national data protection authorities and the security and confidentiality of the personal data. The Data Protection Directive and GDPR also impose strict rules on the transfer of personal data out of the EU, to the U.S. Failure to comply with the requirements of the Data Protection Directive, the GDPR and the related national data protection laws of the EU Member States may result in fines and other administrative penalties. The GDPR introduces new data protection requirements in the EU and substantial fines for breaches of the data protection rules. The GDPR regulations may impose additional responsibility and liability in relation to personal data that we process, including in respect of clinical trials, and we may be required to put in place additional mechanisms ensuring compliance with the new data protection rules. This may be onerous and adversely affect our business, financial condition, results of operations and prospects.

Current and future legislation

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

The ACA, for example, contains provisions that subject biological products to potential competition by lower-cost biosimilars and may reduce the profitability of drug products through increased rebates for drugs reimbursed by Medicaid programs address 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, increase the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extends the rebate program to individuals enrolled in Medicaid managed care organizations, establish annual fees and taxes on manufacturers of certain branded prescription drugs, and create a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 70% (increased pursuant to the Bipartisan Budget Act of 2018, effective as of 2019) point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D.

Since its enactment, there have been numerous judicial, administrative, executive, and legislative challenges to certain aspects of the ACA, and we expect there will be additional challenges and amendments to the ACA in the future. For example, various portions of the ACA are currently undergoing legal and constitutional challenges in the U.S. Supreme Court, and the Trump Administration issued various Executive Orders which eliminated cost sharing subsidies and various provisions that would impose a fiscal burden on states or a cost, fee, tax, penalty or regulatory burden on individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. Additionally, Congress has introduced several pieces of legislation aimed at significantly revising or repealing the ACA. In December 2018, the CMS published a final rule permitting further collections and payments to and from certain ACA qualified health plans and health insurance issuers under the ACA risk adjustment program in response to the outcome of the federal district court litigation regarding the method CMS uses to determine this risk adjustment. Since then, the ACA

risk adjustment program payment parameters have been updated annually. It is unclear whether the ACA will be overturned, repealed, replaced, or further amended. We cannot predict what affect further changes to the ACA would have on our business, especially given the new Biden Administration.

Additionally, other federal health reform measures have been proposed and adopted in the U.S. since the ACA was enacted:

- The Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. These changes included aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which went into effect in April 2013 and, due to subsequent legislative amendments to the statute, including the BBA, will remain in effect through 2027, unless additional Congressional action is taken. However, pursuant to the Coronavirus Aid, Relief and Economic Security Act, or CARES Act, and subsequent legislation, these Medicare sequester reductions are suspended from May 1, 2020 through March 31, 2021 due to the COVID-19 pandemic. Proposed legislation, if passed, would extend this suspension until the end of the pandemic.

- The American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several providers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

Further, there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which have resulted in several recent Congressional inquiries and proposed and enacted bills designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for products. In addition, the U.S. government, state legislatures, and foreign governments have shown significant interest in implementing cost containment programs, including price-controls, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs to limit the growth of government paid healthcare costs. For example, the U.S. government has passed legislation requiring pharmaceutical manufacturers to provide rebates and discounts to certain entities and governmental payors to participate in federal healthcare programs. The Trump administration's budget proposal for fiscal year 2021 included a $135 billion allowance to support legislative proposals seeking to reduce drug prices, increase competition, lower out-of-pocket drug costs for patients, and increase patient access to lower-cost generic and biosimilar drugs. On March 10, 2020, the Trump administration sent "principles" for drug pricing to Congress, calling for legislation that would, among other things, cap Medicare Part D beneficiary out-of-pocket pharmacy expenses, provide an option to cap Medicare Part D beneficiary monthly out-of-pocket expenses, and place limits on pharmaceutical price increases. Further, the Trump administration also previously released a "Blueprint" to lower drug prices and reduce out-of-pocket costs of drugs that contains additional proposals to increase manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products and reduce the out-of-pocket costs of drug products paid by consumers. The Blueprint contains certain measures that HHS is already working to implement. For example, in May 2019, CMS issued a final rule to allow Medicare Advantage Plans the option of using step therapy for Part B drugs beginning January 1, 2020. This final rule codified CMS's policy change that was effective January 1, 2019. However, it is unclear whether the Biden administration will challenge, reverse, revoke or otherwise modify these executive and administrative actions after January 20, 2021.

Individual states in the U.S. have also increasingly passed legislation and implemented regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. Individual states in the U.S. have also been increasingly passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain

product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

Human Capital

We appreciate the importance of retention, growth, and development of our employees. We believe we offer competitive compensation (including salary, incentive bonus, and equity) and benefits packages. Further, we seek opportunities to cultivate talent throughout the Company. We are focused on understanding our diversity and inclusion strengths and opportunities and executing on a strategy to support further progress. We have created an Employee Resource Group that is aligned around dimensions of diversity, such as gender, ethnicity, sexual orientation, or other shared attributes, which we believe help build community and enable opportunities for development. We continue to focus on building a pipeline for talent to create more opportunities for workplace diversity and to support greater representation within the Company.

As of December 31, 2020, we had 78 full-time employees. Of these employees, 48 are engaged in product development and clinical activities. None of our employees are represented by a labor union or covered by a collective bargaining agreement.

Corporate history and information

We were originally formed in Delaware in August 2017 and until March 29, 2019, we conducted our business through SpringWorks Therapeutics, LLC, a Delaware limited liability company. Pursuant to the terms of a corporate reorganization and merger that was completed on March 29, 2019, or the Reorganization, all of the equity interests in SpringWorks Therapeutics, LLC were exchanged for the same number and class of newly issued securities of SpringWorks Therapeutics, Inc. and, as a result, SpringWorks Therapeutics, LLC became a wholly owned subsidiary of SpringWorks Therapeutics, Inc.

On September 17, 2019, we completed our initial public offering, or IPO, pursuant to which we issued and sold 10,350,000 shares of common stock, including the exercise in full by the underwriters of their option to purchase 1,350,000 additional shares of our common stock, at the public offering price of $18.00 per share, resulting in net proceeds of $169.7 million, after deducting underwriting discounts and commissions and other offering expenses. Upon the closing of the IPO, our outstanding convertible preferred stock automatically converted into shares of common stock.

On October 13, 2020, the Company completed the sale of 5,637,254 shares of common stock in an underwritten public offering, including 735,294 shares of common stock sold pursuant to the underwriter's full exercise of their option to purchase additional shares, at an offering price of $51.00 per share, resulting in net proceeds to the Company of $269.5 million.

We own various U.S. federal trademark applications and unregistered trademarks, including our company name and our logo. All other trademarks or trade names referred to in this Annual Report are the property of their respective owners. Solely for convenience, the trademarks and trade names in this prospectus supplement are referred to without the symbols ® and ™, but such references should not be construed as any indicator that their respective owners will not assert, to the fullest extent under applicable law, their rights thereto.

See Part II—Item 7—Management’s Discussion and Analysis of Financial Condition and Results of Operations and Note 1 to the consolidated financial statements included in Part II—Item 8 for more information about the above-mentioned transactions.

Our principal executive offices are located at 100 Washington Blvd, Stamford, CT 06902, and our phone number is (203) 883-9490. Our website address is http://www.springworkstx.com. The information contained in or accessible from our website is not incorporated into this Annual Report, and you should not consider it part of this Annual Report.

Available Information

Our Internet address is www.springworkstx.com. Our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K, including exhibits, proxy and information statements and amendments to those reports filed or furnished pursuant to Sections 13(a) and 15(d) of the Exchange Act are available through the "Investors" portion of our website free of charge as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. Information on our website is not part of this Annual Report on Form 10-K or any of our other securities filings unless specifically incorporated herein by reference. In addition, our filings with the SEC may be accessed through the SEC's Interactive Data Electronic Applications system at *http://www.sec.gov*. All statements made in any of our securities filings, including all forward-looking statements or information, are made as of the date of the document in which the statement is included, and we do not assume or undertake any obligation to update any of those statements or documents unless we are required to do so by law.

Item 1A. Risk Factors

Careful consideration should be given to the following risk factors, in addition to the other information set forth in this Annual Report on Form 10-K and in other documents that we file with the SEC, in evaluating the Company and our business. Investing in our common stock involves a high degree of risk. If any of the following risks and uncertainties actually occurs, our business, prospects, financial condition and results of operations could be materially and adversely affected. The risks described below are not intended to be exhaustive and are not the only risks facing the Company. New risk factors can emerge from time to time, and it is not possible to predict the impact that any factor or combination of factors may have on our business, prospects, financial condition and results of operations.

Summary of company specific material risk factors

We have included a summary of the material risks that we believe are specific to SpringWorks. The summary does not include all material risks associated with our business and is not a conclusive ranking or prioritization of our risk factors. Further, placement of certain of these risks in the summary section as opposed to others does not constitute guidance that the risk factors included in the summary are the only material risks to consider when considering an investment in our securities. We believe that all risk factors presented in this Annual Report on Form 10-K are important to an understanding of our company and should be given careful consideration. In addition, the summary of company specific material risks does not include the appropriate level of detail necessary to fully understand these risks, and the corresponding risk factors that follow provide essential detail and context necessary to fully understand and appreciate these principal risks associated with our business.

Risks related to our research and development

- *Our business is highly dependent on the success of our lead product candidates, nirogacestat and mirdametinib, as well as other product candidates we may develop. If we are unable to successfully complete clinical development of, obtain regulatory approval for or commercialize our product candidates, or if we experience delays in doing so, our business will be materially harmed.*
- *We were not involved in the early development of our lead product candidates or in the development of third-party agents used in combination with our product candidates; therefore, we are dependent on third parties having accurately generated, collected, interpreted and reported data from certain preclinical and clinical trials for our product candidates.*
- *If our clinical trials fail to replicate positive results from earlier preclinical studies or clinical trials conducted by us or third parties, we may be unable to successfully develop, obtain regulatory approval for or commercialize our product candidates.*
- *Interim "topline" and preliminary data from our clinical trials that we announce or publish from time to time may change as more data becomes available, are not necessarily predictive of the final results of the completed study or the results of other ongoing or future studies, and are subject to audit and verification procedures that could result in material changes in the final data.*
- *As an organization, we have never successfully completed any registrational clinical trials, and we may be unable to do so for any product candidates we may develop.*
- *We expect to develop nirogacestat and mirdametinib, and potentially future product candidates, in combination with other therapies, and safety or supply issues with combination use products may delay or prevent development and approval of such product candidates.*
- *If we encounter difficulties enrolling patients in any of our clinical trials, our clinical development activities could be delayed or otherwise adversely affected.*
- *The target patient populations of nirogacestat for the treatment of desmoid tumors and mirdametinib for the treatment of NF1-PN are small and have not been definitively determined, and if our estimates of the number of treatable patients is lower than expected, our potential revenues from sales of our product candidates, if approved, and our ability to achieve profitability would be compromised.*

Risks related to our reliance on third parties

- *We rely on third parties to conduct certain aspects of our preclinical studies and clinical trials. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or comply with regulatory requirements, we may not be able to obtain regulatory approval for, or commercialize, any potential product candidates.*
- *Because we rely on third-party manufacturing and supply partners, our supply of preclinical and clinical development materials may become limited or interrupted or may not be of satisfactory quantity or quality.*
- *We have not yet manufactured on a commercial scale and expect to rely on third parties to produce and process commercial quantities of our product candidates, if approved.*
- *We are dependent on a small number of suppliers for some of the materials used to manufacture our product candidates, and on one company for the manufacture of the active pharmaceutical ingredient for each of our product candidates.*
- *Our existing and future collaborations will be important to our business. If we are unable to maintain our existing collaborations or enter into new collaborations, or if these collaborations are not successful, our*

business could be adversely affected. In addition, our collaborators have broad discretion in many aspects of their performance of collaboration activities and they may take actions with which we do not agree.

Risks related to our intellectual property

- *We depend on intellectual property licensed from third parties, including from Pfizer for our lead product candidates, and termination of any of these licenses could result in the loss of significant rights, which would harm our business.*
- *If we fail to comply with our obligations under our patent licenses with third parties, we could lose license rights that are important to our business.*

Risks related to government regulation

- *We have been granted Orphan Drug Designation for nirogacestat and mirdametinib and may seek Orphan Drug Designation for other product candidates, but we may be unable to obtain or maintain such designation or the benefits associated with such designation, including the potential for market exclusivity, which may negatively impact our financial performance.*
- *A portion of our manufacturing of our lead product candidates takes place in China through third-party manufacturers. A significant disruption in the operation of those manufacturers, a trade war or political unrest in China could materially adversely affect our business, financial condition and results of operations.*

Risks related to managing our business and operations

- *We will need to grow the size of our organization, and we may experience difficulties in managing this growth.*
- *We have no history of commercializing marketed products. Building our commercialization capabilities will require a significant investment of time and money. There can be no assurance that we will successfully set up our commercialization capabilities.*
- *We do not have the internal research capabilities required to independently discover new product candidates, and we plan to execute our growth strategy by identifying and in-licensing or acquiring additional product candidates that have been discovered and initially developed by others. We may not be successful in executing our growth strategy or such growth strategy may not deliver the anticipated results.*
- *Our current operations are concentrated in two locations, and we or the third parties upon whom we depend may be adversely affected by earthquakes or other natural disasters and our business continuity and disaster recovery plans may not adequately protect us from a serious disaster.*

Risks related to our financial position and need for additional capital

- *We have incurred significant net losses since our inception and anticipate that we will continue to incur net losses in the future.*
- *We have a limited operating history, which may make it difficult to evaluate our prospects and likelihood of success.*
- *We will require additional capital to fund our operations and if we fail to obtain necessary capital, we will not be able to complete the development and commercialization of our product candidates.*
- *Raising additional capital may cause dilution to our existing stockholders, restrict our operations or require us to relinquish rights to our technologies or product candidates.*

Risks related to our common stock

- *We do not intend to pay dividends on our common stock so any returns will be limited to the value of our stock.*
- *Our principal stockholders and management own a significant percentage of our stock and will be able to exert significant control over matters subject to stockholder approval.*
- *Anti-takeover provisions under our charter documents and Delaware law could delay or prevent a change of control which could limit the market price of our common stock and may prevent or frustrate attempts by our stockholders to replace or remove our current management.*
- *Our bylaws designate certain specified courts as the sole and exclusive forums for certain disputes between us and our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.*

Company specific material risk factors

Risks related to our research and development

Our business is highly dependent on the success of our lead product candidates, nirogacestat and mirdametinib, as well as other product candidates we may develop. If we are unable to successfully complete clinical development of, obtain regulatory approval for or commercialize our product candidates, or if we experience delays in doing so, our business will be materially harmed.

To date, we have not yet completed any registrational clinical trials or the development of any product candidates. Our future success and ability to generate revenue from our product candidates, which we do not expect will occur for several years, if ever, is dependent on our ability to successfully develop, obtain regulatory approval for and commercialize one or more product candidates. In July 2020, we announced full enrollment in our potentially registrational Phase 3 clinical trial of nirogacestat and we announced the initiation of a potentially registrational Phase 2b clinical trial of mirdametinib in October 2019. If either of our lead product candidates encounter safety or efficacy problems, development delays or regulatory issues or other problems, including as a result of the COVID-19 pandemic, our development plans and business would be significantly harmed.

All of our other product candidates are in earlier stages of development and will require substantial additional investment for preclinical development, clinical development, regulatory review and approval in one or more jurisdictions.

We may not have the financial resources to continue development of, or to modify existing or enter into new collaborations for, a product candidate if we experience any issues that delay or prevent regulatory approval of, or our ability to commercialize, our product candidates, including:

- our inability to demonstrate to the satisfaction of the FDA or comparable foreign regulatory authorities that our product candidates are safe and effective;
- insufficiency of our financial and other resources to complete the necessary preclinical studies and clinical trials;
- negative or inconclusive results from our preclinical studies, clinical trials or the clinical trials of others for product candidates similar to ours, leading to a decision or requirement to conduct additional preclinical studies or clinical trials or abandon a program;
- product-related adverse events experienced by subjects in our clinical trials or by individuals using drugs or therapeutic biologics similar to our product candidates;
- delays in submitting an IND or comparable foreign applications, or delays or failure in obtaining the necessary approvals from regulators to commence a clinical trial or a suspension or termination of a clinical trial once commenced;
- conditions imposed by the FDA, EMA or comparable foreign regulatory authorities regarding the scope or design of our clinical trials;
- poor effectiveness of our product candidates during clinical trials;
- better than expected performance of control arms, such as placebo groups, which could lead to negative or inconclusive results from our clinical trials;
- delays in enrolling subjects in clinical trials;
- high drop-out rates of subjects from clinical trials;
- inadequate supply or quality of product candidates or other materials necessary for the conduct of our clinical trials;
- greater than anticipated clinical trial or manufacturing costs;
- unfavorable FDA, EMA or comparable regulatory authority inspection and review of a clinical trial site;
- failure of our third-party contractors or investigators to comply with regulatory requirements or otherwise meet their contractual obligations in a timely manner, or at all;
- delays and changes in regulatory requirements, policy and guidelines, including the imposition of additional regulatory oversight around clinical testing generally or with respect to our therapies in particular; or
- varying interpretations of data by the FDA, EMA and comparable foreign regulatory authorities.

We were not involved in the early development of our lead product candidates or in the development of third-party agents used in combination with our product candidates; therefore, we are dependent on third parties having accurately generated, collected, interpreted and reported data from certain preclinical and clinical trials for our product candidates.

We had no involvement with or control over the initial preclinical and clinical development of any of our lead product candidates or third-party agents used in combination with our product candidates. We are dependent on third parties having conducted their research and development in accordance with the applicable protocols and legal, regulatory and scientific standards; having accurately reported the results of all preclinical studies and clinical trials conducted with respect to such product candidates; and having correctly collected and interpreted the data from these trials. If these activities were not compliant, accurate or correct, the clinical development, regulatory approval or commercialization of our product candidates will be adversely affected.

If our clinical trials fail to replicate positive results from earlier preclinical studies or clinical trials conducted by us or third parties, we may be unable to successfully develop, obtain regulatory approval for or commercialize our product candidates.

Our preclinical studies or early clinical trials of our product candidates, whether conducted by us or third parties, may not necessarily be predictive of the results of later clinical trials that we conduct. Similarly, even if we are able to complete our planned clinical trials of our product candidates, positive results from such clinical trials may not be replicated in our subsequent preclinical studies or clinical trials.

Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials after achieving positive results in early-stage development, and we cannot be certain that we will not face similar setbacks. These setbacks have been caused by, among other things, preclinical findings made while clinical trials were underway or safety or efficacy observations made in preclinical studies and clinical trials, including previously unreported adverse events. For example, we are conducting non-clinical and clinical absorption, distribution, metabolism and excretion, or ADME, studies for mirdametinib, and we cannot predict whether findings from these ADME studies will adversely affect our development plans for our product candidates. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses and many companies that believed their product candidates performed satisfactorily in preclinical studies and clinical trials nonetheless failed to obtain FDA, EMA or comparable foreign regulatory authority approval. Furthermore, the approval policies or regulations of the FDA, EMA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval, which may lead to the FDA, EMA or comparable foreign regulatory authorities delaying, limiting or denying approval of our product candidates.

Interim "topline" and preliminary data from our clinical trials that we announce or publish from time to time may change as more data becomes available, are not necessarily predictive of the final results of the completed study or the results of other ongoing or future studies, and are subject to audit and verification procedures that could result in material changes in the final data.

From time to time, we may publicly disclose interim topline or preliminary data from our clinical trials, such as the interim data update from adult patients in the ReNeu trial, our Phase 2b clinical trial of mirdametinib, announced in February 2021. These interim updates are based on a preliminary analysis of then-available data, and the data and related findings and conclusions are subject to change following a more comprehensive review of the data related to the particular study or trial. We also make assumptions, estimations, calculations and conclusions as part of our analyses of data, and we may not have received or had the opportunity to fully and carefully evaluate all data. As a result, any topline results that we report may differ from future results of the same studies, or different conclusions or considerations may qualify such results, once additional data have been received and fully evaluated. For example, our interim data from the ReNeu trial reflected results from the first adult patients enrolled in the trial, but we have not yet reported final data from this trial across all patients, and those results may materially differ from our data in adults. Interim topline or preliminary data also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data we previously published. As a result, interim topline or preliminary data should be viewed with caution until the final data are available. In addition, we may report interim

analyses of only certain endpoints rather than all endpoints. Interim data from clinical trials that we may complete 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. As a result, interim data may not be predictive of the final results of the same study or the results of ongoing or future studies. Differences between preliminary or interim data and final data could significantly harm our business prospects and may cause the trading price of our common stock to fluctuate significantly.

Furthermore, others, including regulatory agencies, may not accept or agree with our assumptions, estimates, calculations, conclusions or analyses or may interpret or weigh the importance of data differently, which could impact the value of the particular program, the approvability or commercialization of the particular product candidate or product and our company in general. In addition, the information we choose to publicly disclose regarding a particular study or clinical trial is typically selected from a more extensive amount of available information. You or others may not agree with what we determine is the material or otherwise appropriate information to include in our disclosure, and any information we determine not to disclose may ultimately be deemed significant with respect to future decisions, conclusions, views, activities or otherwise regarding a particular product, product candidate or our business. If the interim topline or preliminary data that we report differ from late, final or actual results, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for, and commercialize, the product candidate being studied or any of our other product candidates may be harmed, which could harm our business, financial condition, results of operations and prospects.

As an organization, we have never successfully completed any registrational clinical trials, and we may be unable to do so for any product candidates we may develop.

We will need to successfully complete registrational clinical trials in order to obtain the approval of the FDA, EMA or comparable foreign regulatory authorities to market any product candidates. Carrying out clinical trials, including later-stage registrational clinical trials, is a complicated process. As an organization, we have not previously completed any registrational clinical trials. In order to do so, we will need to build and expand our clinical development and regulatory capabilities, and we may be unable to recruit and train qualified personnel. We also expect to continue to rely on third parties to conduct our clinical trials. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or comply with regulatory requirements, we may not be able to obtain regulatory approval of or commercialize any potential product candidates. Consequently, we may be unable to successfully and efficiently execute and complete necessary clinical trials in a way that leads to NDA submission and approval of our product candidates. We may require more time and incur greater costs than our competitors and may not succeed in obtaining regulatory approval of any product candidates that we develop. Failure to commence or complete, or delays in, our planned clinical trials, could prevent us from or delay us in commercializing our product candidates.

We expect to develop nirogacestat and mirdametinib, and potentially future product candidates, in combination with other therapies, and safety or supply issues with combination use products may delay or prevent development and approval of such product candidates.

We intend to develop nirogacestat and mirdametinib, and likely other future product candidates, in combination with one or more other approved or unapproved rational therapies to treat cancer or other diseases. For example, we are currently evaluating mirdametinib in combination with lifirafenib, BeiGene’s RAF dimer inhibitor, and nirogacestat in combination with five BCMA-directed therapies across modalities through our collaborations with industry leaders developing such therapies.

Even if any product candidate we develop were to receive marketing approval or be commercialized for use in combination with other existing therapies, we would continue to be subject to the risks that the FDA, EMA or comparable foreign regulatory authorities outside of the U.S. could revoke approval of the therapy used in combination with our product or that safety, efficacy, manufacturing or supply issues could arise with any of those existing therapies. If the therapies we use in combination with our product candidates are replaced as the standard of care for the indications we choose for any of our product candidates, the FDA, EMA or comparable foreign regulatory authorities may require us to conduct additional clinical trials. The occurrence of any of these risks could result in our own products, if approved, being removed from the market or being less successful commercially.

We also may choose to evaluate nirogacestat, mirdametinib or any other future product candidates in combination with one or more cancer therapies that have not yet been approved for marketing by the FDA, EMA or comparable foreign regulatory authorities. We will not be able to market and sell nirogacestat, mirdametinib or any product candidate we develop in combination with an unapproved cancer therapy for a combination indication if that unapproved cancer therapy does not ultimately obtain marketing approval either alone or in combination with our product. In addition, unapproved cancer therapies face the same risks described with respect to our product candidates currently in development and clinical trials, including the potential for serious adverse effects, delay in their clinical trials and lack of FDA approval.

If the FDA, EMA or comparable foreign regulatory authorities do not approve these other drugs or revoke their approval of, or if safety, efficacy, quality, manufacturing or supply issues arise with, the drugs we choose to evaluate in combination with our product candidate we develop, we may be unable to obtain approval of or market such combination therapy.

If we encounter difficulties enrolling patients in any of our clinical trials, our clinical development activities could be delayed or otherwise adversely affected.

The timely completion of clinical trials in accordance with their protocols depends, among other things, on our ability to enroll a sufficient number of patients who remain in the trial until its conclusion. We may experience difficulties in patient enrollment in our clinical trials for a variety of reasons, including:

- the patient eligibility and exclusion criteria defined in the protocol;
- the size of the patient population required for analysis of the clinical trial's primary endpoints;
- delays in our research programs or clinical supply chain resulting from factors related to the COVID-19 pandemic;
- the proximity of patients to clinical trial sites;
- the design of the clinical trial;
- our ability to recruit clinical trial investigators with the appropriate competencies and experience, and the ability of these investigators to identify and enroll suitable patients;
- perception of the safety profile of our product candidates;
- our ability to obtain and maintain patient consents; and
- the risk that patients enrolled in clinical trials will drop out of the trials before completion.

For example, we are developing nirogacestat for the treatment of desmoid tumors and mirdametinib for the treatment of NF1-PN, both of which are rare diseases with small patient populations. As a result, although we have completed enrollment in our DeFi trial, we may encounter difficulties enrolling subjects in our clinical trials for these product candidates due, in part, to the small size of these patient populations. In addition, our clinical trials will compete with other clinical trials for product candidates that are in the same therapeutic areas as our product candidates, and this competition will reduce the number and types of patients available to us, because some patients who might have opted to enroll in our trials may instead opt to enroll in a clinical trial being conducted by one of our competitors. Since the number of qualified clinical investigators is limited, we expect to conduct some of our clinical trials at the same clinical trial sites that some of our competitors use, which will reduce the number of patients who are available for our clinical trials in such clinical trial site. In addition, in the case of mirdametinib, we may face difficulty with enrollment due to physician or patient perception of an adverse tolerability profile.

Delays in patient enrollment may result in increased costs or may affect the timing or outcome of our clinical trials, which could prevent completion of these trials and adversely affect our ability to advance the development of our product candidates.

The target patient populations of nirogacestat for the treatment of desmoid tumors and mirdametinib for the treatment of NF1-PN are small and have not been definitively determined, and if our estimates of the number of treatable patients is lower than expected, our potential revenues from sales of our product candidates, if approved, and our ability to achieve profitability would be compromised.

Our estimates of both the number of patients who have the diseases we are targeting, as well as the subset of patients with these diseases in a position to receive our product candidates, if approved, are based on our beliefs and estimates, and these estimates may prove to be incorrect. These estimates have been derived from a variety of sources, including scientific literature, input from physicians that treat patients with the diseases we are targeting, patient foundations and secondary market research databases. Further, new studies may change the estimated incidence or prevalence of these diseases, and any regulatory approvals that we may receive for a product candidate may include limitations for use or contraindications that decrease the addressable patient population. Accordingly, the target patient populations may turn out to be lower than expected, in which case the potential revenues from sales of our product candidates, if approved, would be lower than expected.

Risks related to our reliance on third parties

We rely on third parties to conduct certain aspects of our preclinical studies and clinical trials. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or comply with regulatory requirements, we may not be able to obtain regulatory approval for, or commercialize, any potential product candidates.

We depend upon third parties to conduct certain aspects of our preclinical studies and depend on third parties, including independent investigators, to conduct our clinical trials, under agreements with universities, medical institutions, contract research organizations, or CROs, strategic partners and others. We expect to negotiate budgets and contracts with such third parties, which may result in delays to our development timelines and increased costs.

We commenced operations in August 2017 and we continue to build our infrastructure and hire personnel necessary to execute our operational plans. We will rely especially heavily on third parties over the course of our clinical trials, and, as a result, may have limited control over the clinical investigators and limited visibility into their day-to-day activities, including with respect to their compliance with the approved clinical protocol. Nevertheless, we are responsible for ensuring that each of our clinical trials is conducted in accordance with the applicable protocol, legal and regulatory requirements and scientific standards, and our reliance on third parties does not relieve us of our regulatory responsibilities. We and these third parties are required to comply with GCP requirements, which are regulations and guidelines enforced by the FDA and comparable foreign regulatory authorities for product candidates in clinical development. Regulatory authorities enforce these GCP requirements through periodic inspections of clinical trial sponsors, clinical investigators and clinical trial sites. If we or any of these third parties fail to comply with applicable GCP requirements, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or comparable foreign regulatory authorities may require us to suspend or terminate these trials or perform additional preclinical studies or clinical trials before approving our marketing applications. We cannot be certain that, upon inspection, such regulatory authorities will determine that any of our clinical trials comply with GCP requirements. In addition, our clinical trials must be conducted with product produced under cGMP requirements and may require a large number of patients.

Our failure or any failure by these third parties to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process. Moreover, our business may be adversely affected if any of these third parties violates federal or state fraud and abuse or false claims laws and regulations or healthcare privacy and security laws.

Any third parties conducting aspects of our preclinical studies or our clinical trials will not be our employees and, except for remedies that may be available to us under our agreements with such third parties, we cannot control whether or not they devote sufficient time and resources to our preclinical studies and clinical programs. These third parties may also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical trials or other product development activities, which could affect their performance on our behalf. If these third

parties do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the preclinical or clinical data they obtain is compromised due to the failure to adhere to our protocols or regulatory requirements or for other reasons, our development timelines, including clinical development timelines, may be extended, delayed or terminated and we may not be able to complete development of, obtain regulatory approval of or successfully commercialize our product candidates. As a result, our financial results and the commercial prospects for our product candidates would be harmed, our costs could increase and our ability to generate revenue could be delayed or precluded entirely.

If any of our relationships with these third-party CROs or others terminate, we may not be able to enter into arrangements with alternative CROs or other third parties or to do so on commercially reasonable terms.

Switching or adding additional CROs involves additional cost and requires management's time and focus. In addition, there is a natural transition period when a new CRO begins work. As a result, delays may occur, which can materially impact our ability to meet our desired development timelines. The COVID-19 global pandemic and government measures taken in response have also had a significant impact on our CROs, and we expect that they will face further disruption which may affect our ability to initiate and complete our pre-clinical studies and clinical trials. Though we carefully manage our relationships with our CROs, investigators and other third parties, there can be no assurance that we will not encounter challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, financial condition and prospects.

Because we rely on third-party manufacturing and supply partners, our supply of preclinical and clinical development materials may become limited or interrupted or may not be of satisfactory quantity or quality.

We rely on third-party contract manufacturers to manufacture all of our preclinical and clinical trial product supplies. We do not own manufacturing facilities for producing any product supplies. There can be no assurance that our preclinical and clinical development product supplies will not be limited, interrupted, of satisfactory quality or continue to be available at acceptable prices. In particular, any replacement of our manufacturers could require significant effort and expertise because there may be a limited number of qualified replacements.

The manufacturing process for a product candidate is subject to FDA, EMA and comparable foreign regulatory authority review. Suppliers and manufacturers must meet applicable manufacturing requirements and undergo rigorous facility and process validation tests required by regulatory authorities in order to comply with regulatory standards, such as cGMPs. In the event that any of our manufacturers fails to comply with such requirements or to perform its obligations to us in relation to quality, timing or otherwise, or if our supply of components or other materials becomes limited or interrupted for other reasons, we may be forced to manufacture the materials ourselves, for which we currently do not have the capabilities or resources, or enter into an agreement with another third party, which we may not be able to do on reasonable terms, if at all. In either scenario, our clinical trials supply could be delayed significantly as we establish alternative supply sources. In some cases, the technical skills or technology required to manufacture our product candidates may be unique or proprietary to the original manufacturer and we may have difficulty, or there may be contractual restrictions prohibiting us from, transferring such skills or technology to another third party and a feasible alternative may not exist. These factors would increase our reliance on such manufacturer or require us to obtain a license from such manufacturer in order to have another third party manufacture our product candidates. If we are required to change manufacturers for any reason, we will be required to verify that the new manufacturer maintains facilities and procedures that comply with quality standards and with all applicable regulations and guidelines. The delays associated with the verification of a new manufacturer could negatively affect our ability to develop product candidates in a timely manner or within budget. Furthermore, a manufacturer may possess technology related to the manufacture of our product candidate that such manufacturer owns independently. This would increase our reliance on such manufacturer or require us to obtain a license from such manufacturer in order to have another manufacturer manufacture our product candidates. In addition, changes in manufacturers often involve changes in manufacturing procedures and processes, which could require that we conduct bridging studies between our prior clinical supply and that of any new manufacturer. We may be unsuccessful in demonstrating the comparability of clinical supplies which could require the conduct of additional clinical trials.

Our or a third party's failure to execute on our manufacturing requirements and comply with cGMP could adversely affect our business in a number of ways, including:

- an inability to initiate or continue clinical trials of product candidates under development;
- delay in submitting regulatory applications, or receiving regulatory approvals, for product candidates;
- loss of the cooperation of an existing or future collaborator;
- subjecting third-party manufacturing facilities to additional inspections by regulatory authorities;
- requirements to cease distribution or to recall batches of our product candidates; and
- in the event of approval to market and commercialize a product candidate, an inability to meet commercial demands for our products.

In addition, we contract with packaging providers with the appropriate expertise, facilities and scale to meet our needs. Failure to maintain cGMP can result in a contractor receiving FDA sanctions, which can impact our ability to operate or lead to delays in any clinical development programs. We believe that our current packaging contractors operate in accordance with cGMP, but we can give no assurance that FDA, EMA or comparable foreign regulatory authorities will not conclude that a lack of compliance exists. In addition, any delay in contracting for packaging services, or failure of the contract manufacturer to perform the services as needed, may delay any clinical trials, registration and launches, which could negatively affect our business. The extent to which the COVID-19 pandemic impacts our ability to procure our preclinical and clinical trial product supplies will depend on the severity and duration of the spread of the virus, and the actions undertaken to contain COVID-19 or treat its effects and may cause delays. If our current third-party contract manufacturers cannot perform as agreed, we may be required to replace such manufacturers and we may be unable to replace them on a timely basis or at all. Our current and anticipated future dependence upon others for the manufacture of our product candidates or products may adversely affect our future profit margins and our ability to commercialize any products that receive marketing approval on a timely and competitive basis.

Our product candidates and any drugs that we may develop may compete with other product candidates and drugs for access to manufacturing facilities. There are no assurances we would be able to enter into similar commercial arrangements with other 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 have not yet manufactured on a commercial scale and expect to rely on third parties to produce and process commercial quantities of our product candidates, if approved.

We expect to continue to rely on third-party manufacturers if we receive regulatory approval for our product candidates. We have not yet entered into any arrangement with a third party for the manufacture and supply of commercial quantities of our product candidates. To the extent that we enter into future manufacturing arrangements with third parties for commercial supply of our product candidates, if approved, we will depend on these third parties to perform their obligations in a timely manner consistent with contractual and regulatory requirements, including those related to quality control and assurance.

The facilities used by our contract manufacturers to manufacture our product candidates must be approved by the FDA, EMA or comparable foreign regulatory authorities following inspections that will be conducted after we submit an application to the FDA, EMA or comparable foreign regulatory authorities. We do not directly control the manufacturing process of, and will be completely dependent on, our contract manufacturing partners for compliance with cGMP requirements for the manufacture of our product candidates. If our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA, EMA or comparable foreign regulatory authorities, they will not be able to secure and/or maintain regulatory approval for their manufacturing facilities. In addition, we have no direct control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel. If the FDA, EMA or a comparable foreign regulatory authority does not approve these facilities for the manufacture of our product candidates or if it withdraws any approval in the future, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for or market our product candidates, if approved.

We are dependent on a small number of suppliers for some of the materials used to manufacture our product candidates, and on one company for the manufacture of the active pharmaceutical ingredient for each of our product candidates.

We currently depend on a small number of suppliers for some of the materials used in, and processes required to develop, our product candidates. We cannot ensure that these suppliers or service providers will remain in business or have sufficient capacity or supply to meet our needs, or that they will not be purchased by one of our competitors or another company that is not interested in continuing to work with us. Our use of a small number of suppliers exposes us to several risks, including disruptions in supply, price increases or late deliveries. There are, in general, relatively few alternative sources of supply for substitute materials. Our current vendors may be unable or unwilling to meet our future demands for our clinical trials or commercial sale. Finding suitable replacement suppliers, materials and processes could take a substantial amount of time and it may be difficult to establish replacement suppliers who meet regulatory requirements. Any disruption or delay in supply could compromise our ability to pursue development and eventual commercialization of our product candidates.

Our existing and future collaborations will be important to our business. If we are unable to maintain our existing collaborations or enter into new collaborations, or if these collaborations are not successful, our business could be adversely affected. In addition, our collaborators have broad discretion in many aspects of their performance of collaboration activities and they may take actions with which we do not agree.

An important part of our strategy is to evaluate and, as deemed appropriate, extend our current or enter into additional partnerships in the future, including potentially with major biopharmaceutical companies. We have limited capabilities for product development and do not yet have any capability for commercialization. Accordingly, we have entered into collaborations with other companies to provide us with important technologies in order to more fully develop our product candidates and we may enter into collaborations with other companies to provide us with important technologies or funding for our programs.

Any current or future collaborations we may extend or enter into may pose a number of risks, including the following:

- collaborators have significant discretion in determining the efforts and resources that they will apply;
- collaborators may not perform their obligations as expected;
- collaborators may not pursue development and commercialization of any product candidates that achieve regulatory approval or may elect not to continue or renew development or commercialization programs or license arrangements based on clinical trial results, changes in the collaborators' strategic focus or available funding, or external factors, such as a strategic transaction that may divert resources or create 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, products that compete directly or indirectly with our products and product candidates if the collaborators believe that the competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- for collaborations involving combination therapies that have not yet been tested together, treatment emergent adverse events may be unforeseen and may negatively impact the monotherapy development of our product candidates;
- product candidates discovered in collaboration with us may be viewed by our collaborators as competitive with their own product candidates or products, which may cause collaborators to cease to devote resources to the commercialization of our product candidates;
- collaborators may fail to comply with applicable regulatory requirements regarding the development, manufacture, distribution or marketing of a product candidate or product;

- collaborators with marketing and distribution rights to one or more of our product candidates that achieve regulatory approval may not commit sufficient resources to the marketing and distribution of such product or products;
- disagreements with collaborators, including disagreements over proprietary rights, contract interpretation or the preferred course of development, might cause delays or terminations 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 maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;
- collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability; and
- collaborations may be terminated by the collaborator, and, if terminated, we could lose license rights to the applicable product candidates or could be required to raise additional capital to pursue further development or commercialization of the applicable product candidates.

Under our collaboration agreement with BeiGene, the combination of mirdametinib and lifirafenib is being evaluated in a Phase 1b/2 clinical trial. Additionally, under our five collaboration agreements with industry leading BCMA therapy developers, the combination of nirogacestat and the BCMA therapy of each such developer is being evaluated in relapsed or refractory multiple myeloma patients. Under these existing collaboration arrangements, upon completion of the relevant clinical trials, we and our collaboration partner will have the opportunity to negotiate in good faith to provide for the expansion of the respective clinical collaboration and the potential establishment of a commercial relationship. However, our partners have no obligation to continue development of the combination products, regardless of the applicable clinical trial results. We also jointly formed MapKure with BeiGene for the development of BGB-3245, and although we contribute to clinical development and other operational activities, and have representation on MapKure's Board Of Directors and Joint Steering Committee, we do not control the development process. MapKure may pursue a development plan that differs from our expectations, which may or may not be successful.

If our collaborations do not result in the successful discovery, development and commercialization of product candidates or if one of our collaborators elects not to enter into collaboration agreements to pursue future development, we may not receive any future funding or milestone or royalty payments under such collaborations. Risks relating to product development, regulatory approval and commercialization described in this report may also apply to the activities of our collaborators.

Additionally, if one of our collaborators terminates its agreement with us, we may find it more difficult to attract new collaborators and our perception in the business and financial communities could be adversely affected. Furthermore, we face significant competition in seeking appropriate partners for our product candidates and the negotiation process is time-consuming and complex. In order for us to successfully partner our product candidates, potential partners must view our product candidates as economically valuable in markets they determine to be attractive in light of the terms that we are seeking and other available products for licensing by other companies. In addition, there have been a significant number of recent business combinations among large biopharmaceutical companies that have resulted in a reduced number of potential future collaborators. Our ability to reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. If we are unable to reach agreements with suitable collaborators on a timely basis, on acceptable terms, or at all, we may have to curtail the development of a product candidate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities or planning, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to increase our expenditures to fund development or commercialization activities on our own, we may need to obtain additional expertise or capital, which may not be available to us on acceptable terms, or at all. If we fail to enter into collaborations or do not have sufficient funds or expertise to undertake the necessary development and commercialization activities, we may not be able to further develop our product candidates, bring them to market and generate revenue from sales of drugs or continue to develop our technology, and our business may be materially and

adversely affected. Even if we are successful in our efforts to establish new strategic partnerships, the terms that we agree upon may not be favorable to us, and we may not be able to maintain such strategic partnerships if, for example, development or approval of a product candidate is delayed or sales of an approved product are disappointing. Any delay in entering into new strategic partnership agreements related to our product candidates could delay the development and commercialization of our product candidates and reduce their competitiveness even if they reach the market.

Risks related to our intellectual property

We depend on intellectual property licensed from third parties, including from Pfizer for our lead product candidates, and termination of any of these licenses could result in the loss of significant rights, which would harm our business.

We are dependent on patents, know-how and proprietary technology, both our own and licensed from others. All patents covering nirogacestat and mirdametinib and any combination therapies using our product candidates are licensed from third parties. Any termination of a product license could result in the loss of significant rights and would cause material adverse harm to our ability to commercialize our product candidates.

Disputes may also arise between us and our licensors regarding intellectual property subject to a license agreement, including:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- whether and the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement;
- our right to sublicense patent and other rights to third parties under collaborative development relationships;
- our diligence obligations with respect to the use of licensed technology in relation to our development and commercialization of our product candidates and what activities satisfy those diligence obligations; and
- the ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and our partners.

If disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates.

We are generally also subject to all of the same risks with respect to protection of intellectual property that we own, as we are for intellectual property that we license, which are described below. If we or our licensors fail to adequately protect this intellectual property, our ability to commercialize products could materially suffer.

If we fail to comply with our obligations under our patent licenses with third parties, we could lose license rights that are important to our business.

We are a party to license agreements pursuant to which we in-license key patents for our product candidates. At the time we began our operations in August 2017, we entered into four license agreements with Pfizer, including a license agreement for each of our lead product candidates, nirogacestat and mirdametinib, both of which agreements were amended and restated in 2019. Each of our existing licenses imposes various diligence, milestone payment, royalty, insurance and other obligations on us. If we fail to comply with these obligations, our licensors may have the right to terminate the license, in which event we would not be able to develop or market the products covered by such licensed intellectual property. While we assigned the Pfizer license agreement covering our FAAH inhibitor program in connection with the sale of that program to Jazz in October 2020, there can be no assurance that Jazz will comply with the terms of such license, which could result in its termination and our inability to recover that asset as a remedy for a potential material breach of Jazz's obligations to us in connection with such sale.

We may have limited control over the maintenance and prosecution of these in-licensed rights, activities or any other intellectual property that may be related to our in-licensed intellectual property. For example, we cannot be certain that such activities by these licensors have been or will be conducted in compliance with applicable laws and regulations or

will result in valid and enforceable patents and other intellectual property rights. We have limited control over the manner in which our licensors initiate an infringement proceeding against a third-party infringer of the intellectual property rights, or defend certain of the intellectual property that is licensed to us. It is possible that the licensors' infringement proceeding or defense activities may be less vigorous than had we conducted them ourselves.

Risks related to government regulation

We have been granted Orphan Drug Designation for nirogacestat and mirdametinib and may seek Orphan Drug Designation for other product candidates, but we may be unable to obtain or maintain such designation or the benefits associated with such designation, including the potential for market exclusivity, which may negatively impact our financial performance.

Regulatory authorities in some jurisdictions, including the U.S. and Europe, may designate drugs and therapeutic biologics for relatively small patient populations as orphan drugs. Under the Orphan Drug Act, the FDA may designate a drug or therapeutic biologic as an orphan drug if it is a drug or therapeutic biologic 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 U.S., or a patient population greater than 200,000 in the U.S. where there is no reasonable expectation that the cost of developing the drug or therapeutic biologic will be recovered from sales in the U.S. In the U.S., Orphan Drug Designation entitles a party to financial incentives such as opportunities for grant funding toward clinical trial costs, tax advantages and user-fee waivers. Such a designation, however, may be revoked by the FDA in certain circumstances, such as if the agency finds that the applicant's request for designation request omitted material information required under the Orphan Drug Act and its implementing regulations. If a product that has Orphan Drug Designation subsequently receives the first FDA approval for the disease for which it has such designation, the product is entitled to orphan drug exclusivity, which means that the FDA may not approve any other applications, including a full NDA or BLA, to market the same product for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity or where the manufacturer is unable to assure sufficient product quantity.

In June 2018, the FDA granted Orphan Drug Designation to nirogacestat for the treatment of desmoid tumors and in September 2019, the European Commission granted nirogacestat Orphan Drug Designation for the treatment of soft tissue sarcoma. In October 2018, the FDA granted Orphan Drug Designation to mirdametinib for the treatment of NF1 and in July 2019 the European Commission granted mirdametinib Orphan Drug Designation for the treatment of NF1. We may seek Orphan Drug Designations for nirogacestat and mirdametinib for other indications or for our other product candidates. There can be no assurances that we will be able to obtain such designations.

Even if we obtain Orphan Drug Designation for any of our future product candidates in specific indications, we may not be the first to obtain marketing approval of nirogacestat, mirdametinib or any other such product candidates for the orphan-designated indication due to the uncertainties associated with developing pharmaceutical products. In addition, exclusive marketing rights in the U.S. 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 the manufacturer is unable to assure sufficient quantities of the product to meet the needs of patients with the rare disease or condition.

Further, even if we obtain orphan drug exclusivity in the U.S. for a product, that exclusivity may not effectively protect the product from competition because different drugs or therapeutic biologics with different active moieties can be approved for the same condition. Even after an orphan product is approved, the FDA can subsequently approve the same drug or therapeutic biologic with the same active moiety for the same condition if the FDA concludes that the later drug or therapeutic biologic is safer, more effective or makes a major contribution to patient care. In Europe, we could be prevented from marketing our products if a similar medicinal product is granted Orphan Drug Designation for the same indications that we are pursuing. Once authorized, with a limited number of exceptions, neither the competent authorities of the EU member states, the EMA or the European Commission are permitted to accept applications or grant marketing authorization for other similar medicinal products with the same therapeutic indication. Marketing authorization could also be granted to a similar medicinal product with the same orphan indication if the latter product is safer, more effective or otherwise clinically superior to the original orphan medicinal product.

A U.S. composition of matter patent covering the chemical structure of nirogacestat expires in 2025 and a U.S. composition of matter patent that covers the polymorphic form of nirogacestat that is currently in clinical development expires in 2039. A U.S. composition of matter patent covering the chemical structure of mirdametinib expires in 2021. Notwithstanding expected patent life, if orphan drug exclusivity does not protect these products from competition, our business and financial condition could be materially adversely affected. Orphan Drug Designation neither shortens the development time or regulatory review time of a drug or therapeutic biologic nor gives the drug or therapeutic biologic any advantage in the regulatory review or approval process. In addition, while we may seek Orphan Drug Designation for our future product candidates, we may never receive such designations.

A portion of our manufacturing of our lead product candidates takes place in China through third-party manufacturers. A significant disruption in the operation of those manufacturers, a trade war or political unrest in China could materially adversely affect our business, financial condition and results of operations.

We currently contract manufacturing operations to third parties, and clinical quantities of our lead product candidates are manufactured by these third parties outside the U.S., including in China, and we expect to continue to use such third-party manufacturers for such product candidates. Any disruption in production or inability of our manufacturers in China to produce adequate quantities to meet our needs, whether as a result of a natural disaster or other causes, could impair our ability to operate our business on a day-to-day basis and to continue our development of our product candidates. Furthermore, since these manufacturers are located in China, we are exposed to the possibility of product supply disruption and increased costs in the event of changes in the policies of the U.S. or Chinese governments, political unrest or unstable economic conditions in China. For example, a trade war could lead to tariffs on the chemical intermediates we use that are manufactured in China. Any of these matters could materially and adversely affect our business and results of operations. Any recall of the manufacturing lots or similar action regarding our product candidates used in clinical trials could delay the trials or detract from the integrity of the trial data and its potential use in future regulatory filings. In addition, manufacturing interruptions or failure to comply with regulatory requirements by any of these manufacturers could significantly delay clinical development of potential products and reduce third-party or clinical researcher interest and support of proposed trials. These interruptions or failures could also impede commercialization of our product candidates and impair our competitive position. Further, we may be exposed to fluctuations in the value of the local currency in China. Future appreciation of the local currency could increase our costs. In addition, our labor costs could continue to rise as wage rates increase due to increased demand for skilled laborers and the availability of skilled labor declines in China.

Risks related to managing our business and operations

We will need to grow the size of our organization, and we may experience difficulties in managing this growth.

As of December 31, 2020, we had 78 full-time employees. As our clinical development and commercialization plans and strategies develop, and as we continue to operate as a public company, we expect we will need additional managerial, clinical, manufacturing, medical, regulatory, sales, marketing, financial, legal and other personnel. Future growth would impose significant added responsibilities on members of management, including:

- recruiting, integrating, retaining and motivating additional employees;
- managing our development efforts effectively, including the clinical, manufacturing and quality review process for our product candidates, while complying with our contractual obligations to contractors, collaboration partners and other third parties; and
- improving our operational, financial and management controls, reporting systems and procedures.

Our future financial performance and our ability to commercialize our product candidates, if approved, will depend, in part, on our ability to effectively manage any future growth, and our management may also have to divert a disproportionate amount of its attention away from day-to-day activities in order to devote a substantial amount of time to managing these growth activities.

We currently rely, and for the foreseeable future will continue to rely, in substantial part on third parties, including independent organizations, advisors and consultants, to provide certain services to support and perform our operations.

There can be no assurance that the services of these third parties will continue to be available to us on a timely basis when needed, or that we can find qualified replacements. In addition, if we are unable to effectively manage our outsourced activities or if the quality, accuracy or quantity of the services provided is compromised for any reason, our clinical trials may be delayed or terminated, and we may not be able to obtain, or may be substantially delayed in obtaining, regulatory approval of our product candidates or otherwise advance our business. There can be no assurance that we will be able to manage our existing consultants or find other suitable outside contractors and consultants on economically reasonable terms, or at all.

If we are not able to effectively expand our organization by hiring new employees and expanding our groups of consultants and contractors, we may not be able to successfully execute the tasks necessary to further develop and commercialize our product candidates and, accordingly, may not achieve our development and commercialization goals.

We have no history of commercializing marketed products. Building our commercialization capabilities will require a significant investment of time and money. There can be no assurance that we will successfully set up our commercialization capabilities.

We are currently in the early stages of building our commercial capabilities to allow us to market our product candidates, if approved, either alone or in combination with others. Establishing commercialization capabilities will require substantial investment of time and money and may divert significant management focus and resources. In addition, we will be competing with larger biopharmaceutical and biotechnology companies with established commercialization and marketing capabilities as we seek to recruit suitable personnel. Accordingly, there can be no assurance that our efforts to set up commercialization capabilities will be successful.

We do not have the internal research capabilities required to independently discover new product candidates, and we plan to execute our growth strategy by identifying and in-licensing or acquiring additional product candidates that have been discovered and initially developed by others. We may not be successful in executing our growth strategy or such growth strategy may not deliver the anticipated results.

We do not have an internal discovery and preclinical research and development department to independently discover and initially develop new product candidates. We plan to source new product candidates, including those that may be complementary to our existing product candidates, by in-licensing or acquiring them from other companies, academic institutions or other asset originators. If we are unable to identify, in-license or acquire and integrate product candidates, our ability to pursue our growth strategy would be limited.

Research programs and business development efforts to identify new product candidates require substantial technical, financial and human resources, and we have no immediate plans to develop an internal discovery and preclinical research and development group. In-licensing and acquiring product candidates or development programs often requires significant payments and expenses and may consume valuable resources. We will need to devote a substantial amount of time and personnel to develop and commercialize any in-licensed or acquired technology or product candidate, in addition to doing so for our existing product candidates. Our business development efforts or acquisition or licensing attempts may fail to yield additional complementary or successful product candidates for clinical development and commercialization for a number of reasons, including the following:

- our identification or business development methodology or search criteria and process may be unsuccessful in identifying potential product candidates with a high probability of success for development progression;
- we may not be able or willing to assemble sufficient resources or expertise to identify and in-license or acquire additional product candidates;
- for product candidates we seek to in-license or acquire, we may not be able to agree to acceptable terms with the licensor or owner of those product candidates;
- any product candidates that we do in-license or acquire may not succeed in preclinical studies or clinical trials;
- we may not succeed in formulation or process development of such in-licensed or acquired product candidates;

- such in-licensed or acquired product candidates may be shown to have harmful side effects or may have other characteristics that may make the products unlikely to receive regulatory approval or be unmarketable if approved;
- competitors may develop alternatives that render such in-licensed product candidates obsolete or less attractive;
- in-licensed or acquired product candidates may be covered by third parties' patents or other exclusive rights that we may not be able to access;
- in-licensed or acquired product candidates that we develop may not allow us to best make use of our expertise and our development and commercial infrastructure as currently expected;
- the market for a product candidate that we in-license or acquire may change during the course of our development of the product candidate so that such product candidate may become unreasonable to continue to develop;
- a product candidate that we in-license or acquire may not be capable of being produced in commercial quantities at an acceptable cost, or at all; and
- a product candidate that we in-license or acquire may not be accepted as safe and effective by patients, the medical community or third-party payors.

If any of these events occur, we may not be successful in executing our growth strategy or our growth strategy may not deliver the anticipated results.

Our current operations are concentrated in two locations, and we or the third parties upon whom we depend may be adversely affected by earthquakes or other natural disasters and our business continuity and disaster recovery plans may not adequately protect us from a serious disaster.

Our current headquarters are located in Stamford, Connecticut. Our development operations are currently located in Durham, North Carolina. We currently outsource our manufacturing operations to third parties, and clinical quantities of our product candidates are manufactured by these third parties outside the U.S., including in Canada, China and France. Any unplanned event, such as flood, fire, explosion, earthquake, extreme weather condition, medical epidemics, power shortage, telecommunication failure or other natural or manmade accidents or incidents that result in us being unable to fully utilize our facilities, or the manufacturing facilities of our third-party contract manufacturers, may have a material and adverse effect on our ability to operate our business, particularly on a daily basis, and have significant negative consequences on our financial and operating conditions.

Loss of access to these facilities may result in increased costs, delays in the development of our product candidates or interruption of our business operations. Earthquakes or other natural disasters could further disrupt our operations and have a material and adverse effect on our business, financial condition, results of operations and prospects. If a natural disaster, power outage or other event occurred that prevented us from using all or a significant portion of our headquarters or our development operations, that damaged critical infrastructure, such as the manufacturing facilities of our third-party contract manufacturers, or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible, for us to continue our business for a substantial period of time. Disaster recovery and business continuity plans may prove inadequate in the event of a serious disaster or similar event. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans, which could have a material adverse effect on our business. As part of our risk management approach, we maintain insurance coverage at levels that we believe are appropriate for our business. However, in the event of an accident or incident at these facilities, we cannot assure you that the amounts of insurance will be sufficient to satisfy any damages and losses. If our facilities, or the manufacturing facilities of our third-party contract manufacturers, are unable to operate because of an accident or incident or for any other reason, even for a short period of time, any or all of our research and development programs may be harmed. Any business interruption may have a material and adverse effect on our business, financial condition, results of operations and prospects.

Risks related to our financial position and need for additional capital

We have incurred significant net losses since our inception and anticipate that we will continue to incur net losses in the future.

We have incurred significant net losses in each reporting period since our inception. To date, we have financed our operations principally through equity financings. We have derived all of our revenue from the nonrefundable upfront payment we received under the Jazz asset purchase and license agreement and we do not have any products approved for commercial sale or sources of recurring revenue. If our product candidates are not successfully developed and approved, we may never generate any revenue from them. We continue to incur significant research and development and other expenses related to our ongoing operations. As a result, we are not profitable and have incurred losses in each annual period since our inception. Our net losses were $45.6 million and $58.3 million for the year ended December 31, 2020 and December 31, 2019, respectively. As of December 31, 2020 and December 31, 2019, we had an accumulated deficit of $118.6 million and $73.0 million, respectively. We expect to continue to incur significant losses for the foreseeable future, and we expect these losses to increase as we continue our research and development of, and seek regulatory approvals for, our product candidates, including our lead product candidates, nirogacestat and mirdametinib, and any future product candidates.

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

- advance the development of our lead product candidates, nirogacestat and mirdametinib, through potentially registrational clinical trials and potentially for other indications;
- advance our development programs for our other product candidates through clinical development and into later-stage clinical development;
- seek marketing approvals for any product candidates that successfully complete clinical trials;
- invest in or in-license other technologies or product candidates for further preclinical and clinical development;
- hire additional personnel, including clinical, quality control, scientific, medical, business development and finance personnel, and continue to build our infrastructure;
- expand our operational, financial and management systems and increase personnel, including personnel to support our clinical development, manufacturing and commercialization efforts and our operations as a public company;
- maintain, expand and protect our intellectual property portfolio; and
- establish a sales, marketing and distribution infrastructure to commercialize any products for which we may obtain marketing approval and intend to commercialize on our own or jointly with third parties.

To become and remain profitable, we or any potential future collaborators must develop and eventually commercialize products with significant market potential. This will require us to be successful in a range of challenging activities, including completing preclinical studies and clinical trials, obtaining marketing approval for product candidates, manufacturing, obtaining reimbursement approval, marketing and selling products for which we may obtain marketing approval and satisfying any post-marketing requirements. We may never succeed in any or all of these activities and, even if we do, we may never generate revenue that is 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 or continue our operations. A decline in the value of our company also could cause stockholders to lose all or part of their investment. Market volatility resulting from the COVID-19 pandemic or other factors could also adversely impact our ability to access capital as and when needed.

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, register 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.

We have a limited operating history, which may make it difficult to evaluate our prospects and likelihood of success.

We are a clinical-stage biopharmaceutical company with a limited operating history. We were formed in August 2017 and our operations to date have been focused on preparing and executing our clinical trials for our product candidates, building our infrastructure, raising capital and executing partnerships. Consequently, we have limited operations upon which to evaluate our business, and predictions about our future success or viability may not be as accurate as they could be if we had a longer operating history or a history of successfully developing and commercializing drug products. Investment in biopharmaceutical product development is highly speculative because it entails substantial upfront capital expenditures and significant risk that any potential product candidate will fail to demonstrate adequate activity or an acceptable safety profile, gain regulatory approval, secure market access and reimbursement and become commercially viable.

Although we announced the full enrollment of the DeFi trial, a potentially registrational Phase 3 clinical trial of nirogacestat, in July 2020, and in October 2019 commenced a potentially registrational Phase 2b clinical trial of mirdametinib, we have not yet demonstrated the ability to successfully complete clinical trials for any product candidate, we have no products approved for commercial sale and we have not generated any revenue from product sales to date. In addition, as a business with a limited operating history, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors and risks frequently experienced by early-stage biopharmaceutical companies in rapidly evolving fields, or other known or unknown factors and risks that may be infrequent or unique.

In addition, we will need to transition at some point from a company with a development focus to a company capable of supporting commercial activities, and may not be successful in such a transition.

We will require additional capital to fund our operations and if we fail to obtain necessary capital, we will not be able to complete the development and commercialization of our product candidates.

Our operations have consumed substantial amounts of cash since inception. We expect to continue to spend substantial amounts of cash to conduct further research and development and clinical trials of our product candidates to seek regulatory approvals for our product candidates and to launch and commercialize any products for which we receive regulatory approval. As of December 31, 2020, we had $561.8 million in cash, cash equivalents and marketable securities. Based on our current operating plan, we believe that our cash, cash equivalents and marketable securities will be sufficient to fund our operating expenses and capital expenditure requirements through at least 2022. However, our future capital requirements and the period for which our existing resources will support our operations may vary significantly from what we expect, and we will in any event require additional capital in order to complete clinical development and obtain regulatory approval of our product candidates. Our monthly spending levels will vary based on new and ongoing development and corporate activities. Because the length of time and activities associated with development of our product candidates is highly uncertain, we are unable to estimate the actual funds we will require for development and any approved marketing and commercialization activities.

Our future funding requirements will depend on many factors, including, but not limited to:

- the initiation, progress, timing, costs and results of clinical trials for our product candidates; including any unforeseen costs we may incur as a result of clinical trial delays due to the COVID-19 pandemic or other causes;
- the clinical and preclinical development and manufacturing plans we establish for these product candidates;
- the number and characteristics of product candidates that we develop or in-license;
- the cost of identifying and evaluating potential product candidates for acquisition or license, including the cost of preclinical activities or clinical activities;
- the terms of any collaboration or licensing agreements we may choose to enter into;
- the outcome, timing and cost of meeting regulatory requirements established by the FDA, the EMA, and other comparable foreign regulatory authorities;

- the cost of filing, prosecuting, defending and enforcing our patent claims and other intellectual property rights;
- the cost of defending intellectual property disputes, including patent infringement actions brought by third parties against us or our product candidates;
- the effect of competing technological and market developments;
- the cost and timing of completion of commercial-scale manufacturing activities; and
- the degree of commercial success achieved following the successful completion of development and regulatory approval activities for a product candidate.

While we successfully completed a follow-on public offering in October 2020 in which we raised approximately $269.5 million, net of expenses, if we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may have to significantly delay, scale back or discontinue the development or commercialization of one or more of our product candidates or one or more of our other research and development initiatives. Any of the above events could significantly harm our business, prospects, financial condition and results of operations and cause the price of our common stock to decline.

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

We do not have any committed external source of funds or other support for our development efforts and we cannot be certain that additional funding will be available on acceptable terms, or at all. Until we can generate sufficient product or royalty revenue to finance our cash requirements, which we may never do, we expect to finance our future cash needs through a combination of public or private equity offerings, debt financings, collaborations, strategic alliances, licensing arrangements and other marketing or distribution arrangements. If we raise additional funds through public or private equity offerings, the terms of these securities may include liquidation or other preferences that adversely affect our stockholders' rights. Further, to the extent that we raise additional capital through the sale of common stock or securities convertible or exchangeable into common stock, existing stockholder ownership interest may be diluted. In addition, any debt financing may subject us to fixed payment obligations and covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. If we raise additional capital through marketing and distribution arrangements or other collaborations, strategic alliances or licensing arrangements with third parties, we may have to relinquish certain valuable rights to our product candidates, technologies, future revenue streams or research programs or grant licenses on terms that may not be favorable to us. We also could be required to seek commercial or development partners for our lead products or any future product candidate at an earlier stage than otherwise would be desirable or relinquish our rights to product candidates or technologies that we otherwise would seek to develop or commercialize ourselves.

Risks related to our common stock

We do not intend to pay dividends on our common stock so any returns will be limited to the value of our stock.

We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. Furthermore, future debt or other financing arrangements may contain terms prohibiting or limiting the amount of dividends that may be declared or paid on our common stock. Any return to stockholders will therefore be limited to the appreciation of their stock.

Our principal stockholders and management own a significant percentage of our stock and will be able to exert significant control over matters subject to stockholder approval.

Our executive officers, directors and their affiliates and certain significant stockholders beneficially hold, in the aggregate, as of December 31, 2020, approximately 48% of our outstanding voting stock. Therefore, these stockholders will have the ability to influence us through this ownership position. These stockholders may be able to determine all matters requiring stockholder approval. For example, these stockholders may be able to control elections of directors, amendments of our organizational documents, or approval of any merger, sale of assets, or other major corporate transaction. This may prevent or discourage unsolicited acquisition proposals or offers for our common stock that stockholders may feel are in their best interest as one of our stockholders.

Anti-takeover provisions under our charter documents and Delaware law could delay or prevent a change of control which could limit the market price of our common stock and may prevent or frustrate attempts by our stockholders to replace or remove our current management.

Our amended and restated certificate of incorporation and amended and restated bylaws, contain provisions that could delay or prevent a change of control of our company or changes in our board of directors that our stockholders might consider favorable. Some of these provisions include:

- a board of directors divided into three classes serving staggered three-year terms, such that not all members of the board will be elected at one time;
- a prohibition on stockholder action through written consent, which requires that all stockholder actions be taken at a meeting of our stockholders;
- a requirement that special meetings of stockholders be called only by the chairman of the board of directors, the chief executive officer or by a majority of the total number of authorized directors;
- advance notice requirements for stockholder proposals and nominations for election to our board of directors;
- a requirement that no member of our board of directors may be removed from office by our stockholders except for cause and, in addition to any other vote required by law, upon the approval of not less than two-thirds of all outstanding shares of our voting stock then entitled to vote in the election of directors;
- a requirement of approval of not less than two-thirds of all outstanding shares of our voting stock to amend any bylaws by stockholder action or to amend specific provisions of our certificate of incorporation; and
  the authority of the board of directors to issue convertible preferred stock on terms determined by the board of directors without stockholder approval and which convertible preferred stock may include rights superior to the rights of the holders of common stock.

In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which may prohibit certain business combinations with stockholders owning 15% or more of our outstanding voting stock. These anti-takeover provisions and other provisions in our amended and restated certificate of incorporation and amended and restated bylaws could make it more difficult for stockholders or potential acquirers to obtain control of our board of directors or initiate actions that are opposed by the then-current board of directors and could also delay or impede a merger, tender offer or proxy contest involving our company. These provisions could also discourage proxy contests and make it more difficult for stockholders to elect directors of their choosing or cause us to take other corporate actions they desire. Any delay or prevention of a change of control transaction or changes in our board of directors could cause the market price of our common stock to decline.

Our bylaws designate certain specified courts as the sole and exclusive forums for certain disputes between us and our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our by-laws provide that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware, or the Chancery Court, will be the sole and exclusive forum for state law claims for (i) any derivative action or proceeding brought on our behalf, (ii) any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers or other employees to us or our stockholders, (iii) any action asserting a claim pursuant to any provision of the General Corporation Law of the State of Delaware, our certificate of incorporation or our bylaws, (iv) any action to interpret, apply, enforce or determine the validity of our certificate of incorporation or bylaws, or (v) any action asserting a claim governed by the internal affairs doctrine, or the Delaware Forum Provision. The Delaware Forum Provision does not apply to any causes of action arising under the Securities Act of 1933, as amended, or the Securities Act, or the Securities Exchange Act of 1934, as amended, or the Exchange Act. Our bylaws further provide that, unless we consent in writing to the selection of an alternative forum, the U.S. District Court for the District of Connecticut will be the sole and exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act, as amended, or the Federal Forum Provision. Our by-laws provide that any person or entity purchasing or otherwise acquiring any interest in shares of our capital stock is deemed to have notice of and consented to the foregoing Delaware Forum Provision and the Federal Forum Provision; provided, however, that

stockholders cannot and will not be deemed to have waived our compliance with the federal securities laws and the rules and regulations thereunder.

The Delaware Forum Provision and the Federal Forum Provision may impose additional litigation costs on stockholders in pursuing the claims identified above, particularly if the stockholders do not reside in or near the State of Delaware or the State of Connecticut. Additionally, the Delaware Forum Provision and the Federal Forum Provision may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage such lawsuits. In addition, while the Delaware Supreme Court ruled in March 2020 that federal forum selection provisions purporting to require claims under the Securities Act be brought in federal court are "facially valid" under Delaware law, there is uncertainty as to whether other courts will enforce our Federal Forum Provision. If the Federal Forum Provision is found to be unenforceable in an action, we may incur additional costs associated with resolving such an action. The Federal Forum Provision may also impose additional litigation costs on stockholders who assert that the provision is not enforceable or invalid. The Chancery Court or the U.S. District Court for the District of Connecticut may also reach different judgments or results than would other courts, including courts where a stockholder considering an action may be located or would otherwise choose to bring the action, and such judgments may be more, or less, favorable to us than our stockholders.

General risk factors

Risks related to research and development and the biopharmaceutical industry

Clinical development involves a lengthy and expensive process, with an uncertain outcome. We may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates.

To obtain the requisite regulatory approvals to commercialize any product candidate, we must demonstrate through extensive preclinical studies and clinical trials that such product candidate is safe and effective in humans. Clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. We may be unable to establish clinical endpoints that applicable regulatory authorities would consider clinically meaningful, and a clinical trial can fail at any stage of testing.

Differences in trial design between early-stage clinical trials and later-stage clinical trials make it difficult to extrapolate the results of earlier clinical trials to later clinical trials. Moreover, clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in clinical trials have nonetheless failed to obtain marketing approval of their products. Additionally, we are conducting and plan to conduct some open-label trials, where both the patient and investigator know whether the patient is receiving the investigational product candidate or either an existing approved drug or placebo. Most typically, open-label clinical trials test only the investigational product candidate and sometimes may do so at different dose levels. Open-label clinical trials are subject to various limitations that may exaggerate any therapeutic effect as patients in those trials are aware when they are receiving treatment. Open-label clinical trials may be subject to a "patient bias" where patients perceive their symptoms to have improved merely due to their awareness of receiving an experimental treatment. In addition, open-label clinical trials may be subject to an "investigator bias" where those assessing and reviewing the outcomes of the clinical trials are aware of which patients have received treatment and may interpret the information of the treated group more favorably given this knowledge. Where a randomized, placebo-controlled clinical trial is designed to allow enrolled subjects to cross-over to the treatment arm, there may be a risk of inadvertent unblinding of subjects prior to cross-over, which may limit the clinical meaningfulness of those data and may require the conduct of additional clinical trials. As such, the results from an open-label trial may not be predictive of future clinical trial results with any of our product candidates for which we include an open-label clinical trial when studied in a controlled environment with a placebo or active control.

Successful completion of clinical trials is a prerequisite to submitting a NDA to the FDA, an MAA to the EMA and similar marketing applications to comparable foreign regulatory authorities for each product candidate and, consequently, the ultimate approval and commercial marketing of any product candidates.

Although we have initiated potentially registrational clinical trials for nirogacestat and mirdametinib, we do not know whether these trials or any of our clinical trials, including trials for our combination therapies using nirogacestat and mirdametinib, will be completed on schedule, if at all, or in some cases whether such clinical trials will begin.
We may experience delays in initiating or completing clinical trials and preparing for regulatory submissions. We also may experience numerous unforeseen events during, or as a result of, any future clinical trials that we could conduct that could delay or prevent our ability to receive marketing approval or commercialize our current product candidates or any future product candidates, including:

- delays in our clinical trials and preclinical programs resulting from factors related to the COVID-19 pandemic;
- regulators or IRBs, ethics committees may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- we may experience delays in reaching, or fail to reach, agreement on acceptable terms with prospective clinical trial sites and prospective CROs, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and clinical trial sites;
- clinical trials of any product candidates may fail to show acceptable safety or efficacy, or produce negative or inconclusive results and we may decide, or regulators may require us, to conduct additional preclinical studies or clinical trials or we may decide to abandon product development programs;
- the number of subjects required for clinical trials of any product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate or subjects may drop out of these clinical trials or fail to return for post-treatment follow-up at a higher rate than we anticipate;
- our third-party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all, or may deviate from the clinical trial protocol or drop out of the trial, which may require that we add new clinical trial sites or investigators;
- we may elect to, or regulators, IRBs or ethics committees may require, that we or our investigators suspend or terminate clinical research or trials for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks;
- the cost of clinical trials of any 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 inadequate to initiate or complete a given clinical trial;
- our product candidates may have undesirable side effects or other unexpected characteristics, causing us or our investigators, regulators, IRBs or ethics committees to suspend or terminate the clinical trials;
- reports from clinical testing of other therapies may raise safety or efficacy concerns about our product candidates; and
- the FDA, EMA or comparable regulatory authorities may require us to submit additional data, such as long-term toxicology studies, or impose other requirements before permitting us to initiate a clinical trial.

We could also encounter delays if a clinical trial is suspended or terminated by us, the IRBs of the institutions in which such clinical trials are being conducted, or the FDA, EMA or comparable regulatory authorities, or recommended for suspension or termination by the Data Safety Monitoring Board, DSMB, for such clinical trial. A suspension or termination may be imposed due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or clinical trial site by the FDA, EMA or comparable foreign regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a product or treatment, failure to establish or achieve clinically meaningful trial endpoints, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. Many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our product candidates. Further, the FDA, EMA or comparable foreign regulatory authorities may disagree with our clinical trial design and our interpretation of data from clinical trials, or may change the requirements for approval even after they have reviewed and commented on the design for our clinical trials.

Our costs will increase if we experience delays in clinical testing or marketing approvals. We do not know whether any of our clinical trials will begin as planned, will need to be reassigned or will be completed on schedule, or at all. Significant clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates and may allow our competitors to bring products to market before we do,

potentially impairing our ability to successfully commercialize our product candidates and harming our business and results of operations. Any delays in our clinical development programs may harm our business, financial condition and results of operations significantly. The clinical trials sponsored by our partners with our product candidates in combination with our partners' therapies pose the same development risks.

The successful development of biopharmaceuticals is highly uncertain.

Successful development of biopharmaceuticals is highly uncertain and is dependent on numerous factors, many of which are beyond our control. Product candidates that appear promising in the early phases of development may fail to reach the market for several reasons including:

- clinical trial results may show the product candidates to be less effective than expected (for example, a clinical trial could fail to meet its primary or key secondary endpoint(s)) or to have unacceptable side effects or toxicities;
- failure to receive the necessary regulatory approvals or a delay in receiving such approvals. Among other things, such delays may be caused by patients who fail the trial screening process, slow enrollment in clinical trials, patients dropping out of trials, patients lost to follow-up;
- length of time to achieve trial endpoints, additional time requirements for data analysis or NDA preparation, discussions with the FDA, an FDA request for additional preclinical or clinical data (such as long-term toxicology studies) or unexpected safety or manufacturing issues;
- preclinical study results may show the product candidate to be less effective than desired or to have harmful side effects;
- supply issues, manufacturing costs and formulation issues, including our inability to successfully combine our product candidates with other therapies;
- post-marketing approval requirements; and
- the proprietary rights of others and their competing products and technologies that may prevent our product candidates from being commercialized.

The length of time necessary to complete clinical trials and to submit an application for marketing approval for a final decision by a regulatory authority varies significantly from one product candidate to the next and from one country to the next, and may be difficult to predict.

Even if we are successful in obtaining marketing approval, commercial success of any approved products will also depend in large part on the availability of coverage and adequate reimbursement from third-party payors, including government payors such as the Medicare and Medicaid programs and managed care organizations in the U.S. or country specific governmental organizations in foreign countries, which may be affected by existing and future healthcare reform measures designed to reduce the cost of healthcare. Third-party payors could require us to conduct additional studies, including post-marketing studies related to the cost effectiveness of a product, to qualify for reimbursement, which could be costly and divert our resources. If government and other healthcare payors were not to provide coverage and adequate reimbursement for our products once approved, market acceptance and commercial success would be reduced.

In addition, if any of our product candidates receive marketing approval, we will be subject to significant regulatory obligations regarding the submission of safety and other post-marketing information and reports and registration, and will need to continue to comply (or ensure that our third-party providers comply) with cGMPs and GCPs for any clinical trials that we conduct post-approval. In addition, there is always the risk that we, a regulatory authority or a third party might identify previously unknown problems with a product post-approval, such as adverse events of unanticipated severity or frequency. Compliance with these requirements is costly, and any failure to comply or other issues with our product candidates post-approval could adversely affect our business, financial condition and results of operations.

Due to our limited resources and access to additional capital, we must prioritize development of certain programs and product candidates; these decisions may prove to be wrong and may adversely affect our business.

We may fail to identify and acquire, through purchase or license, viable new product candidates for clinical development for a number of reasons. If we fail to identify and acquire additional product candidates, our business could be materially harmed.

Efforts to identify and pursue new product candidates and disease targets require substantial technical, financial and human resources, regardless of whether they are ultimately successful. We currently rely on third parties, including current and future collaborators, to perform all of our research and preclinical activities. Programs may initially show promise in preclinical studies, yet fail to yield positive results during clinical development for a number of reasons, including:

- the methodology used may not be successful in identifying potential indications and/or product candidates; or
- product candidates may, after further study, be shown to have harmful adverse effects or other characteristics that indicate they are unlikely to be effective products.

Because we have limited financial and human resources, we intend to initially focus on programs and product candidates for a limited set of indications. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications with our existing product candidates that may later prove to have greater commercial potential or a greater likelihood of success. We may focus our efforts and resources on potential product candidates or other potential programs that ultimately prove to be unsuccessful.

Our future clinical trials or those of our future collaborators may reveal significant adverse events not seen in prior preclinical studies or clinical trials and may result in a safety profile that could inhibit regulatory approval or market acceptance of any of our product candidates.

If significant adverse events or other side effects are observed in any of our clinical trials, we may have difficulty recruiting patients to our clinical trials, patients may drop out of our trials or we may be required to abandon the trials or our development efforts of one or more product candidates altogether. For example, a prior Phase 2 clinical trial of mirdametinib was terminated and enrollment in the Phase 2 portion of a Phase 1/2 clinical trial was halted as a result of adverse events observed at doses of mirdametinib of 15 mg twice daily, or BID, or above using both intermittent and continuous dosing schedules. These adverse events included ocular disorders (visual disturbances, blurred vision and retinal vein occlusion), nervous system disorders (confusion, slowed ideation, slurred speech and hallucinations), musculoskeletal and connective tissue disorders (general weakness and neck muscle weakness associated with mild and moderate elevations in creatine phosphokinase) and cardiac disorders (decreased left ventricular ejection fraction and congestive heart failure). Although these doses were significantly higher than the maximum allowable dose of 4 mg BID in our ongoing Phase 2b clinical trial of mirdametinib in NF1-PN, we plan to treat patients in this trial for a period of up to 24 months, which would be longer than any subjects have been treated with mirdametinib in prior trials. In our ongoing Phase 2b clinical trial, we may observe adverse events similar to those that were seen at higher doses of mirdametinib in prior clinical trials owing to the potentially increased duration of treatment, or other factors. In addition, the trial is enrolling pediatric NF1-PN patients. There is limited safety data of mirdametinib in children under the age of 16 and it is possible that there may be unanticipated adverse events observed in this patient population.

If we elect or are required to delay, suspend or terminate any clinical trial of any product candidates that we develop, the commercial prospects of such product candidates will be harmed and our ability to generate product revenues from any of these product candidates will be delayed or eliminated. Serious adverse events or other adverse events, as well as tolerability issues, observed in clinical trials could hinder or prevent market acceptance of the product candidate at issue.

We, the FDA, EMA or comparable foreign regulatory authorities or an IRB may suspend clinical trials of a product candidate at any time for various reasons, including a belief that subjects in such trials are being exposed to unacceptable health risks or adverse side effects. Some potential therapeutics developed in the biotechnology industry that initially showed therapeutic promise in early-stage trials have later been found to cause side effects that prevented their further development. Even if the side effects do not preclude the product candidate from obtaining or maintaining marketing

approval, restrictions could be imposed on the approval or an approved product could be subject to a "black box" warning, and undesirable side effects may inhibit market acceptance of the approved product due to its tolerability versus other therapies.

We face significant competition from other biopharmaceutical companies, and our operating results will suffer if we fail to compete effectively.

The biopharmaceutical industry is characterized by intense competition and rapid innovation. Our competitors may be able to develop other compounds or drugs that are able to achieve similar or better results. Our potential competitors include major multinational pharmaceutical companies, established biotechnology companies, specialty pharmaceutical companies and universities and other research institutions. Many of our competitors have substantially greater financial, technical and other resources, such as larger research and development staff and experienced marketing and manufacturing organizations and well-established sales forces. Smaller or early-stage companies may also prove to be significant competitors, particularly as they develop novel approaches to treating disease indications that our product candidates are also focused on treating. Established pharmaceutical companies may also invest heavily to accelerate discovery and development of novel therapeutics or to in-license novel therapeutics that could make the product candidates that we develop obsolete. Mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated in our competitors. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our competitors, either alone or with collaboration partners, may succeed in developing, acquiring or licensing on an exclusive basis drug or biologic products that are more effective, safer, more easily commercialized or less costly than our product candidates or may develop proprietary technologies or secure patent protection that we may need for the development of our technologies and products. We believe the key competitive factors that will affect the development and commercial success of our product candidates are efficacy, safety, tolerability, reliability, convenience of use, price and reimbursement.

Even if we obtain regulatory approval of our product candidates, the availability and price of our competitors' products could limit the demand and the price we are able to charge for our product candidates. We may not be able to implement our business plan if the acceptance of our product candidates is inhibited by price competition or the reluctance of physicians to switch from existing methods of treatment to our product candidates, or if physicians switch to other new drug or biologic products or choose to reserve our product candidates for use in limited circumstances.

Even if any product candidate we develop receives marketing approval, it may fail to achieve the degree of market acceptance by physicians, patients, third-party payors and others in the medical community necessary for commercial success.

If any future product candidate we develop receives marketing approval, whether as a single agent or in combination with other therapies, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community. If the product candidates we develop do not achieve an adequate level of acceptance, we may not generate significant product revenues and we may not become profitable. The degree of market acceptance of any product candidate, if approved for commercial sale, will depend on a number of factors, including:

- efficacy and potential advantages compared to other treatments;
- the ability to offer our products, if approved, for sale at competitive prices;
- convenience and ease of administration compared to other treatments;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the strength of marketing and distribution support;
- the ability to obtain sufficient third-party coverage, market access and adequate reimbursement; and
- the prevalence and severity of any side effects.

Changes in methods of product candidate manufacturing or formulation may result in additional costs or delay.

As product candidates proceed through preclinical studies to late-stage clinical trials towards potential approval and commercialization, it is common that various aspects of the development program, such as manufacturing methods and formulation, are altered along the way in an effort to optimize processes and results. Such changes carry the risk that they will not achieve these intended objectives. Any of these changes could cause our product candidates to perform differently and affect the results of planned clinical trials or other future clinical trials conducted with the materials manufactured using altered processes. Such changes may also require additional testing, including bridging or comparability testing to demonstrate the validity of clinical data obtained in clinical trials following manufacturing changes, FDA notification or FDA approval.

Because all prior clinical trials of nirogacestat and mirdametinib were conducted by third parties, we will need to perform analytical and other tests to demonstrate that any new drug product material is comparable in all respects, including potency, to the product used in such earlier clinical trials. There is no assurance that any such product will pass the required comparability testing, that any other future third-party manufacturer that we engage will be successful in producing our product candidates or that any materials produced by any third-party manufacturer that we engage will have the same effect in patients that we have observed to date with respect to materials used in prior clinical trials.
All of the above could delay completion of clinical trials, require the conduct of bridging clinical trials or the repetition of one or more clinical trials, increase clinical trial costs, delay approval of our product candidates and jeopardize our ability to commence sales and generate revenue.

Moreover, we have not yet manufactured or processed on a commercial scale and may not be able to do so for any of our product candidates if approved. We may make changes as we work to optimize our manufacturing processes, but we cannot be sure that even minor changes in our processes will result in therapies that are safe and effective and approved for commercial sale.

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

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

- inability to bring a product candidate to the market;
- decreased demand for our products;
- harm to our reputation;
- withdrawal of clinical trial participants and inability to continue clinical trials;
- initiation of investigations by regulators;
- costs to defend the related litigation;
- diversion of management’s time and our resources;
- substantial monetary awards to clinical trial participants or patients who receive an approved product;
- product recalls, withdrawals or labeling, marketing or promotional restrictions;
- loss of revenue;
- exhaustion of any available insurance and of our capital resources;
- the inability to commercialize any product candidate, if approved; and
- a decline in our stock price.

Our inability to obtain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims could prevent or inhibit the commercialization of products we develop, alone or with collaborators. Even if our agreements with any current or future corporate collaborators entitle us to indemnification against losses, that indemnification may not be available or adequate should any claim arise. Although we currently carry $5.0 million in clinical trial insurance, that amount of insurance coverage may not be adequate, and, in the future, we may be unable to maintain this insurance coverage, or we may not be able to obtain additional or replacement insurance at a reasonable cost, if at all. Our insurance policies also have various exclusions, and we may be subject to a product liability claim for which we have no coverage. We may have to pay any amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay those amounts.

Risks related to intellectual property

Our success depends in part on our ability to protect our intellectual property, and patent terms may be inadequate to protect our competitive position. It is difficult and costly to protect our proprietary rights and technology, and we may not be able to ensure their protection.

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, their respective components, formulations, combination therapies, methods used to manufacture them and methods of treatment, as well as successfully defending these patents against third-party challenges. Our ability to stop unauthorized third parties from making, using, selling, offering to sell or importing our product candidates is affected by the extent to which we have rights under valid and enforceable patents that cover these activities. If our patents expire, or we are unable to secure and maintain patent protection for any product or technology we develop, or if the scope of the patent protection secured is not sufficiently broad, our competitors could develop and commercialize products and technology similar or identical to ours, and our ability to commercialize any product candidates we may develop may be adversely affected. Patents have a limited lifespan. In the U.S., if all maintenance fees are timely paid, the natural expiration of a patent is generally 20 years from its earliest U.S. non-provisional filing date. Various extensions such as patent term adjustments and/or extensions, may be available, but the life of a patent, and the protection it affords, is limited. Our current composition of matter patents covering nirogacestat and mirdametinib, were licensed from Pfizer in connection with the formation of our company. A U.S. composition of matter patent covering the chemical structure of nirogacestat expires in 2025 and a U.S. composition of matter patent that covers the polymorphic form of nirogacestat that is currently in clinical development expires in 2039. A U.S. composition of matter patent covering the chemical structure of mirdametinib expires in 2021. Our earliest patents may expire before, or soon after, either product candidate achieves marketing approval in the U.S. or foreign jurisdictions. Upon the expiration of the current patents, we currently intend to rely on orphan drug exclusivity to market our lead products. Once the patent life has expired, we may be open to competition from competitive products, including generics. As a result, our patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours. The expiration of the patents covering our lead product candidates, and our inability to secure additional patent protection, could also have a material adverse effect on our business, results of operations, financial condition and prospects.

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. 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. Moreover, in some circumstances, we may not have the right to control the preparation, filing and prosecution of patent applications, or to maintain the patents, covering technology that we license from or license to third parties and are reliant on our licensors or licensees.

The strength of patents in the biopharmaceutical field involves complex legal and scientific questions and can be uncertain. The patent applications that we own or in-license now or in the future may fail to result in issued patents with claims that cover our product candidates or uses thereof in the U.S. or in other foreign countries. Even if the patents do successfully issue, third parties may challenge the validity, enforceability or scope thereof, which may result in such patents being narrowed, invalidated or held unenforceable. Furthermore, even if they are unchallenged, the patents and patent applications covering our product candidates may not adequately protect our intellectual property or prevent

others from designing around our claims. If the breadth or strength of protection provided by the patents we hold with respect to our product candidates is threatened, it could dissuade companies from collaborating with us to develop, and threaten our ability to commercialize, our product candidates. Further, if we encounter delays in our clinical trials, the period of time during which we could market our product candidates under patent protection would be reduced.

Since patent applications in the U.S. and most other countries are confidential for a period of time after filing, there is no certainty that any patent application related to a product candidate was the first to be filed. Furthermore, for U.S. applications in which at least one claim is entitled to a priority date before March 16, 2013, an interference proceeding can be provoked by a third party or instituted by the U.S. Patent and Trademark Office, or USPTO, to determine who was the first to invent any of the subject matter covered by the patent claims of an application.

We cannot be certain that we are the first to invent any inventions covered by a pending patent application and, if we are not, we could be subject to priority disputes. We may be required to disclaim part or all of the term of certain patents or all of the term of certain patent applications. There may be prior art of which we are not aware that may affect the validity or enforceability of a patent claim. There also may be prior art of which we are aware, but which we do not believe affects the validity or enforceability of a claim, which may, nonetheless, ultimately be found to affect the validity or enforceability of a claim. No assurance can be given that if challenged, our patents would be declared by a court to be valid or enforceable or that even if found valid and enforceable, a competitor's technology or product would be found by a court to infringe our patents. We may analyze patents or patent applications of our competitors that we believe are relevant to our activities, and consider that we are free to operate in relation to our product candidates, but our competitors may achieve issued claims, including in patents we consider to be unrelated, which block our efforts or may potentially result in our product candidates or our activities infringing such claims. The possibility exists that others will develop products which have the same effect as our products on an independent basis which do not infringe our patents or other intellectual property rights, or will design around the claims of patents that we have had issued that cover our products. In addition, some of our patent applications and patents may cover inventions owned jointly by us and our collaborators. There can be no assurance that we and our collaborators will agree upon matters related to patent filing and prosecution strategy required to execute an effective patent strategy or that decisions made by our collaborators will be consistent with our goals for protecting our solely owned intellectual property.

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. Under the enacted Leahy-Smith America Invents Act, or America Invents Act, enacted in 2013, the U.S. 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. 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. The effects of these changes are currently unclear as the USPTO only recently developed new regulations and procedures in connection with the America Invents Act and many of the substantive changes to patent law, including the "first-to-file" provisions, only became effective in March 2013. In addition, the courts have yet to address many of these provisions and the applicability of the act and new regulations on specific patents discussed herein have not been determined and would need to be reviewed. However, the America Invents Act and its implementation could increase the uncertainties and costs surrounding the prosecution of any patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business and financial condition.

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 compositions of our product candidates but that are not covered by the claims of our patents;
- the active ingredients 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;
- a company or its licensor, as the case may be, may fail to meet its obligations to the U.S. government in regard to any in-licensed patents and patent applications funded by U.S. government grants, leading to the loss of patent rights;

- such company or its licensors, as the case may be, might not have been the first to file patent applications for these inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies;
- it is possible that a pending patent applications will not result in issued patents;
- it is possible that there are prior public disclosures that could invalidate our or our licensors' patents, as the case may be, or parts of our or their patents;
- it is possible that others may circumvent our owned or in-licensed 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 or our licensors', as the case may be, proprietary rights to the same extent as the laws of the U.S.;
- the claims of our owned or in-licensed issued patents or patent applications, if and when issued, may not cover our product candidates;
- our owned or in-licensed 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 owned or in-licensed 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;
- it is possible that owned or in-licensed patents or patent applications omit individual(s) that should be listed as inventor(s) or include individual(s) that should not be listed as inventor(s), which may cause these patents or patents issuing from these patent applications to be held invalid or unenforceable;
- 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;
- it is possible that product candidates 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.

If we are unable to protect the confidentiality of our trade secrets, our business and competitive position would be harmed.

In addition to patent protection, we rely heavily upon know-how and trade secret protection, as well as non-disclosure agreements and invention assignment agreements with our employees, consultants and third parties, to protect our confidential and proprietary information, especially where we do not believe patent protection is appropriate or obtainable. In addition to contractual measures, we try to protect the confidential nature of our proprietary information using physical and technological security measures. Such measures may not, for example, in the case of misappropriation of a trade secret by an employee or third party with authorized access, provide adequate protection for our proprietary information. Our security measures may not prevent an employee or consultant from misappropriating our trade secrets and providing them to a competitor, and recourse we take against such misconduct may not provide an adequate remedy to protect our interests fully. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret can be difficult, expensive and time-consuming, and the outcome is unpredictable. In addition, trade secrets may be independently developed by others in a manner that could prevent legal recourse by us. If any of our confidential or proprietary information, such as our trade secrets, were to be disclosed or misappropriated, or if any such information was independently developed by a competitor, our competitive position could be harmed.

In addition, courts outside the U.S. are sometimes less willing 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. 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. In addition, we take other appropriate precautions, such as physical and technological security measures, to guard against misappropriation of our proprietary technology by third parties.

Third-party claims of intellectual property infringement may prevent or delay our product discovery and development efforts.

Our commercial success depends in part on our ability to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing the proprietary rights of third parties. There is a substantial amount of litigation involving patents and other intellectual property rights in the biotechnology and pharmaceutical industries, as well as administrative proceedings for challenging patents, including interference, derivation, inter partes review, post grant review, and reexamination proceedings before the USPTO or oppositions and other comparable proceedings in foreign jurisdictions. 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 their intellectual property rights. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we are developing our product candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our product candidates may give rise to claims of infringement of 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.

If a third-party claims that we infringe its intellectual property rights, we may face a number of issues, including, but not limited to:

- infringement and other intellectual property claims which, regardless of merit, may be expensive and time-consuming to litigate and may divert our management's attention from our core business;
- 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, or from using our proprietary technologies, unless the third party licenses its product 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 products; 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.

Third parties may assert that we are employing their proprietary technology without authorization. Generally, conducting clinical trials and other development activities in the U.S. is protected under the Safe Harbor exemption as set forth in 35

U.S.C. §271. If and when any of our product candidates are approved by the FDA, that certain third-party may then seek to enforce its patent by filing a patent infringement lawsuit against us. While we do not believe that any claims of such patent that could otherwise materially adversely affect commercialization of our product candidates, if approved, are valid and enforceable, we may be incorrect in this belief, or we may not be able to prove it in a litigation. In this regard, patents issued in the U.S. by law enjoy a presumption of validity that can be rebutted only with evidence that is "clear and convincing," a heightened standard of proof. There may be third-party patents of which we are currently unaware with claims to materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of our product candidates. Because patent applications can take many years to issue, there may be currently pending patent applications which may later result in issued patents that our product candidates may infringe. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. If any third-party patents were held by a court of competent jurisdiction to cover the manufacturing process of our product candidates, constructs or molecules used in or formed during the manufacturing process, or any final product itself, the holders of any such patents may be able to block our ability to commercialize the product candidate unless we obtained a license under the applicable patents, or until such patents expire or they are finally determined to be held invalid or unenforceable. Similarly, if any third-party patent were held by a court of competent jurisdiction to cover aspects of our formulations, processes for manufacture or methods of use, the holders of any such patent may be able to block our ability to develop and commercialize the product candidate unless we obtained a license or until such patent expires or is finally determined to be held invalid or unenforceable. In either case, such a license may not be available on commercially reasonable terms or at all. If we are unable to obtain a necessary license to a third-party patent on commercially reasonable terms, or at all, our ability to commercialize our product candidates may be impaired or delayed, which could in turn significantly harm our business. Even if we obtain a license, it may be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. In addition, if the breadth or strength of protection provided by our patents and any patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates.

Parties making claims against us may seek and obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize our product candidates. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. In the event of a successful claim of infringement against us, we or our licensors may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, obtain one or more licenses from third parties, pay royalties or redesign our infringing products, which may be impossible or require substantial time and monetary expenditure. We cannot predict whether any such license would be available at all or whether it would be available on commercially reasonable terms. Furthermore, even in the absence of litigation, we may need to obtain licenses from third parties to advance our research or allow commercialization of our product candidates. We may fail to obtain any of these licenses at a reasonable cost or on reasonable terms, if at all. In that event, we would be unable to further develop and commercialize our product candidates, which could harm our business significantly.

Third parties may assert that our employees, consultants, collaborators or partners have wrongfully used or disclosed confidential information or misappropriated trade secrets.

As is common in the biotechnology and pharmaceutical industries, we employ individuals who were previously employed at universities or other biopharmaceutical or pharmaceutical companies, including our competitors or potential competitors. Although no claims against us are currently pending, and although we try to ensure that our employees and consultants do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or our employees, consultants or independent contractors have inadvertently or otherwise used or disclosed intellectual property, including trade secrets or other proprietary information, of a former employer or other third parties. 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.

We may not be successful in obtaining or maintaining necessary rights to develop any future product candidates on acceptable terms.

Because our programs may involve additional product candidates that may require the use of proprietary rights held by third parties, the growth of our business may depend in part on our ability to acquire, in-license or use these proprietary rights.

Our product candidates may also require specific formulations to work effectively and these rights may be held by others. We may develop products containing our compounds and pre-existing pharmaceutical compounds. We may be unable to acquire or in-license any compositions, methods of use, processes or other third-party intellectual property rights from third parties that we identify as necessary or important to our business operations. We may fail to obtain any of these licenses at a reasonable cost or on reasonable terms, if at all, which could 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 on such 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, it may be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. In that event, we may be required to expend significant time and resources to develop or license replacement technology.

Additionally, we sometimes collaborate with academic institutions to accelerate our preclinical research or development under written agreements with these institutions. In certain cases, these institutions may provide us with an option to negotiate a license to any of the institution's rights in technology resulting from the collaboration. 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 may offer the intellectual property rights to others, potentially blocking our ability to pursue our program. If we are unable to successfully obtain rights to required third-party intellectual property or to maintain the existing intellectual property rights we have, we may have to abandon development of such program and our business and financial condition could suffer.

The licensing and acquisition of third-party intellectual property rights is a competitive area, and companies, which 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 size, cash resources and greater clinical development and commercialization capabilities. 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.

We may be involved in lawsuits to protect or enforce our patents or the patents of our licensors, which could be expensive, time-consuming and unsuccessful.

Competitors may infringe our patents or the patents of our licensors. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming. In addition, in an infringement proceeding, a court may decide that one or more of our patents is not valid or is unenforceable, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation or defense proceedings could put one or more of our patents at risk of being invalidated, held unenforceable or interpreted narrowly and could put any patent applications at risk of not issuing. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business.

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 European Patent Office, or EPO, or other foreign patent offices. 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 offices 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.

In addition, because some patent applications in the U.S. may be maintained in secrecy until the patents are issued, patent applications in the U.S. 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 for technology covered by issued patents or any pending applications, or that we or, if applicable, a licensor were the first to invent the technology. Our competitors also may have filed, and may in the future file, patent applications covering our products or technology similar to ours. Any such patent application may have priority over our patents or any patent applications, which could require us to obtain rights to issued patents covering such technologies. If another party has filed a U.S. patent application on inventions similar to those owned by or in-licensed to us, we or, in the case of in-licensed technology, the licensor may have to participate in an interference proceeding declared by the USPTO to determine priority of invention in the U.S. If we or one of our licensors is a party to an interference proceeding involving a U.S. patent application on inventions owned by or in-licensed to us, we may incur substantial costs, divert management's time and expend other resources, even if we are successful.

Interference proceedings provoked by third parties or brought by the USPTO may be necessary to determine the priority of inventions with respect to our patents or any patent applications or those of our licensors. An unfavorable outcome could result in a loss of our current patent rights and could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms. Litigation or interference proceedings may result in a decision adverse to our interests and, even if we are successful, may result in substantial costs and distract our management and other employees. We may not be able to prevent, alone or with our licensors, misappropriation of our trade secrets or confidential information, particularly in countries where the laws may not protect those rights as fully as in the U.S.

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 such litigation. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments. 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.

Obtaining and maintaining our patent protection depends on 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.

Periodic maintenance fees on any issued patent are due to be paid to the USPTO and foreign patent agencies in several stages over the lifetime of the patent. The USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other provisions during the patent application process and following the issuance of a patent. While an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Noncompliance events that could result in abandonment or lapse of a patent or patent application include, but are not limited to, failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. In such an event, our competitors might be able to enter the market, which would have a material adverse effect on our business.

Issued patents covering our product candidates could be found invalid or unenforceable if challenged in court or the USPTO.

If we or one of our licensing partners initiate legal proceedings against a third party to enforce a patent covering one of our product candidates, the defendant could counterclaim that the patent covering our product candidate, as applicable, is invalid and/or unenforceable. In patent litigation in the U.S., defendant counterclaims alleging invalidity and/or unenforceability are commonplace, and there are numerous grounds upon which a third party can assert invalidity or unenforceability of a patent. Third parties may also raise similar claims before administrative bodies in the U.S. or abroad, even outside the context of litigation. Such mechanisms include re-examination, post grant review, and equivalent proceedings in foreign jurisdictions (e.g., opposition proceedings). Such proceedings could result in revocation or amendment to our patents in such a way that they no longer cover our product candidates. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to validity, for example, we cannot be certain that there is no invalidating prior art, of which we, our patent counsel and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, or if we are otherwise unable to adequately protect our rights, we would lose at least part, and perhaps all, of the patent protection on our product candidates. Such a loss of patent protection could have a material adverse impact on our business and our ability to commercialize or license our technology and product candidates.

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

As is the case with other biopharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biopharmaceutical industry involve both technological and legal complexity, and is therefore costly, time-consuming and inherently uncertain. In addition, the U.S. has recently enacted and is currently implementing wide-ranging patent reform legislation. 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. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on decisions by the U.S. Congress, the federal courts and the USPTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future. We cannot predict how these decisions or any future decisions by the courts, the U.S. Congress or the USPTO may impact the value of our patents. Similarly, any adverse changes in the patent laws of other jurisdictions could have a material adverse effect on our business and financial condition.

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

Filing, prosecuting and defending patents on product candidates in all countries throughout the world is expensive. While certain of our licensed patents, including patents covering our lead product candidates, have been issued in major markets and other countries, our intellectual property rights in some countries outside the U.S. can be less extensive than those in the U.S. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the U.S. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the U.S., or from selling or importing products made using our inventions in and into the U.S. or other jurisdictions. Competitors may use our technologies 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 that in the U.S. These products may compete with our products 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 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, trade secrets and other intellectual property protection, particularly those relating to biopharmaceutical products, which could make it difficult for us or our licensors 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 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, could put our patents at risk of being invalidated or interpreted narrowly and any patent applications at risk of not issuing and could provoke third parties to assert claims against us or our licensors. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

If we do not obtain patent term extension and 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 Action of 1984, or Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent extension term 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. However, we may not be granted an extension 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 term of any such extension is less than we request, our competitors may obtain approval of competing products following our patent expiration, and our business, financial condition, results of operations and prospects could be materially harmed.

If our trademarks and trade names are not adequately protected, then we may not be able to build name recognition in our markets of interest and our business may be adversely affected.

Our trademarks or trade names may be challenged, infringed, circumvented or declared generic or determined to be infringing on other marks. We may not be able to protect our rights to these trademarks and trade names or may be forced to stop using these names, which we need for name recognition by potential partners or customers in our markets of interest. If we are unable to establish name recognition based on our trademarks and trade names, we may not be able to compete effectively and our business may be adversely affected.

Risks related to government regulation

The regulatory approval process for our product candidates in the U.S., the EU and other jurisdictions is currently uncertain and will be lengthy, time-consuming and inherently unpredictable and we may experience significant delays in the clinical development and regulatory approval, if any, of our product candidates.

The research, testing, manufacturing, labeling, approval, selling, import, export, marketing and distribution of drug products are subject to extensive regulation by the FDA in the U.S., the EMA in the EU, and comparable foreign regulatory authorities. We are not permitted to market any product in any jurisdiction until we receive marketing approval from the appropriate regulatory authority. We have not previously submitted an NDA to the FDA, an MAA to the EMA or similar marketing application to comparable foreign regulatory authorities. In the U.S., an NDA must include extensive preclinical and clinical data and supporting information to establish that the product candidate is safe, pure and potent for each desired indication. An NDA must also include significant information regarding the chemistry, manufacturing and controls for the product, and the manufacturing facilities must complete a successful pre-approval inspection.

The FDA may also require a panel of experts, referred to as an Advisory Committee, to deliberate on the adequacy of the safety and efficacy data to support approval. The opinion of the Advisory Committee, although not binding, may have a significant impact on our ability to obtain approval of any product candidates that we develop based on the completed clinical trials.

In addition, clinical trials can be delayed or terminated for a variety of reasons, including delays or failures related to:

- obtaining regulatory authorization to begin a clinical trial, if applicable;
- the availability of financial resources to begin and complete the planned trials;
- reaching agreement on acceptable terms with prospective 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 approval at each clinical trial site by an independent IRB or ethics committee;
- recruiting suitable patients to participate in a clinical trial in a timely manner;
- having patients complete a clinical trial or return for post-treatment follow-up;
- clinical trial sites deviating from clinical trial protocol, not complying with GCP requirements or dropping out of a trial;
- addressing any patient safety concerns that arise during the course of a clinical trial;
- addressing any conflicts with new or existing laws or regulations;
- adding new clinical trial sites; or
- manufacturing qualified materials under cGMP regulations for use in clinical trials.

Patient enrollment is a significant factor in the timing of clinical trials and is affected by many factors. Further, a clinical trial may be suspended or terminated by us, the IRBs for the institutions in which such clinical trials are being conducted, or the FDA, EMA or comparable foreign regulatory authorities, or recommended for suspension or termination by the DSMB for such clinical trial, due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or clinical trial sites by the FDA, EMA or comparable foreign regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a product candidate, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. If we experience termination of, or delays in the completion of, any clinical trial of our product candidates, the commercial prospects for our product candidates will be harmed, and our ability to generate product revenue will be delayed. In addition, any delays in completing any clinical trials will increase our costs, slow down our product development and approval process and jeopardize our ability to commence product sales and generate revenue.

Separately, in response to the COVID-19 global pandemic, on March 10, 2020, the FDA announced its intention to postpone most inspections of foreign manufacturing facilities and products through at least April 2020, though no set end date has been determined. On March 18, 2020, the FDA announced its intention to temporarily postpone routine surveillance inspections of domestic manufacturing facilities. In April 2020, the FDA stated that its New Drug Program was continuing to meet program user fee performance goals, but due to many agency staff working on COVID-19 activities, it was possible that the FDA would not be able to sustain that level of performance indefinitely. As of June 23, 2020, the FDA noted it was conducting mission critical domestic and foreign inspections to ensure compliance of manufacturing facilities with FDA quality standards. On July 10, 2020, the FDA announced its goal of restarting domestic on-site inspections during the week of July 20, 2020, but such activities will depend on data about the virus' trajectory in a given state and locality and the rules and guidelines that are put in place by state and local governments. The FDA has developed a rating system to assist in determining when and where it is safest to conduct prioritized domestic inspections. Should the FDA determine that an inspection is necessary for approval and an inspection cannot be completed during the review cycle due to restrictions on travel, the FDA has stated that it generally intends to issue a complete response letter. Further, if there is inadequate information to make a determination on the acceptability of a facility, the FDA may defer action on the application until an inspection can be completed. In 2020, several companies announced receipt of complete response letters due to the FDA's inability to complete required inspections for their applications. Regulatory authorities outside the U.S. may adopt similar restrictions or other policy measures in response to the COVID-19 pandemic and provide guidance regarding the conduct of clinical trials, which guidance continues to evolve. Additionally, as of June 23, 2020, the FDA noted it was continuing to ensure timely reviews of applications for medical products during the COVID-19 pandemic in line with its user fee performance goals. On July 16, 2020, FDA noted that it is continuing to expedite oncology product development with its staff teleworking full-time. However, the FDA may not be able to continue its current pace and approval timelines could be extended, including where a pre-approval inspection or an inspection of clinical sites is required and due to the COVID-19 pandemic and travel restrictions the FDA is unable to complete such required inspections during the review period. If global health concerns

continue to prevent the FDA or other regulatory authorities from conducting their regular inspections, reviews or other regulatory activities, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business.

The FDA, EMA or comparable foreign regulatory authorities may disagree with our regulatory plan for our product candidates.

The general approach for FDA approval of a new drug is dispositive data from one or more well-controlled Phase 3 clinical trials of the product candidate in the relevant patient population. Phase 3 clinical trials typically involve a large number of patients, have significant costs and take years to complete.

Our clinical trial results may not support approval of our product candidates. In addition, our product candidates could fail to receive regulatory approval, or regulatory approval could be delayed, for many reasons, including the following:

- the FDA, EMA or comparable foreign regulatory authorities may disagree with the dosing regimen, design or implementation of our clinical trials;
- we may be unable to demonstrate to the satisfaction of the FDA, EMA or comparable foreign regulatory authorities that our product candidates are safe and effective for any of their proposed indications;
- we may encounter safety or efficacy problems caused by the COVID-19 pandemic;
- the results of clinical trials may not meet the level of statistical significance required by the FDA, EMA or comparable foreign regulatory authorities for approval;
- we may be unable to demonstrate that our product candidates' clinical and other benefits outweigh their safety risks;
- the FDA, EMA 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 the satisfaction of the FDA, EMA or comparable foreign regulatory authorities to support the submission of an NDA or other comparable submission in foreign jurisdictions or to obtain regulatory approval in the U.S. or elsewhere;
- the FDA, EMA 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; and
- the approval policies or regulations of the FDA, EMA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval.

We may seek regulatory approval of our product candidates, including nirogacestat, based on an interim analysis conducted of a registrational trial, particularly if the interim analysis is statistically significant for the primary endpoint and the safety data demonstrate an acceptable safety and tolerability profile. The results of any such interim analysis would be discussed with FDA at a pre-NDA meeting to assess the adequacy of the data to support the submission of a NDA; however, if the FDA does not agree that the interim analysis provides a sufficient basis for regulatory approval, we would not submit an NDA until the conclusion of such registrational trial.

Breakthrough Therapy Designation or Fast Track Designation from the FDA may not actually lead to a faster development or regulatory review or approval process.

The FDA has granted Fast Track Designation and Breakthrough Therapy Designation for nirogacestat for the treatment of adult patients with progressive, unresectable, recurrent or refractory desmoid tumors or deep fibromatosis, and has granted Fast Track Designation for mirdametinib for the treatment of patients at least two years of age with NF1-associated inoperable PN that are progressing or causing significant morbidity. We may seek Breakthrough Therapy Designation or Fast Track Designation for our other product candidates.

If a product is intended for the treatment of a serious or life-threatening condition and the product demonstrates the potential to address unmet medical needs for this condition, the product sponsor may apply for Fast Track Designation. The FDA has broad discretion whether or not to grant this designation, so even if we believe one of our product candidates is eligible for this designation, we cannot assure you that the FDA would decide to grant it. Even if we do

receive Fast Track Designation, we may not experience a faster development process, review or approval compared to conventional FDA procedures. The FDA may withdraw Fast Track Designation if it believes that the designation is no longer supported by data from our clinical development program.

A breakthrough therapy is defined as a product that is intended, 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. For products 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.

Designation as a breakthrough therapy is within the discretion of the FDA. Accordingly, even if we believe 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. In any event, the receipt of a Breakthrough Therapy Designation may not result in a faster development process, review or approval compared to products considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if a product candidate qualifies as a breakthrough therapy, the FDA may later decide that the product no longer meets the conditions for qualification and rescind the Breakthrough Therapy Designation.

The results of clinical trials conducted at clinical trial sites outside the U.S. might not be accepted by the FDA, and data developed outside of a foreign jurisdiction similarly might not be accepted by such foreign regulatory authority.

Some of the prior clinical trials for our product candidates were conducted outside the U.S., and we intend to conduct additional clinical trials outside the U.S. Although the FDA, EMA or comparable foreign regulatory authorities may accept data from clinical trials conducted outside the relevant jurisdiction, acceptance of these data is subject to certain conditions. For example, the FDA requires that the clinical trial must be well designed and conducted and performed by qualified investigators in accordance with ethical principles such as IRB or ethics committee approval and informed consent, the trial population must adequately represent the U.S. population, and the data must be applicable to the U.S. population and U.S. medical practice in ways that the FDA deems clinically meaningful. In addition, while these clinical trials are subject to the applicable local laws, acceptance of the data by the FDA will be dependent upon its determination that the trials were conducted consistent with all applicable U.S. laws and regulations. There can be no assurance that the FDA will accept data from trials conducted outside of the U.S. as adequate support of a marketing application. Similarly, we must also ensure that any data submitted to foreign regulatory authorities adheres to their standards and requirements for clinical trials and there can be no assurance a comparable foreign regulatory authority would accept data from trials conducted outside of its jurisdiction.

Our relationships with healthcare providers and 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 criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings.

Healthcare providers, physicians and third-party payors in the U.S. and elsewhere play a primary role in the recommendation and prescription of pharmaceutical products. Arrangements with third-party payors and customers can expose pharmaceutical manufacturers to broadly applicable fraud and abuse and other healthcare laws and regulations, including, without limitation, the AKS and the federal False Claims Act, or FCA, which may constrain the business or financial arrangements and relationships through which such companies sell, market and distribute pharmaceutical products. In particular, the research of our product candidates, as well as the promotion, sales and marketing of healthcare items and services, as well as certain business arrangements in the healthcare industry, are subject to extensive laws designed 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, structuring and commission(s), certain customer incentive programs and other business arrangements generally. Activities subject to these laws also involve the improper use of information obtained in the course of patient recruitment for clinical trials. The applicable

federal, state and foreign healthcare laws and regulations that may affect our ability to operate include, but are not limited to:

- the AKS, which prohibits, among other things, knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe or rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce, or in return for, either the referral of an individual, or the purchase, lease, order or recommendation of any good, facility, item or service for which payment may be made, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs. A person or entity can be found guilty of violating the statute without actual knowledge of the statute or specific intent to violate it. In addition, a claim including items or services resulting from a violation of the AKS constitutes a false or fraudulent claim for purposes of the FCA. The AKS has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers, and formulary managers on the other. There are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution. On November 20, 2020, the Office of Inspector General, or OIG, finalized further modifications to the AKS. Under the final rules, the OIG added safe harbor protections under the AKS for certain coordinated care and value-based arrangements among clinicians, providers, and others. These rules (with exceptions) became effective January 19, 2021. We continue to evaluate what effect, if any, these rules will have on our business;
- the federal civil and criminal false claims laws and civil monetary penalty laws, including the FCA, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, false or fraudulent claims for payment to, or approval by Medicare, Medicaid or other federal healthcare programs, knowingly making, using or causing to be made or used a false record or statement material to a false or fraudulent claim or an obligation to pay or transmit money to the federal government, or knowingly concealing or knowingly and improperly avoiding or decreasing or concealing an obligation to pay money to the federal government. Manufacturers can be held liable under the FCA even when they do not submit claims directly to government payors if they are deemed to “cause” the submission of false or fraudulent claims. The government may deem manufacturers to have “caused” the submission of false or fraudulent claims by, for example, providing inaccurate billing or coding information to customers or promoting a product off-label. The FCA also permits a private individual acting as a “whistleblower” to bring actions on behalf of the federal government alleging violations of the FCA and to share in any monetary recovery. When an entity is determined to have violated the FCA, the government may impose civil fines and penalties ranging, plus treble damages, and exclude the entity and its products from participation in Medicare, Medicaid and other federal healthcare programs;
- HIPAA, which created additional federal criminal statutes that prohibit knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or 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 healthcare benefit program, regardless of the payor (e.g., public or private) and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false statements in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters. Similar to the AKS, a person or entity can be found guilty of violating HIPAA without actual knowledge of the statute or specific intent to violate it;
- HIPAA, as amended by HITECH, and their respective implementing regulations, which impose, among other things, requirements on certain healthcare providers, health plans and healthcare clearinghouses, known as covered entities, as well as their respective business associates, independent contractors that perform services for covered entities that involve the use, or disclosure of, individually identifiable health information, relating to the privacy, security and transmission of individually identifiable health information. HITECH also created new 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 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, created under the Patient Protection and ACA, as amended, and its implementing regulations, which require some manufacturers of drugs, devices, biologicals and medical

supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program (with certain exceptions) to report annually to CMS of HHS, information related to payments or other transfers of value made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Effective January 1, 2022, these reporting obligations will extend to include transfers of value made to certain non-physician providers such as physician assistants and nurse practitioners; and

- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, which may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers, and may be broader in scope than their federal equivalents; state and foreign laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government or otherwise restrict payments that may be made to healthcare providers; state and foreign laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers, marketing expenditures or drug pricing; state and local laws that require the registration of pharmaceutical sales representatives; and state and foreign laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

The distribution of pharmaceutical products is subject to additional requirements and regulations, including extensive record-keeping, licensing, storage and security requirements intended to prevent the unauthorized sale of pharmaceutical products. Pharmaceutical companies may also be subject to federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers.

The scope and enforcement of each of these laws is uncertain and subject to rapid change in the current environment of healthcare reform, especially in light of the lack of applicable precedent and regulations. Federal and state enforcement bodies continue to closely scrutinize interactions between healthcare companies and healthcare providers, which has led to a number of investigations, prosecutions, convictions and settlements in the healthcare industry. Ensuring business arrangements comply with applicable healthcare laws, as well as responding to possible investigations by government authorities, can be time and resource-consuming and can divert a company's attention from the business.

It is possible that governmental and enforcement authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law interpreting applicable fraud and abuse or other healthcare laws and regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of civil, criminal and administrative penalties, damages, fines, disgorgement, imprisonment, exclusion from participation in federal and state funded healthcare programs, contractual damages and the curtailment or restricting of our operations, as well as additional reporting obligations and oversight if we become subject to a corporate integrity agreement or other agreement to resolve allegations of non-compliance with these laws. Further, if any of the physicians or other healthcare providers or entities with whom we expect to do business is found to be not in compliance with applicable laws, they may be subject to significant criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs. Any action for violation of these laws, even if successfully defended, could cause a biopharmaceutical manufacturer to incur significant legal expenses and divert management's attention from the operation of the business. Prohibitions or restrictions on sales or withdrawal of future marketed products could materially affect business in an adverse way.

Obtaining and maintaining regulatory approval of our product candidates in one jurisdiction does not mean that we will be successful in obtaining regulatory approval of our product candidates in other jurisdictions.

Obtaining and maintaining regulatory approval of our product candidates in one jurisdiction does not guarantee that we will be able to obtain or maintain regulatory approval in any other jurisdiction, while a failure or delay in obtaining regulatory approval in one jurisdiction may have a negative effect on the regulatory approval process in others. For example, even if the FDA grants marketing approval of a product candidate, the EMA or comparable foreign regulatory authorities must also approve the manufacturing, marketing and promotion of the product candidate in those countries.

Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from, and greater than, those in the U.S., including additional preclinical studies or clinical trials, as clinical trials conducted in one jurisdiction may not be accepted by regulatory authorities in other jurisdictions. In many jurisdictions outside the U.S., a product candidate must be approved for reimbursement before it can be approved for sale in that jurisdiction. In some cases, the price that we intend to charge for our products is also subject to approval.

We may also submit marketing applications in other countries. Regulatory authorities in jurisdictions outside of the U.S. have requirements for approval of product candidates with which we must comply prior to marketing in those jurisdictions. Obtaining foreign regulatory approvals and compliance with foreign regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our products in certain countries. If we fail to comply with the regulatory requirements in international markets and/or receive applicable marketing approvals, our target market will be reduced and our ability to realize the full market potential of our product candidates will be harmed.

Even if we receive regulatory approval of any product candidates, we will be subject to ongoing regulatory obligations and continued regulatory review, which may result in significant additional expense and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our product candidates.

If any of our product candidates are approved, they will be subject to ongoing regulatory requirements for manufacturing, labeling, packaging, storage, advertising, promotion, sampling, record-keeping, conduct of post-marketing studies and submission of safety, efficacy and other post-marketing information, including both federal and state requirements in the U.S. and requirements of comparable foreign regulatory authorities. In addition, we will be subject to continued compliance with cGMP and GCP requirements for any clinical trials that we conduct post-approval.

Manufacturers and manufacturers' facilities are required to comply with extensive FDA, EMA and comparable foreign regulatory authority requirements, including ensuring that quality control and manufacturing procedures conform to cGMP regulations. As such, we and our contract manufacturers will be subject to continual review and inspections to assess compliance with cGMP and adherence to commitments made in any NDA, BLA, or other marketing application and previous responses to inspection observations. Accordingly, we and others with whom we work must continue to expend time, money and effort in all areas of regulatory compliance, including manufacturing, production and quality control.

Any regulatory approvals that we receive for our product candidates may be subject to limitations on the approved indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase 4 clinical trials and surveillance to monitor the safety and efficacy of the product candidate. Certain endpoint data we hope to include in any approved product labeling also may not make it into such labeling, including exploratory or secondary endpoint data such as patient-reported outcome measures. The FDA may also require a REMS program as a condition of approval of our product candidates, which could entail requirements for long-term patient follow-up, a medication guide, physician communication plans or additional elements to ensure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. In addition, if the FDA, EMA or a comparable foreign regulatory authority approves our product candidates, we will have to comply with requirements including submissions of safety and other post-marketing information and reports and registration.

The FDA may impose consent decrees or withdraw 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 our product candidates, including adverse events of unanticipated severity or frequency, or with our third-party manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information, imposition of post-marketing studies or clinical trials

to assess new safety risks or imposition of distribution restrictions or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of our products, withdrawal of the product from the market or voluntary or mandatory product recalls;
- fines, warning letters or holds on clinical trials;
- refusal by the FDA to approve pending applications or supplements to approved applications filed by us or suspension or revocation of license approvals;
- product seizure or detention or refusal to permit the import or export of our product candidates; and
- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Products may be promoted only for the approved indications and in accordance with the provisions of the approved label. The policies of the FDA, EMA and comparable foreign regulatory authorities may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the U.S. or abroad. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability.

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

The success of our product candidates, if approved, depends on the availability of coverage and adequate reimbursement from third-party payors. We cannot be sure that coverage and reimbursement will be available for, or accurately estimate the potential revenue from, our product candidates or assure that coverage and reimbursement will be available for any product that we may develop.

Patients who are provided medical treatment for their conditions generally rely on third-party payors to reimburse all or part of the costs associated with their treatment. Coverage and adequate reimbursement from governmental healthcare programs, such as Medicare and Medicaid, and commercial payors is critical to new product acceptance.

Government authorities and other third-party payors, such as private health insurers and health maintenance organizations, decide which drugs and treatments they will cover and the amount of reimbursement. Coverage and reimbursement by a third-party payor may depend upon a number of factors, including the third-party payor’s determination that use of a product is:

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

In the U.S., no uniform policy of coverage and reimbursement for products exists among third-party payors. As a result, 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. Even if we obtain coverage for a given product, the resulting reimbursement payment rates might not be adequate for us to achieve or sustain profitability or may require co-payments that patients find unacceptably high. Additionally, third-party payors may not cover, or provide adequate reimbursement for, long-term follow-up evaluations required following the use of product candidates, once approved. Patients are unlikely to use our product candidates, once approved, unless coverage is provided and reimbursement is adequate to cover a significant portion of their cost. There is significant uncertainty related to insurance coverage and reimbursement of newly approved

products. It is difficult to predict at this time what third-party payors will decide with respect to the coverage and reimbursement for our product candidates. Further, due to the COVID-19 pandemic, millions of individuals have lost or will be losing employer-based insurance coverage, which may adversely affect our ability to commercialize our product candidates even if there is adequate coverage and reimbursement from third-party payors.

Payment methodologies may be subject to changes in healthcare legislation and regulatory initiatives. For example, the Middle Class Tax Relief and Job Creation Act of 2012 required that CMS, the agency responsible for administering the Medicare program, reduce the Medicare clinical laboratory fee schedule by 2% in 2013, which served as a base for 2014 and subsequent years. In addition, effective January 1, 2014, CMS also began bundling the Medicare payments for certain laboratory tests ordered while a patient received services in a hospital outpatient setting. Additional state and federal healthcare reform measures are expected to 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 certain pharmaceutical products or additional pricing pressures.

Moreover, increasing efforts by governmental and third-party payors in the U.S. and abroad to cap or reduce healthcare costs may cause such organizations to limit both coverage and the level of reimbursement for newly approved products and, as a result, they may not cover or provide adequate payment for our product candidates. There has been increasing legislative and enforcement interest in the U.S. with respect to specialty drug pricing practices. Specifically, there have been several recent U.S. Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs and reform government program reimbursement methodologies for drugs. We expect to experience pricing pressures in connection with the sale of any of our product candidates due to the trend toward managed healthcare, the increasing influence of health maintenance organizations, cost containment initiatives and additional legislative changes.

At the state level, legislatures are increasingly passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

Ongoing healthcare legislative and regulatory reform measures may have a material adverse effect on our business and results of operations.

Changes in regulations, statutes or the interpretation of existing regulations could impact our business in the future by requiring, for example: (i) changes to our manufacturing arrangements; (ii) additions or modifications to product labeling; (iii) the recall or discontinuation of our products; or (iv) additional record-keeping requirements. If any such changes were to be imposed, they could adversely affect the operation of our business.

In the U.S., there have been and continue to be a number of legislative initiatives to contain healthcare costs. For example, in March 2010, the ACA was passed, which substantially changed the way healthcare is financed by both governmental and private insurers, and significantly impacted the U.S. biopharmaceutical industry. The ACA, among other things, addressed 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, increased the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extended the rebate program to individuals enrolled in Medicaid managed care organizations, established annual fees and taxes on manufacturers of certain branded prescription drugs and created a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% (increased to 70% pursuant to the Bipartisan Budget Act of 2018, effective as of 2019) point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer’s outpatient drugs to be covered under Medicare Part D.

Since its enactment, there have been numerous judicial, administrative, executive and Congressional legislative challenges to certain aspects of the ACA, and we expect there will be additional challenges and amendments to the ACA in the future. For example, various portions of the ACA are currently undergoing constitutional challenges in the U.S. Supreme Court, and the Trump Administration issued various Executive Orders eliminating cost sharing subsidies and

various provisions that would impose a fiscal burden on states or a cost, fee, tax, penalty or regulatory burden on individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. Additionally, Congress has introduced several pieces of legislation aimed at significantly revising or repealing the ACA. In December 2018, CMS published a final rule permitting further collections and payments to and from certain ACA qualified health plans and health insurance issuers under the ACA risk adjustment program in response to the outcome of the federal district court litigation regarding the method CMS uses to determine this risk adjustment. Since then, the ACA risk adjustment program payment parameters have been updated annually. It is unclear whether the ACA will be overturned, repealed, replaced, or further amended, and we cannot predict what affect further changes to the ACA would have on our business, especially given the transition to the Biden Administration.

Other legislative changes have been proposed and adopted in the U.S. since the ACA was enacted. The Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs, including aggregate reductions of Medicare payments to providers of 2% per fiscal year. These reductions went into effect on April 1, 2013 and, due to subsequent legislative amendments to the statute, including the BBA, will remain in effect through 2030, unless additional congressional action is taken. However, pursuant to the CARES Act, these reductions were suspended from May 1, 2020 through December 31, 2020 due to the COVID-19 pandemic. Proposed legislation, if passed, would extend this suspension until the end of the pandemic. On January 2, 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, further 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.

As discussed above, there has been increasing legislative and enforcement interest in the U.S. with respect to specialty drug pricing practices. See "—Coverage and reimbursement may be limited or unavailable in certain market segments for our product candidates, if approved, which could make it difficult for us to sell any product candidates profitably." At the federal level, the Trump administration's budget proposal for fiscal year 2021 included a $135 billion allowance to support legislative proposals seeking to reduce drug prices, increase competition, lower out-of-pocket drug costs for patients, and increase patient access to lower-cost generic and biosimilar drugs. On March 10, 2020, the Trump administration sent "principles" for drug pricing to Congress, calling for legislation that would, among other things, cap Medicare Part D beneficiary out-of-pocket pharmacy expenses, provide an option to cap Medicare Part D beneficiary monthly out-of-pocket expenses, and place limits on pharmaceutical price increases. Further, the Trump administration also previously released a "Blueprint" to lower drug prices and reduce out of pocket costs of drugs that contains additional proposals to increase manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products and reduce the out of pocket costs of drug products paid by consumers. HHS has already started the process of soliciting feedback on some of these measures and, at the same time, is immediately implementing others under its existing authority. For example, in May 2019, CMS issued a final rule to allow Medicare Advantage Plans the option of using step therapy for Part B drugs beginning January 1, 2020. However, it is unclear whether the Biden administration will challenge, reverse, revoke or otherwise modify these executive and administrative actions after January 20, 2021. In addition, there have been several changes to the 340B drug pricing program, which imposes ceilings on prices that drug manufacturers can charge for medications sold to certain health care facilities. On December 27, 2018, the District Court for the District of Columbia invalidated a reimbursement formula change under the 340B drug pricing program, and CMS subsequently altered the FYs 2019 and 2018 reimbursement formula on specified covered outpatient drugs, or SCODs. The court ruled this change was not an "adjustment" which was within the Secretary's discretion to make but was instead a fundamental change in the reimbursement calculation. However, most recently, on July 31, 2020, the U.S. Court of Appeals for the District of Columbia Circuit overturned the district court's decision and found that the changes were within the Secretary's authority. On September 14, 2020, the plaintiffs-appellees filed a Petition for Rehearing En Banc (i.e., before the full court), which was denied on October 16, 2020. It is unclear how these developments could affect covered hospitals who might purchase our future products and affect the rates we may charge such facilities for our approved products in the future, if any.

Individual states in the U.S. have also increasingly passed legislation and implemented regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain

product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. See "—Coverage and reimbursement may be limited or unavailable in certain market segments for our product candidates, if approved, which could make it difficult for us to sell any product candidates profitably."

These laws, and future state and federal healthcare reform measures may be adopted in the future, any of which 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.

Off-label use or misuse of our products may harm our reputation in the marketplace or result in injuries that lead to costly product liability suits.

We are developing nirogacestat for the treatment of desmoid tumors and mirdametinib for the treatment of NF1-PN. If our product candidates are approved by the FDA, we may only promote or market our product candidates for their specifically approved indications and in a manner consistent with the approved labeling. We will train our marketing and sales force against promoting our product candidates for uses outside of the approved indications for use, known as "off-label uses." We cannot, however, prevent a physician from using our products off label, when in the physician's independent professional medical judgment he or she deems it appropriate. Furthermore, the use of our products for indications other than those approved by the FDA may not effectively treat such conditions. Any such off-label use of our product candidates could harm our reputation in the marketplace among physicians and patients. There may also be increased risk of injury to patients if physicians attempt to use our products for these uses for which they are not approved, which could lead to product liability suits that that might require significant financial and management resources and that could harm our reputation. Additionally, the FDA imposes stringent restrictions on manufacturers' communications regarding off-label use and if we, or our collaborators, do not promote our products, if approved, in a manner consistent with the approved labeling, we, or they, may be subject to warnings or enforcement action for off-label marketing. Violation of the FDCA and other statutes, including the FCA, 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.

Disruptions at the FDA, the Securities and Exchange Commission, or SEC, and other government agencies caused by funding shortages or global health concerns could hinder their ability to hire and retain key leadership and other personnel, or otherwise prevent new or modified products from being developed, approved or commercialized in a timely manner or at all, or otherwise prevent those agencies from performing normal business functions on which the operation of our business may rely, which could negatively impact our business.

The ability of the FDA to review and approve new products can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept the payment of user fees, and statutory, regulatory, and policy changes, and other events that may otherwise affect the FDA's ability to perform routine functions. Average review times at the agency have fluctuated in recent years as a result. In addition, government funding of the SEC and other government agencies on which our operations may rely, including those that fund research and development activities is subject to the political process, which is inherently fluid and unpredictable.

Disruptions at the FDA and other agencies may also slow the time necessary for new drugs to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, in recent years, including in 2018 and 2019, the U.S. government shut down several times and certain regulatory agencies, such as the FDA and the SEC, had to furlough critical employees and stop critical activities. Since March 2020, foreign and domestic inspections by the FDA have largely been on hold with the FDA announcing plans in July 2020 to resume prioritized domestic inspections. Should the FDA determine that an inspection is necessary for approval of a marketing application and an inspection cannot be completed during the review cycle due to restrictions on travel, the FDA has stated that it generally intends to issue a complete response letter. Further, if there is inadequate information to make a determination on the acceptability of a facility, the FDA may defer action on the application until an inspection can be completed. In 2020, several companies announced receipt of complete response letters due to the FDA's inability to complete required inspections for their applications. Regulatory authorities outside the U.S. may adopt similar restrictions or other policy measures in response to the COVID-19 pandemic and may experience delays in their

regulatory activities. Additionally, as of June 23, 2020, the FDA noted it is continuing to ensure timely reviews of applications for medical products during the COVID-19 pandemic in line with its user fee performance goals. On July 16, 2020, the FDA noted that it is continuing to expedite oncology product development with its staff teleworking full-time. However, the FDA may not be able to continue its current pace and approval timelines could be extended, including where a pre-approval inspection or an inspection of clinical sites is required and due to the COVID-19 pandemic and travel restrictions the FDA is unable to complete such required inspections during the review period. If a prolonged government shutdown occurs, or if global health concerns continue to prevent the FDA or other regulatory authorities from conducting their regular inspections, reviews, or other regulatory activities, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business. Further, in our operations as a public company, future government shutdowns or delays could impact our ability to access the public markets and obtain necessary capital in order to properly capitalize and continue our operations.

EU drug marketing and reimbursement regulations may materially affect our ability to market and receive coverage for our products in the European member states.

We intend to seek approval to market our product candidates in both the U.S. and in selected foreign jurisdictions. If we obtain approval in one or more foreign jurisdictions for our product candidates, we will be subject to rules and regulations in those jurisdictions. In some foreign countries, particularly those in the EU, the pricing of drugs is subject to governmental control and other market regulations which could put pressure on the pricing and usage of our product candidates. In these countries, pricing negotiations with governmental authorities can take considerable time after obtaining marketing approval of a product candidate. In addition, market acceptance and sales of our product candidates will depend significantly on the availability of adequate coverage and reimbursement from third-party payors for our product candidates and may be affected by existing and future healthcare reform measures.

Much like the AKS prohibition in the U.S., the provision of benefits or advantages to physicians to induce or encourage the prescription, recommendation, endorsement, purchase, supply, order or use of medicinal products is also prohibited in the EU. The provision of benefits or advantages to physicians is governed by the national anti-bribery and other laws of EU Member States, and operations in the United Kingdom would be subject to relevant United Kingdom laws, including the United Kingdom Bribery Act 2010. Infringement of these laws could result in substantial fines and imprisonment.

Payments made to physicians in certain EU Member States must be publicly disclosed. Moreover, agreements with physicians often must be the subject of prior notification and approval by the physician’s employer, his or her competent professional organization and/or the regulatory authorities of the individual EU Member States. These requirements are provided in the national laws, industry codes or professional codes of conduct, applicable in the EU Member States. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines or imprisonment.

In addition, in most foreign countries, including the EEA, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing and reimbursement vary widely from country to country. For example, the EU provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. 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. A member state may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profitability of the Company placing the medicinal product on the market. In some countries, we may be required to conduct a clinical study or other studies that compare the cost-effectiveness of any of our product candidates to other available therapies in order to obtain or maintain reimbursement or pricing approval. There can be no assurance that any country that has price controls or reimbursement limitations for biopharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our products. Historically, products launched in the EU do not follow price structures of the U.S. and generally prices tend to be significantly lower. 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 pricing is set at unsatisfactory levels or if reimbursement of our products is unavailable or limited in scope or amount, our

revenues from sales and the potential profitability of any of our product candidates in those countries would be negatively affected.

We may incur substantial costs in our efforts to comply with evolving global data protection laws and regulations, and any failure or perceived failure by us to comply with such laws and regulations may harm our business and operations.

The global data protection landscape is rapidly evolving, and we may be or become subject to or affected by numerous federal, state and foreign laws and regulations, as well as regulatory guidance, governing the collection, use, disclosure, transfer, security and processing of personal data, such as information that we collect about participants and healthcare providers in connection with clinical trials. Implementation standards and enforcement practices are likely to remain uncertain for the foreseeable future, which may create uncertainty in our business, affect our or our service providers' ability to operate in certain jurisdictions or to collect, store, transfer use and share personal data, result in liability or impose additional compliance or other costs on us. Any failure or perceived failure by us to comply with federal, state, or foreign laws or self-regulatory standards could result in negative publicity, diversion of management time and effort and proceedings against us by governmental entities or others. For example, California recently passed the California Data Privacy Protection Act, which went into effect in January 2020 and provides broad rights to California consumers with respect to the collection and use of their information by businesses. While there is currently an exception for protected health information that is subject to HIPAA and clinical trial regulations, as currently written, the CCPA may impact our business activities. The California Attorney General has proposed draft regulations, which have not been finalized to date, that may further impact our business activities if they are adopted. Despite the delay in adopting regulations, the California State Attorney General commenced enforcement actions against violators starting July 1, 2020. The uncertainty surrounding the implementation of CCPA exemplifies the vulnerability of our business to the evolving regulatory environment related to personal data and protected health information. The new California law further expands the privacy and process enhancements and commitment of resources in support of compliance with California's regulatory requirements and may lead to similar laws in other U.S. states or at a national level.

In addition to our operations in the U.S., which may be subject to healthcare and other laws relating to the privacy and security of health information and other personal information, may seek to conduct clinical trials in EEA and may become subject to additional European data privacy laws, regulations and guidelines. The GDPR, (EU) 2016/679, became effective on May 25, 2018, and deals with the processing of personal data and on the free movement of such data. The GDPR imposes a broad range of strict requirements on companies subject to the GDPR, including requirements relating to having legal bases for processing personal information relating to identified and/or identifiable individuals and transferring such information outside the EEA, including to the U.S., providing details to those individuals regarding the processing of their personal information, keeping personal information secure, having data processing agreements with third parties who process personal information, responding to individuals' requests to exercise their rights in respect of their personal information, reporting security breaches involving personal data to the competent national data protection authority and affected individuals, appointing data protection officers, conducting data protection impact assessments, maintaining internal records and appropriately deleting personal information in line with retention periods. The GDPR increases substantially the penalties to which we could be subject in the event of any non-compliance, including fines of up to 10,000,000 Euros or up to 2% of our total worldwide annual turnover for certain comparatively minor offenses, or up to 20,000,000 Euros or up to 4% of our total worldwide annual turnover for more serious offenses. Given the limited enforcement of the GDPR to date, we face uncertainty as to the exact interpretation of the new requirements on our trials and we may be unsuccessful in implementing all measures required by data protection authorities or courts in interpretation of the new law.

In particular, national laws of member states of the EU are in the process of being adapted to the requirements under the GDPR, thereby implementing national laws which may partially deviate from the GDPR and impose different obligations from country to country, so that we do not expect to operate in a uniform legal landscape in the EEA. Also, as it relates to processing and transfer of genetic data, the GDPR specifically allows national laws to impose additional and more specific requirements or restrictions, and European laws have historically differed quite substantially in this field, leading to additional uncertainty. Further, the impact of "Brexit", whereby the United Kingdom formally withdrew from the EU on January 31, 2020 is uncertain and cannot be predicted at this time.

In the event we commence clinical trials in the EEA, we must also ensure that we maintain adequate safeguards to enable the transfer of personal data outside of the EEA, in particular to the U.S., in compliance with European data protection laws. We expect that we will continue to face uncertainty as to whether our efforts to comply with any obligations under European privacy laws will be sufficient. If we are investigated by a European data protection authority, we may face fines and other penalties. Any such investigation or charges by European data protection authorities could have a negative effect on our existing business and on our ability to attract and retain new clients or biopharmaceutical partners. We may also experience hesitancy, reluctance or refusal by European or multi-national clients or biopharmaceutical partners to continue to use our products and solutions due to the potential risk exposure as a result of the current (and, in particular, future) data protection obligations imposed on them by certain data protection authorities in interpretation of current law, including the GDPR. Such clients or biopharmaceutical partners may also view any alternative approaches to compliance as being too costly, too burdensome, too legally uncertain or otherwise objectionable and therefore decide not to do business with us. Any of the forgoing could materially harm our business, prospects, financial condition and results of operations.

Additional laws and regulations governing international operations could negatively impact or restrict our operations.

If we further expand our operations outside of the U.S., we must dedicate additional resources to comply with numerous laws and regulations in each jurisdiction in which we plan to operate. The U.S. Foreign Corrupt Practices Act, or FCPA, prohibits any U.S. individual or business from paying, offering, authorizing payment or offering 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 U.S. to comply with certain accounting provisions requiring the Company to maintain books and records that accurately and fairly reflect all transactions of the corporation, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations.

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

Various laws, regulations and executive orders also restrict the use and dissemination outside of the U.S., 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 U.S., it will require us to dedicate additional resources to comply with these laws, and these laws may preclude us from developing, manufacturing or selling certain products and product candidates outside of the U.S., which could limit our growth potential and increase our development costs.

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

We are subject to certain U.S. and foreign anti-corruption, anti-money laundering, export control, sanctions and other trade laws and regulations. We can face serious consequences for violations.

Among other matters, U.S. and foreign anti-corruption, anti-money laundering, export control, sanctions and other trade laws and regulations, which are collectively referred to as Trade Laws, prohibit companies and their employees, agents, clinical research organizations, legal counsel, accountants, consultants, contractors and other partners from authorizing, promising, offering, providing, soliciting or receiving, directly or indirectly, corrupt or improper payments or anything else of value to or from recipients in the public or private sector. Violations of Trade Laws can result in substantial criminal fines and civil penalties, imprisonment, the loss of trade privileges, debarment, tax reassessments, breach of contract and fraud litigation, reputational harm and other consequences. We have direct or indirect interactions with

officials and employees of government agencies or government-affiliated hospitals, universities and other organizations. We also expect our non-U.S. activities to increase in time. We plan to engage third parties for clinical trials and/or to obtain necessary permits, licenses, patent registrations and other regulatory approvals and we can be held liable for the corrupt or other illegal activities of our personnel, agents or partners, even if we do not explicitly authorize or have prior knowledge of such activities.

Risks related to managing business and operations

The outbreak of the novel coronavirus disease, COVID-19, could adversely impact our business, including our preclinical studies and clinical trials.

In December 2019, a novel strain of coronavirus, severe acute respiratory syndrome coronavirus 2, or SARS-CoV-2, was identified in Wuhan, China. This disease resulting from SARS-CoV-2, or COVID-19, has now become a global pandemic. The outbreak and government measures taken in response have had a significant impact, both directly and indirectly, on businesses and commerce throughout the world generally: worker shortages have occurred; supply chains have been disrupted; facilities and production have been suspended; and demand for certain goods and services, such as medical services and supplies, has spiked, while demand for other goods and services, such as travel, has fallen. In response to the spread of COVID-19, our personnel have been continuing their work outside of our offices. While, as of the date of this report, we have not experienced any material disruptions to the execution of the research and development activities that we currently have underway, as a result of the pandemic we may experience disruptions that could severely impact research and development timelines and outcomes, including, but not limited to:

- delays or difficulties in enrolling patients in our clinical trials;
- delays or difficulties in clinical site initiation, including difficulties in recruiting clinical site investigators and clinical site staff;
- diversion of healthcare resources away from the conduct of clinical trials, including the diversion of hospitals serving as our clinical trial sites and hospital staff supporting the conduct of our clinical trials;
- interruption of key clinical trial activities, such as clinical trial site data monitoring, due to limitations on travel imposed or recommended by federal, state or foreign governments, employers and others or interruption of clinical trial subject visits and study procedures (such as procedures that are deemed non-essential under law, regulation or institutional policies), which may impact the integrity of subject data and clinical study endpoints and the inability of patients to travel to trial sites or complete scheduled study visits;
- interruption or delays in the operations of the FDA or other regulatory authorities, which may impact review and approval timelines;
- interruption of, or delays in receiving, supplies of our product candidates from our contract manufacturing organizations due to staffing shortages, production slowdowns or stoppages and disruptions in delivery systems;
- interruptions in preclinical studies due to restricted or limited operations at our contracted research facilities;
- unforeseen costs we may incur as a result of the impact of the COVID-19 pandemic, including the costs of mitigation efforts;
- deterioration of worldwide credit and financial markets that could limit our ability to obtain external financing to fund our operations and capital expenditures;
- investment-related risks, including difficulties in liquidating investments due to current market conditions and adverse investment performance;

- limitations on employee resources that would otherwise be focused on the conduct of our research and development activities, including because of sickness of employees or their families or the desire of employees to avoid contact with large groups of people; or

- interruptions or limitations of the types described affecting our service providers and collaboration partners, including CROs running clinical trials and collaboration partners sponsoring clinical trials in which we are supplying our product candidates or otherwise participating.

Two vaccines for COVID-19 were granted Emergency Use Authorization by the FDA in late 2020, and more are likely to be authorized in the coming months. The resultant demand for vaccines and potential for manufacturing facilities and materials to be commandeered under the Defense Production Act of 1950, or equivalent foreign legislation, may make it more difficult to obtain materials or manufacturing slots for the products needed for our clinical trials, which could lead to delays in these trials. In addition, the trading prices for common stock of other biopharmaceutical companies have been highly volatile as a result of the COVID-19 pandemic. The COVID-19 pandemic continues to rapidly evolve. The extent to which the outbreak impacts our business, preclinical studies and clinical trials will depend on future developments, which are highly uncertain and cannot be predicted with confidence, such as the ultimate geographic spread of the disease, the duration of the pandemic, travel restrictions and social distancing in the U.S. and other countries, business closures or business disruptions and the effectiveness of actions taken in the U.S. and other countries to diagnose, contain and treat the disease. If we or any of the third parties with whom we engage were to experience shutdowns or other business disruptions, our ability to conduct our business and development activities in the manner and on the timelines presently planned could be materially and negatively impacted. There can be no assurance that any such disruptions or delays will not materially adversely impact our business, results of operations, access to financial resources and our financial condition.

If we lose key management personnel, or if we fail to recruit additional highly skilled personnel, our ability to pursue our business strategy will be impaired, could result in loss of markets or market share and could make us less competitive.

Our ability to compete in the highly competitive biopharmaceutical industries depends upon our ability to attract and retain highly qualified managerial, scientific and medical personnel. We are highly dependent on our management, scientific and medical personnel, including Saqib Islam, our Chief Executive Officer, Frank Perier, our Chief Financial Officer, Badreddin Edris, our Chief Operating Officer, Jens Renstrup, our Chief Medical Officer and L. Mary Smith, our Chief Development Officer. The loss of the services of any of our executive officers, other key employees, and other scientific and medical advisors, and our inability to find suitable replacements for these individuals could harm our business.

Competition for skilled personnel in our industry is intense and may limit our ability to hire and retain highly qualified personnel on acceptable terms, in a timely manner or at all. To induce valuable employees to remain at our company, in addition to salary and cash incentives, we have provided equity incentive awards that vest over time. The value to employees of restricted stock awards and stock options that vest over time may be significantly affected by movements in our stock price that are beyond our control, and may at any time be insufficient to counteract more lucrative offers from other companies. Despite our efforts to retain valuable employees, members of our management, scientific and development teams are at-will employees and may terminate their employment with us on short notice. We do not maintain “key man” insurance policies on the lives of these individuals or the lives of any of our other employees. Given the stage of our programs and our plans to expand operations, our success also depends on our ability to continue to attract, retain and motivate highly skilled junior, mid-level and senior personnel across our organization.

Our internal computer systems, or those used by our vendors, or other contractors or consultants, may fail or suffer security breaches.

Despite the implementation of security measures, our internal computer systems and those of our CROs and other third parties, including our contractors and consultants, are vulnerable to damage from computer viruses and unauthorized access. Like other companies of our size and in our industry, we have been the target of phishing attacks and attacks on our data and systems. Companies have experienced an increase in phishing and social engineering attacks from third

parties in connection with the COVID-19 global pandemic. While we believe we have not experienced any material system failure or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our development programs and our business operations. For example, the loss of preclinical or clinical data could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of financial or confidential information, we could incur liability and the further development and commercialization of our product candidates could be delayed.

We could also be subject to risks caused by misappropriation, misuse, leakage, falsification or intentional or accidental release or loss of information maintained in the information systems and networks of our company and our contractors or consultants. In addition, outside parties may attempt to penetrate our systems or those of our contractors or consultants or fraudulently induce our personnel or the personnel of our contractors or consultants to disclose sensitive information in order to gain access to our data and/or systems. We may experience threats to our data and systems, including malicious codes and viruses, phishing and other cyber-attacks. The number and complexity of these threats continue to increase over time. If a material breach of our information technology systems or those of our contractors or consultants occurs, the market perception of the effectiveness of our security measures could be harmed and our reputation and credibility could be damaged. We could be required to expend significant amounts of money and other resources to repair or replace information systems or networks. In addition, we could be subject to regulatory actions and/or claims made by individuals and groups in private litigation involving privacy issues related to data collection and use practices and other data privacy laws and regulations, including claims for misuse or inappropriate disclosure of data, as well as unfair or deceptive practices. Although we develop and maintain systems and controls designed to prevent these events from occurring, and we have a process to identify and mitigate threats, the development and maintenance of these systems, controls and processes is costly and requires ongoing monitoring and updating as technologies change and efforts to overcome security measures become increasingly sophisticated. Moreover, despite our efforts, the possibility of these events occurring cannot be eliminated entirely. In addition, there can be no assurance that our internal information technology systems or those of our third-party contractors, or our consultants' efforts to implement adequate security and control measures, will be sufficient to protect us against breakdowns, service disruption, data deterioration or loss in the event of a system malfunction, or prevent data from being stolen or corrupted in the event of a cyberattack, security breach, industrial espionage attacks or insider threat attacks which could result in financial, legal, business or reputational harm.

Our employees, independent contractors, consultants, academic collaborators, partners and vendors may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements.

We are exposed to the risk of employee fraud or other illegal activity by our employees, independent contractors, consultants, academic collaborators, partners and vendors. Misconduct by these parties could include intentional, reckless and/or negligent conduct that fails to comply with the laws of the FDA, EMA and comparable foreign regulatory authorities, provide true, complete and accurate information to the FDA, EMA and comparable foreign regulatory authorities, comply with manufacturing standards we have established, comply with healthcare fraud and abuse laws in the U.S. and similar foreign fraudulent misconduct laws, or report financial information or data accurately or to disclose unauthorized activities to us. If we obtain FDA approval of any of our product candidates and begin commercializing those products in the U.S., our potential exposure under such laws will increase significantly, and our costs associated with compliance with such laws are also likely to increase. These laws may impact, among other things, our current activities with principal investigators and research patients, as well as proposed and future sales, marketing and education programs. We have adopted a code of business conduct and ethics, but it is not always possible to identify and deter misconduct by our employees, independent contractors, consultants, academic collaborators, partners and vendors, and the precautions we take to detect and prevent such activities 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 comply with these laws or regulations. If any actions are instituted against us and we are not successful in defending ourselves or asserting our rights, those actions could result in the imposition of civil, criminal and administrative penalties, damages, monetary fines, imprisonment, disgorgement, possible exclusion from participation in government healthcare programs, additional reporting obligations and oversight if we become subject to a corporate integrity agreement or other agreement to resolve allegations of non-compliance with these laws, contractual damages, reputational harm, diminished profits and future earnings and the curtailment of our operations.

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 harm our business.

We are subject to numerous environmental, health and safety laws and regulations, including those governing the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our development activities involve the use of biological and hazardous materials and can produce hazardous waste products. We cannot eliminate the risk of contamination or injury from these materials, which could cause an interruption of our commercialization efforts, research and development efforts and business operations, environmental damage resulting in costly clean-up and liabilities under applicable laws and regulations governing the use, storage, handling and disposal of these materials and specified waste products. Although we believe that the safety procedures utilized by our third-party manufacturers for handling and disposing of these materials generally comply with the standards prescribed by these laws and regulations, we cannot guarantee that this is the case or eliminate the risk of accidental contamination or injury from these materials. In such an event, we may be held liable for any resulting damages and such liability could exceed our resources and state or federal or other applicable authorities may curtail our use of certain materials and/or interrupt our business operations. Furthermore, environmental laws and regulations are complex, change frequently and have tended to become more stringent. We cannot predict the impact of such changes and cannot be certain of our future compliance. 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 production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries resulting from the use of hazardous materials or other work-related injuries, this insurance may not provide adequate coverage against potential liabilities. We do not carry specific biological waste or hazardous waste insurance coverage, workers compensation or property and casualty and general liability insurance policies that include coverage for damages and fines arising from biological or hazardous waste exposure or contamination.

Changes in tax law could adversely affect our business and financial condition.

The rules dealing with U.S. federal, state, and local income taxation are constantly under review by persons involved in the legislative process and by the Internal Revenue Service and the U.S. Treasury Department. Changes to tax laws (which changes may have retroactive application) could adversely affect us or holders of our common stock. In recent years, many such changes have been made and changes are likely to continue to occur in the future. Future changes in tax laws could have a material adverse effect on our business, cash flow, financial condition or results of operations. Shareholders should consult with their legal and tax advisers regarding the implications of potential changes in tax laws on an investment in our common stock.

Our ability to use our net operating loss carryforwards and certain tax credit carryforwards may be subject to limitation.

As of December 31, 2020, we have federal, state and city net operating loss carryforwards of $110.9 million, $0.6 million and $3.7 million, respectively, which are available to reduce future taxable income. Federal net operating loss carryforwards of $34.8 million, $55.9 million and $16.0 million reported in 2020, 2019 and 2018, will be available to offset 80% of taxable income for an indefinite period of time, until fully utilized. Federal net operating loss carryforwards of $4.3 million reported in 2017 and the state and city net operating loss carryforwards expire at various dates through 2038. We also have federal tax credits of $7.2 million, which may be used to offset future tax liabilities. These tax credit carryforwards will expire at various dates beginning in 2038.

Under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, changes in our ownership may limit the amount of our net operating loss carryforwards and tax credit carryforwards that could be utilized annually to offset our future taxable income, if any. This limitation would generally apply in the event of a cumulative change in ownership of our company of more than 50% within a three-year period. Any such limitation may significantly reduce our ability to utilize our net operating loss carryforwards and tax credit carryforwards before they expire. Private placements and other transactions that have occurred since our inception, as well as our initial public offering, may trigger such an ownership

change pursuant to Sections 382 and 383. Any such limitation, whether as the result of the initial public offering, prior private placements, sales of our common stock by our existing stockholders or additional sales of our common stock by us, could have a material adverse effect on our results of operations in future years. Under current law, federal net operating losses generated after December 31, 2017 are not subject to expiration and generally may not be carried back to prior taxable years except that net operating losses generated in 2018, 2019 and 2020 may be carried back five taxable years. Additionally, as noted above, for taxable years beginning after December 31, 2020, the deductibility of such federal net operating losses is limited to 80% of our taxable income in any future taxable year.

The United Kingdom's withdrawal from the EU may have a negative effect on global economic conditions, financial markets and our business, which could reduce the price of our ordinary shares.

Following the result of a referendum in 2016, the United Kingdom left the EU on January 31, 2020, commonly referred to as Brexit. Pursuant to the formal withdrawal arrangements agreed between the United Kingdom and the EU, the United Kingdom will be subject to a transition period until December 31, 2020, or the Transition Period, during which EU rules will continue to apply. Negotiations between the United Kingdom and the EU are expected to continue in relation to the customs and trading relationship between the United Kingdom and the EU following the expiry of the Transition Period.

Since a significant proportion of the regulatory framework in the United Kingdom applicable to our business and our product candidates is derived from EU directives and regulations, Brexit, following the Transition Period, could materially impact the regulatory regime with respect to the development, manufacture, importation, approval and commercialization of our product candidates in the United Kingdom or the EU. For example, as a result of the uncertainty surrounding Brexit, the EMA relocated to Amsterdam from London. Following the Transition Period, the United Kingdom will no longer be covered by the centralized procedures for obtaining EU-wide marketing and manufacturing authorizations from the EMA and, unless a specific agreement is entered into, a separate process for authorization of drug products will be required in the United Kingdom, the potential process for which is currently unclear. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would prevent us from commercializing our product candidates in the United Kingdom or the EU and restrict our ability to generate revenue and achieve and sustain profitability. In addition, we may be required to pay taxes or duties or be subjected to other hurdles in connection with the importation of our product candidates into the EU, or we may incur expenses in establishing a manufacturing facility in the EU in order to circumvent such hurdles. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek regulatory approval in the United Kingdom or the EU for our product candidates, or incur significant additional expenses to operate our business, which could significantly and materially harm or delay our ability to generate revenues or achieve profitability of our business. Any further changes in international trade, tariff and import/export regulations as a result of Brexit or otherwise may impose unexpected duty costs or other non-tariff barriers on us. These developments, or the perception that any of them could occur, may significantly reduce global trade and, in particular, trade between the impacted nations and the United Kingdom. It is also possible that Brexit may negatively affect our ability to attract and retain employees, particularly those from the EU.

Unfavorable global economic conditions could adversely affect our business, financial condition or results of operations.

Our results of operations could be adversely affected by general conditions in the global economy and in the global financial markets. Portions of our future clinical trials may be conducted outside of the U.S. and unfavorable economic conditions resulting in the weakening of the U.S. dollar would make those clinical trials more costly to operate. Furthermore, the most recent global financial crisis caused extreme volatility and disruptions in the capital and credit markets. A severe or prolonged economic downturn could result in a variety of risks to our business, including a reduced ability to raise additional capital when needed on acceptable terms, if at all. A weak or declining economy or international trade disputes could also strain our suppliers, some of which are located outside of the U.S., possibly resulting in supply disruption. Any of the foregoing could harm our business and we cannot anticipate all of the ways in which the current economic climate and financial market conditions could adversely impact our business.

Risks related to a company's financial position and need for additional capital

The amount of our future losses is uncertain and our quarterly and annual operating results may fluctuate significantly or may fall below the expectations of investors or securities analysts, each of which may cause our stock price to fluctuate or decline.

Our quarterly and annual operating results may fluctuate significantly in the future due to a variety of factors, many of which are outside of our control and may be difficult to predict, including the following:

- the timing and success or failure of clinical trials for our product candidates or competing product candidates, or any other change in the competitive landscape of our industry, including consolidation among our competitors or partners;
- our ability to successfully recruit and retain subjects for clinical trials, and any delays caused by difficulties in such efforts;
- our ability to obtain marketing approval for our product candidates, and the timing and scope of any such approvals we may receive;
- the timing and cost of, and level of investment in, research and development activities relating to our product candidates, which may change from time to time;
- the cost of manufacturing our product candidates, which may vary depending on the quantity of production and the terms of our agreements with manufacturers;
- our ability to attract, hire and retain qualified personnel;
- expenditures that we will or may incur to develop additional product candidates;
- the level of demand for our product candidates should they receive approval, which may vary significantly;
- the timing and level of investment in commercialization efforts to support product candidates, both before and after regulatory approval is obtained;
- the risk/benefit profile, cost and reimbursement policies with respect to our product candidates, if approved, and existing and potential future therapeutics that compete with our product candidates; and
- future accounting pronouncements or changes in our accounting policies.

The cumulative effects of these factors could result in large fluctuations and unpredictability in our quarterly and annual operating results. As a result, comparing our operating results on a period-to-period basis may not be meaningful. This variability and unpredictability could also result in our failing to meet the expectations of industry or financial analysts or investors for any period. If our revenue or operating results fall below the expectations of analysts or investors or below any forecasts we may provide to the market, or if the forecasts we provide to the market are below the expectations of analysts or investors, the price of our common stock could decline substantially. Such a stock price decline could occur even when we have met any previously publicly stated guidance we may provide.

Risks related to common stock

An active trading market for our common stock may not be sustained.

Our shares of common stock began trading on The Nasdaq Global Select Market on September 13, 2019. Given the limited trading history of our common stock, there is a risk that an active trading market for our shares will not be sustained, which could put downward pressure on the market price of our common stock and thereby affect the ability of our stockholders to sell their shares. Further, an inactive market may also impair our ability to raise capital by selling shares of our common stock and may impair our ability to enter into strategic partnerships or acquire companies or products by using our shares of common stock as consideration.

The price of our stock may be volatile, and Stockholders could lose all or part of their investment.

The trading price of our common stock is likely to be highly volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control, including limited trading volume. In addition to the factors discussed in this "Risk factors" section and elsewhere in this report, these factors include:

- the commencement, enrollment or results of our ongoing potentially registrational clinical trials for nirogacestat and mirdametinib;
- any delay in our regulatory filings for our product candidates and any adverse development or perceived adverse development with respect to the applicable regulatory authority's review of such filings, including without limitation the FDA's issuance of a "refusal to file" letter or a request for additional information;
- adverse results from or delays in future clinical trials;
- our decision to initiate a clinical trial, not to initiate a clinical trial or to terminate an existing clinical trial;
- adverse regulatory decisions, including failure to receive regulatory approval of our product candidates or any future product candidate;
- changes in laws or regulations applicable to our product candidates or any future product candidate, including but not limited to clinical trial requirements for approvals;
- changes in the structure of healthcare payment systems;
- adverse developments concerning our manufacturers;
- our inability to obtain adequate product supply for any approved product or inability to do so at acceptable prices;
- our inability to establish collaborations or partnerships, if needed;
- our failure to commercialize our product candidates, if approved;
- additions or departures of key medical, scientific or management personnel;
- unanticipated serious safety concerns related to the use of our product candidates;
- introduction of new products or services offered by us or our competitors;
- clinical trial results for other product candidates that could compete with our product candidates;
- announcements of significant acquisitions, strategic partnerships, joint ventures or capital commitments by us or our competitors;
- our ability to effectively manage our growth;
- actual or anticipated variations in quarterly operating results;
- our cash position;
- our failure to meet the estimates and projections of the investment community or that we may otherwise provide to the public;
- publication of research reports about us or our industry, or product candidates in particular, or positive or negative recommendations or withdrawal of research coverage by securities analysts;
- changes in the market valuations of similar companies;
- overall performance of the equity markets;
- sales of our common stock by us or our stockholders in the future;
- trading volume of our common stock;
- changes in accounting practices;
- ineffectiveness of our internal controls;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- significant lawsuits, including patent or stockholder litigation;
- general political and economic conditions; and
- other events or factors, many of which are beyond our control.

In addition, the stock market in general, and the market for biopharmaceutical companies in particular, have experienced extreme price and volume fluctuations resulting from the COVID-19 pandemic or other macroeconomic factors and have

often been unrelated or disproportionate to the operating performance of these companies. Broad market and industry factors may negatively affect the market price of our common stock, regardless of our actual operating performance. If the market price of our common stock does not exceed a stockholder's purchase price, such stockholder may not realize any return on their investment in us and may lose some or all of their investment. In the past, securities class action litigation has often been instituted against companies following periods of volatility in the market price of a company's securities. This type of litigation, if instituted, could result in substantial costs and a diversion of management's attention and resources, which would harm our business, operating results or financial condition.

We incur significant costs as a result of operating as a public company, and our management is required to devote substantial time to new and existing compliance initiatives.

As a public company, we incur significant legal, accounting and other expenses. We are subject to the reporting requirements of the Exchange Act, which require, among other things, that we file, with the SEC, annual, quarterly and current reports with respect to our business and financial condition. In addition, the Sarbanes-Oxley Act, as well as rules subsequently adopted by the SEC and Nasdaq to implement provisions of the Sarbanes-Oxley Act, impose significant requirements on public companies, including requiring establishment and maintenance of effective disclosure and financial controls and changes in corporate governance practices. Further, in July 2010, the Dodd-Frank Wall Street Reform and Consumer Protection Act, or the Dodd-Frank Act, was enacted. There are significant corporate governance and executive compensation related provisions in the Dodd-Frank Act that require the SEC to adopt additional rules and regulations in these areas such as "say on pay" and proxy access.

We became a large accelerated filer on December 31, 2020, based on the market value of our common stock held by non-affiliates as of the last day of the second quarter in 2020. Accordingly, at such time we ceased to be eligible for the emerging growth company, or EGC, provisions of the JOBS Act, and we became subject to the requirements of the Dodd-Frank Act.

Stockholder activism, the current political environment and the current high level of government intervention and regulatory reform may lead to substantial new regulations and disclosure obligations, which may lead to additional compliance costs and impact the manner in which we operate our business in ways we cannot currently anticipate.

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.

If our existing stockholders sell, or indicate an intention to sell, substantial amounts of our common stock in the public market, the trading price of our common stock could decline. As of December 31, 2020, the Company had 48,819,591 shares of common stock outstanding, of which 686,868 shares are restricted share awards subject to future vesting. Lock up agreements covering an aggregate of 21,426,719 shares entered into by certain shareholders in connection with our recently completed follow-on public offering expired on January 5, 2021.

As of December 31, 2020, approximately 43.9% of our shares of common stock outstanding are held by directors, executive officers and other affiliates and will be subject to certain limitations of Rule 144 under the Securities Act.

In addition, shares of common stock that are either subject to outstanding options or reserved for future issuance under our existing equity compensation plans will become eligible for sale in the public market to the extent permitted by the provisions of various vesting schedules and Rule 144 and Rule 701 under the Securities Act. If these additional shares of common stock are sold, or if it is perceived that they will be sold, in the public market, the trading price of our common stock could decline. Additionally, the number of shares of our common stock reserved for issuance under the 2019 Stock Option and Equity Incentive Plan will automatically increase on January 1 of each year, with January 1, 2020 being the first of such increases and continuing through and including January 1, 2030, by 5% of the total number of shares of our capital stock outstanding on December 31 of the preceding calendar year, or a lesser number of shares determined by our board of directors. Unless our board of directors elects not to increase the number of shares available for future grant each year, our stockholders may experience additional dilution.

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

The trading market for our common stock will depend in part on the research and reports that securities or industry analysts publish about us or our business. If one or more of the analysts who covers us downgrades our stock or publishes inaccurate or unfavorable research about our business, our stock price may decline. If one or more of these analysts ceases coverage of our company or fails to publish reports on us regularly, demand for our stock could decrease, which might cause our stock price and trading volume to decline.

If we fail to maintain an effective system of internal control over financial reporting, we may not be able to accurately report our financial results or prevent fraud. As a result, stockholders could lose confidence in our financial and other public reporting, which would harm our business and the trading price of our common stock.

Effective internal controls over financial reporting are necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, are designed to prevent fraud. Any failure to implement required new or improved controls, or difficulties encountered in their implementation could cause us to fail to meet our reporting obligations. In addition, any testing by us conducted in connection with Section 404, or any subsequent testing by our independent registered public accounting firm, may reveal deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses or that may require prospective or retroactive changes to our financial statements or identify other areas for further attention or improvement. Inferior internal controls could also cause investors to lose confidence in our reported financial information, which could have a negative effect on the trading price of our stock.

We will be required to disclose changes made in our internal controls and procedures on a quarterly basis and our management will be required to assess the effectiveness of these controls annually.

As of December 31, 2020, we became a large accelerated filer based on the market value of our common stock held by non-affiliates as of the last day of the second quarter in 2020 and no longer qualify as an EGC. Accordingly, our independent registered public accounting firm is required to attest to the effectiveness of our internal controls over financial reporting pursuant to Section 404. An independent assessment of the effectiveness of our internal controls over financial reporting could detect problems that our management’s assessment did not, and could lead to additional findings, potentially including material weaknesses. Material weaknesses in our internal controls over financial reporting could lead to restatements of our financial statements and require us to incur the expense of remediation.

Our disclosure controls and procedures may not prevent or detect all errors or acts of fraud.

We are subject to certain reporting requirements of the Exchange Act. Our disclosure controls and procedures are designed to reasonably assure that information required to be disclosed by us in reports we file or submit under the Exchange Act is accumulated and communicated to management, recorded, processed, summarized and reported within the time periods specified in the rules and forms of the SEC. We believe that any disclosure controls and procedures or internal controls and procedures, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. These inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people or by an unauthorized override of the controls. Accordingly, because of the inherent limitations in our control system, misstatements or insufficient disclosures due to error or fraud may occur and not be detected.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Our headquarters are based in Stamford, Connecticut, where we have leased approximately 24,000 square feet of office space under a lease that expires in November 2022. Our development operations are based in Durham, North Carolina, where we have leased approximately 10,350 square feet of office space under a lease that expires in 2023, with two five-year renewal options. We believe that our office spaces are sufficient for our current needs.

Item 3. Legal Proceedings

We are not currently a party to any material legal proceedings.

Item 4. Mine Safety Disclosures

None.

PART II

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

Market Information

Our Common Stock has been listed on The NASDAQ Global Select Market under the symbol "SWTX" since September 13, 2019. Prior to that date, there was no public trading market for our common stock.

Holders of our Common Stock

As of February 18, 2021, there were approximately 21 shareholders of record of our Common Stock.

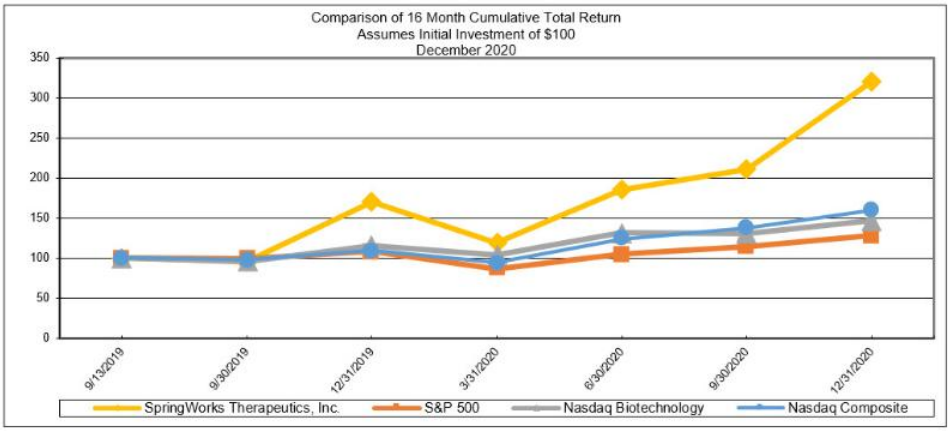
Dividend Policy

We have never paid cash dividends on our Common Stock and do not anticipate paying any in the foreseeable future.

Stock Performance Graph

This performance graph shall not be deemed "filed" for purposes of Section 18 of the Exchange Act, or incorporated by reference into any of our filings under the Securities Act or the Exchange Act, except as shall be expressly set forth by specific reference in such filing.

The following graph shows the value of an investment of $100 from September 13, 2019, or the date our common stock commenced trading on The Nasdaq Global Select Market, through December 31, 2020, in our common stock, the Standard & Poor's 500 Index (S&P 500), the Nasdaq Biotechnology Index, and Nasdaq Composite Index. The historical stock price performance of our common stock shown in the performance graph is not necessarily indicative of future stock price performance.



	Cumulative Total Return date ended						
	9/13/2019	9/30/2019	12/31/2019	3/31/2020	6/30/2020	9/30/2020	12/31/2020
SpringWorks Therapeutics, Inc.	100	95.80	170.08	119.31	185.59	210.65	320.46
S&P 500	100	99.03	108.01	86.84	104.68	114.03	127.88
Nasdaq Biotechnology	100	95.49	115.76	103.86	131.81	130.72	146.34
Nasdaq Composite	100	97.86	110.06	94.70	124.00	137.94	159.49

Equity Compensation Plans

The information required by Item 5 of Form 10-K regarding equity compensation plans is incorporated herein by reference to Item 12 of Part III of this Annual Report on Form 10-K.

Recent Sales of Unregistered Securities

The information required by Item 701 of Regulation S-K was previously included in the Quarterly Report on Form 10-Q filed on November 12, 2020.

Purchase of Equity Securities

None.

Use of Proceeds from our Public Offering of Common Stock

On September 17, 2019, we completed the initial public offering of our common stock pursuant to which we issued and sold 10,350,000 shares of our common stock at a price to the public of $18.00 per share.

The offer and sale of all of the shares of our common stock in our IPO were registered under the Securities Act pursuant to a registration statement on Form S-1, as amended (File No. 333-233351), which was declared effective by the SEC on September 12, 2019. Following the sale of all of the shares offered in connection with the closing of our IPO, the offering terminated. J.P. Morgan Securities LLC, Goldman Sachs & Co. LLC and Cowen and Company, LLC acted as joint book-running managers of our IPO.

We received aggregate gross proceeds from our IPO of $186.3 million, or aggregate net proceeds of $169.7 million after deducting underwriting discounts and commissions and other offering costs. None of the underwriting discounts and commissions or offering expenses were incurred or paid, directly or indirectly, to any of our directors or officers or their associates or to persons owning 10% or more of our common stock or to any of our affiliates.

On October 13, 2020, the Company completed the sale of 5,637,254 shares of common stock in an underwritten public offering, including 735,294 shares of common stock sold pursuant to the underwriter's full exercise of their option to purchase additional shares, at an offering price of $51.00 per share, resulting in net proceeds to the Company of $269.5 million.

There has been no material change in our planned use of the net proceeds from the aforementioned follow-on offering as described in our final prospectus filed pursuant to Rule 424(b)(5) under the Securities Act with the SEC on October 8, 2020.

Item 6. Selected Financial Data

Not applicable.

Item 7. Management's discussion and analysis of financial conditions and results of operations

You should read the following discussion and analysis of our financial condition and results of operations together with the section titled "Selected financial data" and the consolidated financial statements and related notes included elsewhere in this Annual Report on Form 10-K, or Annual Report. Unless the context otherwise requires, all references to "we," "us," "our," or the "Company" refer to SpringWorks Therapeutics, Inc., together with its subsidiaries. This discussion contains forward-looking statements based upon current expectations that involve risks and uncertainties. Our actual results may differ materially from those anticipated in these forward-looking statements as a result of various factors, including those identified below and those discussed in the section titled "Risk factors" and in other parts of this Annual Report.

Overview

We are a clinical-stage biopharmaceutical company applying a precision medicine approach to acquiring, developing and commercializing life-changing medicines for underserved patient populations suffering from devastating rare diseases and cancer. We have a differentiated portfolio of small molecule targeted oncology product candidates and are advancing two potentially registrational clinical trials in rare tumor types, as well as several other programs addressing highly prevalent, genetically defined cancers. Our strategic approach and operational excellence in clinical development have enabled us to rapidly advance our two lead product candidates into late-stage clinical trials while simultaneously entering into multiple shared-value partnerships with industry leaders to expand our portfolio. From this foundation, we are continuing to build a differentiated global biopharmaceutical company intensely focused on understanding patients and their diseases in order to develop transformative targeted medicines.

As described in Part I, Item 1. "Business," we currently have three product candidates in clinical development. Refer to Part I, Item 1. "Business" for a summary of our clinical programs.

On October 13, 2020, we completed the sale of 5,637,254 shares of common stock in an underwritten public offering, including 735,294 shares of common stock sold pursuant to the underwriter's full exercise of their option to purchase additional shares, at an offering price of $51.00 per share, resulting in net proceeds to us of $269.5 million.

On September 12, 2019, we completed the initial public offering, or IPO, of our common stock. In connection with the IPO, we issued and sold 10,350,000 shares of our common stock at a price to the public of $18.00 per share. The net proceeds from the IPO were approximately $169.7 million after deducting underwriting discounts and commissions of $13.0 million and offering expenses of approximately $3.5 million.

At the closing of the IPO, 196,076,779 shares of outstanding convertible preferred stock were automatically converted into 29,794,359 shares of common stock at a conversion rate of one-for-6.5810. Following the IPO, there were no shares of preferred stock outstanding.

We were originally formed as SpringWorks Therapeutics, LLC, a Delaware limited liability company in August 2017. Concurrent with our formation, we acquired exclusive worldwide licenses to nirogacestat and mirdametinib from Pfizer Inc., or Pfizer. From our inception to March 29, 2019, we conducted our business through SpringWorks Therapeutics, LLC and were treated as a partnership for income tax purposes. Pursuant to the terms of a corporate reorganization that was completed on March 29, 2019, all of the equity interests in SpringWorks Therapeutics, LLC were exchanged for the same number and class of newly issued securities of SpringWorks Therapeutics, Inc., and, as a result, SpringWorks Therapeutics, LLC became a wholly owned subsidiary of SpringWorks Therapeutics, Inc. Following the Reorganization, we now conduct our business as SpringWorks Therapeutics, Inc.

Since our inception in August 2017, we have devoted substantially all of our resources to conducting research and development activities for our product candidates, executing our business development strategy, building our intellectual

property portfolio, organizing and staffing our company, business planning, raising capital and providing general and administrative support for these activities.

To date, we have derived all of our revenue from the nonrefundable upfront payment we received under the asset purchase and license agreement with Jazz Pharmaceuticals Ireland Limited, or Jazz. We do not have any products approved for commercial sale or sources of recurring revenue. We had cash, cash equivalents and available-for-sale marketable securities of $561.8 million and $327.7 million as of December 31, 2020 and December 31, 2019, respectively. Since inception, we have funded our operations primarily with net proceeds of $102.3 million from the sale of our Series A convertible preferred units prior to the Reorganization, $124.6 million in net proceeds from the sale of our Series B convertible preferred stock following the Reorganization, net proceeds of $169.7 from our IPO in September 2019 and net proceeds of $269.5 million from our follow-on financing in October 2020. We believe that our cash, cash equivalents and marketable securities will enable us to fund our operational expenses and capital expenditure requirements through at least 2022.

Since inception, we have incurred significant operating losses. Our net losses were $45.6 million, $58.3 million, and $17.8 million for the years ended December 31, 2020, December 31, 2019, and December 31, 2018, respectively. We had an accumulated deficit of $118.6 million and $73.0 million as of December 31, 2020 and December 31, 2019, respectively. We expect to continue to incur significant expenses and operating losses for the foreseeable future. In addition, we anticipate that our expenses will increase significantly in connection with our ongoing activities, as we:

- advance our product candidates through clinical development, including our ongoing potentially registrational Phase 3 clinical trial for nirogacestat and ongoing potentially registrational Phase 2b clinical trial for mirdametinib;
- advance our other preclinical and clinical development programs, including our combination therapies, into and through clinical development;
- seek regulatory approvals for any product candidates that successfully complete clinical trials;
- increase the amount of research and development activities to identify, acquire and develop product candidates;
- hire additional clinical, quality control, medical, scientific and other technical personnel;
- expand our operational, financial and management systems and increase personnel, including personnel to support our clinical development, manufacturing, business development and commercialization efforts and our operations as a public company;
- maintain, expand and protect our intellectual property portfolio;
- complete commercial-scale outsourced manufacturing activities;
- establish sales, marketing and distribution capabilities for any product candidates for which we may receive regulatory approval in regions where we choose to commercialize our products on our own or jointly with third parties; and
- invest in or in-license other technologies or product candidates.

We will not generate revenue from product sales unless and until we successfully complete clinical development and obtain regulatory approval for our product candidates. In addition, if we obtain regulatory approval for nirogacestat or mirdametinib, we expect to incur significant expenses related to developing our commercialization capabilities to support product sales, marketing and distribution activities, either alone or in collaboration with others.

Our license and collaboration agreements

Pfizer license agreements

In August 2017, we entered into a license agreement, or the Nirogacestat License Agreement, with Pfizer pursuant to which we acquired exclusive worldwide rights to nirogacestat. We subsequently amended the Nirogacestat License Agreement in July of 2019 with regard to certain provisions relating to intellectual property. Pursuant to the Nirogacestat License Agreement, as amended, we are required to pay Pfizer payments of up to an aggregate of $232.5 million upon achievement of certain commercial milestone events. We will pay Pfizer tiered royalties on sales of nirogacestat at percentages ranging from the mid-single digits to the low 20s, which may be subject to deductions for expiration of valid claims, amounts due under third-party licenses and generic competition.

In August 2017, we entered into a license agreement, or the Mirdametinib License Agreement, with Pfizer (collectively with the Nirogacestat License Agreement referred to as the "Pfizer License Agreements") pursuant to which we acquired exclusive worldwide rights to mirdametinib. We subsequently amended the Mirdametinib License Agreement in August of 2019 with regard to certain provisions relating to intellectual property. Pursuant to the Mirdametinib License Agreement, as amended, we are required to pay Pfizer up to an aggregate of $229.8 million upon achievement of certain commercial milestone events. We will pay Pfizer tiered royalties on sales of mirdametinib at percentages ranging from the mid-single digits to the low 20s, which may be subject to deductions for expiration of valid claims, amounts due under third-party licenses and generic competition.

In connection with entering into the Pfizer License Agreements, we issued an aggregate of 6,437,500 Junior Series A convertible preferred units to Pfizer, which units were converted into 6,437,500 shares of our Junior Series A convertible preferred stock pursuant to the Reorganization. At the closing of the IPO, the Junior Series A shares were automatically converted into shares of common stock at a conversion rate of 6.5810-for-one (or 978,194 common shares). As of December 31, 2020, we had not made any milestone or royalty payments under the Pfizer License Agreements.

BeiGene clinical collaboration agreement

In August 2018, we entered into a clinical collaboration agreement with BeiGene, Ltd., or BeiGene, to evaluate the safety, tolerability and preliminary efficacy of combining lifirafenib and mirdametinib, in a Phase 1b clinical trial for patients with advanced or refractory solid tumors. Each party will be solely responsible for its costs associated with manufacturing and supply of its compound for the clinical trial. We and BeiGene will share equally the other costs associated with the clinical trial.

GSK clinical trial collaboration and supply agreement

In June 2019, we entered into a clinical trial collaboration and supply agreement with GlaxoSmithKline, or GSK, to evaluate nirogacestat in combination with belantamab mafodotin in patients with relapsed or refractory multiple myeloma, in an adaptive Phase 1b clinical trial. GSK will be responsible for the conduct and expenses of the collaboration, which will be governed by a joint development committee with equal representation from each party.

Allogene clinical trial collaboration and supply agreement

In January 2020, we entered into a clinical trial collaboration and supply agreement with Allogene Therapeutics, Inc., or Allogene, to evaluate nirogacestat in combination with ALLO-715, Allogene's investigational allogeneic B-cell maturation antigen, or BCMA, targeted chimeric antigen receptor, or CAR, T cell product, in patients with relapsed or refractory multiple myeloma. Allogene is responsible for administering the Phase 1 clinical trial and is responsible for all costs associated with the direct conduct of the clinical trial, other than the manufacture and supply of nirogacestat and certain expenses related to intellectual property rights. The collaboration is managed by a joint development committee with equal representation by us and Allogene.

Janssen clinical collaboration agreement

In September 2020, we entered into a clinical collaboration and supply agreement with Janssen Biotech, Inc., or Janssen, to evaluate our investigational gamma secretase inhibitor, or GSI, nirogacestat, in combination with Janssen's bispecific antibody targeting BCMA, and CD3, teclistamab, in patients with relapsed or refractory multiple myeloma. Janssen is responsible for administering the Phase 1 clinical trial and is responsible for all costs associated with the direct conduct of the clinical trial, other than the manufacture and supply of nirogacestat and certain expenses related to intellectual property rights. The collaboration is managed by a joint oversight committee of equal representation by us and Janssen.

Precision BioSciences clinical collaboration agreement

In September 2020, we entered into a clinical trial collaboration agreement with Precision BioSciences, Inc., or Precision, to evaluate nirogacestat in combination with PBCAR269A, an investigational allogeneic CAR-T cell therapy candidate targeting BCMA, in patients with relapsed or refractory multiple myeloma. Precision is responsible for administering the Phase 1/2a clinical trial and is responsible for all costs associated with the direct conduct of the clinical trial, other than the manufacture and supply of nirogacestat and certain expenses related to intellectual property rights. The collaboration is managed by a joint steering committee of equal representation by us and Precision.

Pfizer clinical collaboration agreement

In October 2020, we entered into a clinical trial collaboration and supply agreement with Pfizer, to evaluate nirogacestat in combination with Pfizer's bispecific antibody targeting BCMA and CD3, elranatamab, in patients with relapsed or refractory multiple myeloma. Pfizer is responsible for administering the Phase 1b/2 clinical trial and is responsible for all costs associated with the direct conduct of the clinical trial, other than the manufacture and supply of nirogacestat and certain expenses related to intellectual property rights. The collaboration is managed by a joint development committee of equal representation by us and Pfizer.

Jazz Pharmaceuticals asset purchase and exclusive license agreement

In October 2020, we and Jazz announced an asset purchase and exclusive license agreement, pursuant to which Jazz acquired our fatty acid amide hydrolase, or FAAH, inhibitor program including PF-04457845. Jazz made an upfront payment of $35 million to us with potential future payments of up to $375 million based upon the achievement of certain clinical development, regulatory, and commercial milestones. In addition, Jazz is obligated to pay us sales-based royalties on future net sales of PF-04457845.

See "Business—License and collaboration agreements" for more information on our license and collaboration agreements.

COVID-19 Impact

In December 2019, a novel strain of the coronavirus disease, severe acute respiratory syndrome coronavirus 2, or SARS-CoV-2, COVID-19, was identified in Wuhan, China. This virus disease resulting from COVID-19 has now become a global pandemic. Since the onset of COVID-19, we have undertaken a number of business continuity measures to mitigate potential disruption to our operations and preserve the integrity of our research and development programs. As of the date of this report we have not experienced any material disruptions to the execution of the research and development activities that we currently have underway, however, as a result of the pandemic we may experience disruptions that could impact our research and development timelines and outcomes. We are continuing to evaluate the impact of the COVID-19 pandemic on our business.

Based on our cash, cash equivalents and marketable securities balance at December 30, 2020, of $561.8 million, management estimates that its current liquidity position will enable it to meet operating expenses. For further details on our liquidity position, see the "Results of Operations" section.

Components of our results of operations

Revenue

To date, we have derived all of our revenue from the nonrefundable upfront payment we received under the Jazz asset purchase and license agreement. We have not generated, and do not expect to generate, any commercial revenue from the sale of products in the near future, if at all. If our development efforts for our current product candidates or additional product candidates that we may develop in the future are successful and can be commercialized, we may generate revenue in the future from product sales. We do not have any sources of recurring revenue. We may enter into collaboration and license agreements from time to time that provide for certain payments due to us. Accordingly, we may generate revenue from such collaboration or license agreements in the future.

Research and development expenses

Our research and development expenses consist of expenses incurred in connection with the development of our product candidates. These expenses include:

- employee-related expenses, which include salaries, benefits and stock-based compensation for our research and development personnel;
- fees paid to consultants for services directly related to our research and development programs;
- expenses incurred under agreements with third-party contract research organizations, or CROs, investigative clinical trial sites, academic institutions and consultants that conduct research and development activities on our behalf or in collaboration with us;
- costs associated with preclinical studies and clinical trials;
- costs associated with the manufacture of drug substance and finished drug product for preclinical testing and clinical trials;
- costs associated with technology and intellectual property licenses; and
- an allocated portion of facilities and facility-related costs, which include expenses for rent and other facility-related costs and other supplies.

Expenditures for clinical development, including upfront licensing fees and milestone payments associated with our product candidates, are charged to research and development expense as incurred. These expenses consist of expenses incurred in performing development activities, including salaries and benefits, materials and supplies, preclinical expenses, clinical trial and related clinical manufacturing expenses, depreciation of equipment, contract services and other outside expenses. Costs for certain development activities, such as manufacturing and clinical trials, are recognized based on an evaluation of the progress to completion of specific tasks using either time-based measures or data such as information provided to us by our vendors on their actual costs incurred.

We expect our research and development expenses to increase substantially for the foreseeable future as we continue to invest in activities related to developing our product candidates and our preclinical programs, and as certain product candidates advance into later stages of development, including our ongoing potentially registrational Phase 3 clinical trial for nirogacestat, or the DeFi trial, and our ongoing potentially registrational Phase 2b clinical trial for mirdametinib, or the ReNeu trial. The process of conducting the necessary clinical trials to obtain regulatory approval is costly and time-consuming, and the successful development of our product candidates is highly uncertain. As a result, we are unable to determine the duration and completion costs of our research and development projects or when and to what extent we will generate revenue from the commercialization and sale of any of our product candidates.

General and administrative expenses

General and administrative expenses consist primarily of salaries and related costs, including stock-based compensation, for personnel in 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 administrative consulting services; insurance costs; administrative 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 anticipate that our general and administrative expenses will increase in the future as we increase our headcount to support our continued development of our product candidates. We also anticipate that we will incur increased accounting, audit, legal, regulatory, compliance and director and officer insurance costs as well as investor and public relations expenses associated with being a public company.

Other income

Other income consists primarily of interest income. Interest income consists of interest earned on our cash, cash equivalents and available-for-sale marketable securities.

Income taxes

Income taxes are accounted for using the asset-and-liability method. Deferred tax assets and liabilities are recognized for the future tax consequences attributable to differences between the financial statement carrying amounts of existing assets and liabilities and their respective tax basis and operating loss and tax credit carryforwards. Deferred tax assets and liabilities are measured using enacted tax rates expected to apply to taxable income in the years in which those temporary differences are expected to be recovered or settled. The effect on deferred tax assets and liabilities of a change in tax rates is recognized as income in the period that includes the enactment date. Changes in deferred tax assets and liabilities are recorded in the provision for income taxes.

We recognize deferred tax assets to the extent that we believe that these assets are more likely than not to be realized. In making such a determination, management considers all available positive and negative evidence, including future reversals of existing taxable temporary differences, projected future taxable income, tax-planning strategies and results of recent operations. Valuation allowances are provided, if based upon the weight of available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized. If management determines that we would be able to realize our deferred tax assets in the future in excess of our net recorded amount, management would make an adjustment to the deferred tax asset valuation allowance, which would reduce the provision for income taxes.

We record uncertain tax positions in accordance with Accounting Standards Codification, or ASC, Topic 740 on the basis of a two-step process in which (1) management determines whether it is more likely than not that the tax positions will be sustained on the basis of the technical merits of the position and (2) for those tax positions that meet the more-likely-than-not recognition threshold, management recognizes the largest amount of tax benefit that is more than 50% likely to be realized upon ultimate settlement with the related tax authority.

We provide reserves for potential payments of tax to various tax authorities related to uncertain tax positions. These reserves are based on a determination of whether and how much of a tax benefit taken by us in its filings or positions is more likely than not to be realized following resolution of any potential contingencies related to the tax benefit. Potential interest related to the underpayment of income taxes will be classified as a component of income tax expense and any related penalties will be classified in income tax expenses in the statement of operations.

SpringWorks Therapeutics, LLC elected to be treated under the partnership provisions of the Internal Revenue Service Code prior to the reorganization in March 29, 2019. However, its five wholly owned subsidiaries, SpringWorks Operating Company, SpringWorks Subsidiary 1, SpringWorks Subsidiary 2, SpringWorks Subsidiary 3, and SpringWorks Subsidiary 4, or the Combined Subsidiaries, are taxable corporations.

Subsequent to the Reorganization, SpringWorks Therapeutics, Inc. became the 100% owner of SpringWorks Therapeutics, LLC, creating a new ultimate parent company, and a consolidated group for income tax reporting. The Reorganization and change in tax status of the reporting entity did not have an impact on the consolidated tax provision.

As of December 31, 2020, we have federal, state and city net operating loss carryforwards of $110.9 million, $0.6 million and $3.7 million, respectively, which are available to reduce future taxable income. Federal net operating loss

carryforwards of $34.8 million, $55.9 million and $16.0 million reported in 2020, 2019 and 2018, will be available to offset 80% of taxable income for an indefinite period of time, until fully utilized. Federal net operating loss carryforwards of $4.3 million reported in 2017 and the state and city net operating loss carryforwards expire at various dates through 2038. We also have federal tax credits of $7.2 million, which may be used to offset future tax liabilities. These tax credit carryforwards will expire at various dates beginning in 2038.

Results of operations

Comparison of the Years Ended December 31, 2020 and December 31, 2019

The following table summarizes our results of operations for the years ended December 31, 2020 and December 31, 2019.

(in thousands)	Year Ended December 31, 2020	2019	$ Change	% Change
License revenue	$ 35,000	$ —	$ 35,000	100 %
Operating expenses:				
Research and development	51,859	42,545	9,314	22 %
General and administrative	29,465	16,694	12,771	77 %
Total operating expenses	81,324	59,239	22,085	37 %
Loss from operations	(46,324)	(59,239)	12,915	(22)%
Other income:				
Interest income, net	1,330	3,547	(2,217)	(63)%
Other income	25	—	25	100 %
Total other income, net	1,355	3,547	(2,192)	(62)%
Equity investment loss	(605)	(2,614)	2,009	(77)%
Net loss	$ (45,574)	$ (58,306)	$ 12,732	(22)%

Revenue

Revenue of $35 million for the year ended December 31, 2020 was attributable to the nonrefundable upfront payment from Jazz in October 2020 related to the asset purchase and exclusive license agreement between us and Jazz.

Research and development expenses

Research and development expense increased by $9.3 million to $51.9 million for the year ended December 31, 2020 from $42.5 million for the year ended December 31, 2019, an increase of 22%.

The increase in research and development expense was attributable to a $6.0 million increase in internal costs driven by the growth in employee costs associated with increases in the number of personnel and an increase in non-cash share-based compensation expense. In addition, research and development expense included a $2.4 million increase in external costs related to drug manufacturing and trial costs, and a $0.9 million increase in facility-related, and other miscellaneous department expenses.

A significant portion of our research and development expenses are external costs, which we track on a program-by-program basis after a clinical product candidate has been identified. Other research and development expenses include internal research and development costs, such as compensation related costs for our research and development employees, as well as depreciation and other indirect costs, which we do not track on a program-by-program basis, as we deploy our internal resources across multiple projects under development.

Our research and development expenses are summarized in the table below:

(in thousands)	Year Ended December 31, 2020	2019	$ Change
Personnel-related	$ 15,900	$ 9,814	$ 6,086
Trial and drug manufacturing	31,766	29,415	2,351
Facility-related and other	4,193	3,316	877
Total research and development expenses	$ 51,859	$ 42,545	$ 9,314

General and administrative expenses

General and administrative expenses were $29.5 million and $16.7 million for the years ended December 31, 2020 and December 31, 2019, respectively, as follows:

(in thousands)	Year Ended December 31, 2020	2019	Change
Personnel-related	$ 16,476	$ 8,745	$ 7,731
Professional and consulting fees	10,437	6,061	4,376
Facility-related and other	2,552	1,888	664
Total general and administrative expenses	$ 29,465	$ 16,694	$ 12,771

The increase in general and administrative expense was primarily attributable to the hiring of additional personnel in our general and administrative functions, as we continued to expand our operations to support the organization, and an increase in non-cash share-based compensation expense. In addition, general and administrative expense included an increase of $4.4 million in consulting and professional services, including legal, regulatory and compliance.

Other income

The decrease in other income is driven by a decrease in interest income, net, during the year ended December 31, 2020 as compared to the year ended December 31, 2019. This decrease was attributable to a significant decline in interest rates as a result of the economic impact of the COVID-19 pandemic, which drove a lower return on cash, cash equivalents and marketable securities during the year ended December 31, 2020.

Comparison of the Years Ended December 31, 2019 and December 31, 2018

The following table summarizes our results of operations for the years ended December 31, 2019 and December 31, 2018.

(in thousands)	Year Ended December 31, 2019	2018	$ Change	% Change
Operating expenses:				
Research and development	$ 42,545	$ 9,898	$ 32,647	330 %
General and administrative	16,694	8,593	8,101	94 %
Total operating expenses	59,239	18,491	40,748	220 %
Loss from operations	(59,239)	(18,491)	(40,748)	220 %
Other income:				
Interest income, net	3,547	678	2,869	423 %
Total other income, net	3,547	678	2,869	423 %
Equity investment loss	(2,614)	—	(2,614)	100 %
Net loss	$ (58,306)	$ (17,813)	$ (40,493)	227 %

Research and development expenses

Research and development expense increased by $32.6 million to $42.5 million for the year ended December 31, 2019 from $9.9 million for the year ended December 31, 2018, an increase of 330%.

The increase in research and development expense was attributable to a $25.2 million increase in external costs related to drug manufacturing and trial costs. In addition, research and development expense included a $6.7 million increase in internal costs driven by the growth in employee costs associated with increases in the number of personnel and an increase in non-cash share-based compensation expense.

A significant portion of our research and development expenses are external costs, which we track on a program-by-program basis after a clinical product candidate has been identified. Other research and development expenses include internal research and development costs, such as compensation related costs for our research and development employees, as well as depreciation and other indirect costs, which we do not track on a program-by-program basis, as we deploy our internal resources across multiple projects under development.

These external and internal research and development expenses are summarized by program in the table below:

	Year Ended December 31,		
(in thousands)	**2019**	**2018**	**$ Change**
Personnel-related	$ 9,814	$ 3,135	$ 6,679
Trial and drug manufacturing	29,415	4,171	25,244
Facility-related and other	3,316	2,592	724
Total research and development expenses	$ 42,545	$ 9,898	$ 32,647

General and administrative expenses

General and administrative expenses were $16.7 million and $8.6 million for the years ended December 31, 2020 and December 31, 2019, respectively, as follows:

	Year Ended December 31,		
(in thousands)	**2019**	**2018**	**Change**
Personnel-related	$ 8,745	$ 4,551	$ 4,194
Professional and consulting fees	6,061	3,235	2,826
Facility-related and other	1,888	807	1,081
Total general and administrative expenses	$ 16,694	$ 8,593	$ 8,101

The increase in personnel-related costs of $4.2 million was driven by a $2.7 million increase due to the hiring of additional personnel in our general and administrative functions as we continued to expand our operations to support the organization as well as a $1.5 million increase in non-cash share-based compensation expense. The increase in professional and consulting fees of $2.8 million was primarily due to consulting fees for market research and commercial planning efforts.

Other income

The increase in other income was driven by an increase in interest income, net, during the year ended December 31, 2019 as compared to the year ended December 31, 2018. This increase was attributable to the higher cash balances in 2019 as compared to 2018.

Liquidity and capital resources

Sources of Liquidity

We have incurred operating losses and experienced negative operating cash flows since our inception and anticipate that we will continue to incur losses for at least the foreseeable future. Our net loss was $45.6 million and $58.3 million for the year ended December 31, 2020 and 2019, respectively. We had an accumulated deficit of $118.6 million and $73.0 million at December 31, 2020 and December 31, 2019, respectively. Based on our cash, cash equivalents and marketable securities balances at December 31, 2020, management estimates that our liquidity position will enable it to meet operating expenses through at least twelve months after the date that this Annual Report is filed. Our marketable securities consist of high-quality, highly liquid available-for-sale debt securities including corporate debt securities, U.S. government securities and commercial paper.

Funding requirements

Our primary use of cash is to fund operating expenses, primarily research and development expenditures. Cash used to fund operating expenses is impacted by the timing of when we pay these expenses, as reflected in the change in our outstanding accounts payable, accrued expenses and prepaid expenses.

We believe that our cash, cash equivalents and marketable securities balance as of December 31, 2020, will be sufficient to fund our operating expenses and capital expenditure requirements through at least 2022. We have based this estimate on assumptions that may prove to be wrong, and we could utilize our available capital resources sooner than we currently expect.

Our future funding requirements will depend on many factors, including the following:

- the initiation, progress, timing, costs and results of preclinical studies and clinical trials for our product candidates, including the DeFi trial and the ReNeu trial;
- the clinical development plans we establish for these product candidates;
- the number and characteristics of product candidates that we develop;
- the outcome, timing and cost of meeting regulatory requirements established by the U.S. Food and Drug Administration, or FDA, European Medicines Agency, or EMA, and other comparable foreign regulatory authorities;
- the terms of our existing and any future license or collaboration agreements we may choose to enter into, including the amount of upfront, milestone and royalty obligations;
- the other costs associated with in-licensing new technologies, such as any increased costs of research and development and personnel;
- the cost of filing, prosecuting, defending and enforcing our patent claims and other intellectual property rights;
- the cost of defending intellectual property disputes, including patent infringement actions brought by third parties against us or our product candidates;
- the effect of competing technological and market developments;
- the cost and timing of completion of commercial-scale outsourced manufacturing activities;
- the cost of establishing sales, marketing and distribution capabilities for any product candidates for which we may receive regulatory approval in regions where we choose to commercialize our products on our own; and
- the degree of commercial success achieved following the successful completion of development and regulatory approval activities for a product candidate.

We will need additional funds to meet operational needs and capital requirements for clinical trials, other research and development expenditures, and business development activities. Because of the numerous risks and uncertainties associated with the development and commercialization of our product candidates, we are unable to estimate the amounts of increased capital outlays and operating expenditures associated with our current and anticipated clinical studies.

Until such time, if ever, as we can generate substantial product revenue, we expect to finance our operations through a combination of equity offerings, debt financings, collaborations, strategic alliances and marketing, distribution or licensing arrangements. To the extent that we raise additional capital through the sale of equity or convertible debt securities, current ownership interests will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect rights of common stockholders. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making acquisitions or capital expenditures or declaring dividends. If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or drug 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 other arrangements when needed, we may be required to delay, limit, reduce or terminate our research, product development or future commercialization efforts, or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Cash flows

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

	Year Ended December 31,		
(in thousands)	**2020**	**2019**	**2018**
Net cash used in operating activities	$ (32,191)	$ (47,444)	$ (14,166)
Net cash used in investing activities	(418,832)	(4,260)	(293)
Net cash provided by financing activities	270,485	333,708	50,376
Net increase in cash and cash equivalents	$ (180,538)	$ 282,004	$ 35,917

Cash flows used in operating activities

Net cash used in operating activities was $32.2 million, $47.5 million, and $14.2 million for the years ended December 31, 2020, December 31, 2019, and December 31, 2018, respectively.

Net cash used in operating activities for the year ended December 31, 2020, was primarily due to our net loss for the year of $45.6 million, adjusted by non-cash charges of $12.0 million and a net change of $1.3 million in our net operating assets and liabilities. The non-cash charges primarily consisted of $10.0 million for equity-based compensation expense, $1.0 million for non-cash operating lease expense amortization and $0.6 million for the equity investment loss associated with our investment in MapKure. The change in our net operating assets and liabilities was primarily due to a net increase of $4.6 million in accounts payable and accrued expenses, partially offset by a $2.0 million increase in prepaid expenses and other non-current assets, and a $1.4 million decrease in the lease liability, driven by cash payments for operating leases.

Net cash used in operating activities for the year ended December 31, 2019, was primarily due to our net loss for the year of $58.3 million, adjusted by non-cash charges of $5.9 million and a net change of $4.9 million in our net operating assets and liabilities. The non-cash charges primarily consisted of $3.1 million for equity-based compensation expense and the equity investment loss associated with our investment in MapKure of $2.6 million. The change in our net operating assets and liabilities was primarily due to an increase of $8.3 million in accounts payable and accrued expenses, partially offset by a $3.0 million increase of prepaid expenses and other non-current assets.

Net cash used in operating activities for the year ended December 31, 2018, was primarily due to our net loss for the year of $17.8 million, adjusted by non-cash charges of $1.1 million and a net change of $2.6 million in our net operating assets and liabilities. The non-cash charges primarily consisted of $1.1 million for equity-based compensation expense. The change in our net operating assets and liabilities was primarily due to an increase of $2.7 million in accounts payable and accrued expenses and a $1.5 million increase in deferred rent, partially offset by a $1.6 million increase of prepaid expenses and other non-current assets.

Cash flows from investing activities

Net cash used in investing activities was $418.8 million for the year ended December 31, 2020, related to the purchase of available-for-sale debt securities of $442.7 million, our June 2020 investment in MapKure of $3.5 million and capital expenditures of $0.6 million, offset by the proceeds from the sale and maturity of available-for-sale debt securities of $28.0 million. Net cash used in investing activities was $4.3 million for the year ended December 31, 2019, primarily related to the $3.6 million investment in MapKure and $0.7 million related to capital expenditures. Net cash used in investing activities was $0.3 million, for the year ended December 31, 2018, related to capital expenditures.

Cash flows provided by financing activities

Net cash provided by financing activities was $270.5 million for the year ended December 31, 2020 and consisted of proceeds from issuance of common stock, net of issuance costs of $269.6 million as well as stock option exercises of $0.9 million. Net cash provided by financing activities was $333.7 million for the year ended December 31, 2019 and $50.4 million for the year ended December 31, 2018. Net cash provided by financing activities for the year ended December 31, 2019 consisted primarily of proceeds from Series A and B convertible preferred shares and the IPO. Net cash provided by financing activities for the year ended December 31, 2018 consisted primarily of proceeds from Series A convertible preferred shares.

Contractual obligations and other commitments

We enter into contracts in the normal course of business for clinical trials, preclinical studies, manufacturing and other services and products for operating purposes. These contracts generally provide for termination following a certain period after notice and therefore we believe that our non-cancelable obligations under these agreements are not material.

We have not recorded any reserves for uncertain tax positions as of December 31, 2020.

Off-balance sheet arrangements

We do not currently have, any off-balance sheet arrangements, as defined under applicable SEC rules.

Critical accounting policies and estimates

This management’s discussion and analysis of our financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with accounting principles generally accepted in the United States. The preparation of these consolidated financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the consolidated financial statements, as well as the reported expenses incurred during the reporting periods. Our estimates are based on our historical experience and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in more detail in Note 3 to our consolidated financial statements appearing elsewhere in this Annual Report, we believe that the following accounting policies are those most critical to the judgments and estimates used in the preparation of our consolidated financial statements.

Revenue

We recognize revenue for consideration received related to the development and commercialization of medicines, which is conducted through various means, including in-house development by the Company, joint development or collaboration agreements with third parties, sale or out licensing of product rights, and others. The terms of these arrangements and agreements may contain multiple promised goods and services, which may include licenses, know-

how, drug product, related agreements and other deliverables. Payments to us under these arrangements may include one or more of the following: upfront license fees; milestone payments; and royalties on future product sales.

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

We recognize revenue in accordance with ASC 606, which applies to all contracts with customers, except for contracts that are within the scope of other standards, such as collaboration arrangements and leases.

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

Once a contract is determined to be within the scope of ASC 606, we assess the goods or services promised within the contract and determine those that are performance obligations.

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

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

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

Licenses of intellectual property: The terms of our license agreements include the license of functional intellectual property, given the functionality of the intellectual property is not expected to change substantially as a result of our ongoing activities. For licenses that are bundled with other promises (that is, for licenses that are not distinct from other promised goods and services in an arrangement), we utilize judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue.

Up-front Fees: If a license agreement is determined to be distinct from the other performance obligations identified in the arrangement, we recognize revenue from the transaction price allocated to the license when the license is transferred to the licensee and the licensee is able to use and benefit from the license. For licenses that are bundled with other promises, we utilize judgment to assess the nature of the combined performance obligation to determine whether the license is deemed to be the predominant item and if the combined performance obligation is satisfied over time or at a point in time.

Milestone Payments: At the inception of each arrangement that includes milestone payments (variable consideration), we evaluate whether the milestones are considered probable of being reached and estimate the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments such as developmental and regulatory approval milestones, are generally not considered probable of being achieved until the related activity has been achieved, due to the uncertain nature of the success of clinical trials and obtaining regulatory approvals, which make it unlikely that a significant revenue reversal could be deemed not probable, until such time that the related event has occurred.

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

Reimbursement, cost-sharing and profit-sharing payments: Under certain arrangements, we have been reimbursed for a portion of our research and development expenses or participates in the cost-sharing of such research and development expenses. Such reimbursements and cost-sharing arrangements have been reflected as a reduction of research and development expense in our consolidated statements of operations, as we do not consider performing research and development services for reimbursement to be a part of our ongoing major or central operations.

Accrued research and development costs

Research and Development expenditures are charged to research and development expense as incurred. These expenses consist of expenses incurred in performing development activities, including salaries and benefits, equity-based compensation expense, preclinical expenses, clinical trial and related clinical manufacturing expenses, contract services and other outside expenses. Expenses incurred for certain research and development activities, including expenses associated with particular activities performed by contract research organizations, investigative sites in connection with clinical trials and contract manufacturing organizations, are recognized based on an evaluation of the progress or completion of specific tasks using either time-based measures or data such as information provided to us by our vendors on actual costs incurred. Payments for these activities are based on the terms of the individual arrangements, which may differ from the pattern of expense recognition. Expenses for research and development activities incurred that have yet to be invoiced by the vendors that perform the related activities are reflected in the consolidated financial statements as accrued research and development expenses. Advance payments for goods or services to be received in the future for research and development activities are deferred and capitalized. The capitalized amounts are expensed as the related goods are delivered or the services are performed.

We do not expect our estimates to be materially different from amounts actually incurred. For the periods presented, we have experienced no material differences between our accrued expenses and actual expenses.

Recent accounting pronouncements

See Note 3 to our consolidated financial statements “Summary of Significant Accounting Policies—Recently Issued Accounting Pronouncements” for more information.

SEC Filing Status

We became a large accelerated filer on December 31, 2020, based on the market value of our common stock held by non-affiliates as of the last day of the second quarter in 2020. Prior to that, we were an emerging growth company, or EGC, as defined in the Jumpstart Our Business Startups Act, or the JOBS Act. Being an EGC allowed us to delay adoption of new or revised accounting pronouncements applicable to public companies until such pronouncements are made applicable to private companies. We had elected to use this extended transition period under the JOBS Act.

We lost the ability to delay adoption of new or revised accounting pronouncements when we became a large accelerated filer as of December 31, 2020. As a result, the financial statements included in this Annual Report reflect the adoption of new accounting standards effective for calendar year end public companies, including the adoption of ASC 842- Leases. Refer to the sections titled Recently Adopted Accounting Pronouncements in the footnotes to the financial statements.

Coronavirus Aid, Relief, and Economic Security Act, or CARES Act

The CARES Act, which was enacted on March 27, 2020, and related notices include several significant provisions, including delaying certain payroll tax payments and estimated income tax payments. The CARES Act did not have a material impact on our financial results, including on our annual estimated effective tax rate, or on our liquidity. We will continue to monitor and assess the impact the CARES Act and similar legislation may have on our business and financial results.

Item 7A. Quantitative and qualitative disclosures about market risk

The primary objectives of our investment activities are to ensure liquidity and to preserve capital. We are exposed to market risks in the ordinary course of our business. These risks include interest rate sensitivities. We had cash, cash equivalents and marketable securities of $561.8 million and $327.7 million as of December 31, 2020 and December 31, 2019, respectively, which consisted of bank deposits, highly liquid money market funds and investments in high-quality, highly liquid available-for-sale debt securities. Historical fluctuations in interest rates have not been significant for us. We had no outstanding debt as of December 31, 2020. Due to the short-term maturities of our cash equivalents and the high-quality, highly liquid nature of our available-for-sale debt marketable securities, an immediate one percentage point change in interest rates would not have a material effect on the fair market value of our cash equivalents. To minimize the risk in the future, we intend to maintain our portfolio of cash equivalents and marketable securities in institutional market funds that are composed of U.S. Treasury and U.S. Treasury-backed repurchase agreements, short-term U.S. Treasury securities and investments in high-quality, highly liquid available-for-sale debt securities including corporate debt securities, government-sponsored enterprise securities and commercial paper. We do not believe that inflation, interest rate changes or exchange rate fluctuations had a significant impact on our results of operations for any periods presented herein.

Item 8. Financial Statements and Supplementary Data

Index to Consolidated Financial Statements

Report of Independent Registered Public Accounting Firm

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

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of SpringWorks Therapeutics, Inc ("the Company") as of December 31, 2020 and 2019, the related consolidated statements of operations, comprehensive loss, preferred unit and members'/stockholders' equity/(deficit), and cash flows for each of the three years in the period ended December 31, 2020, 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, 2020 and 2019, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2020, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company's internal control over financial reporting as of December 31, 2020, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) and our report dated February 25, 2021 expressed an unqualified opinion thereon.

Basis for Opinion

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

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures 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.

Adoption of ASU No. 2016-02

As discussed in Note 3 to the consolidated financial statements, the Company changed its method of accounting for leases in 2020 due to the adoption of Accounting Standards Update (ASU) No. 2016-02, Leases (Topic 842), and the related amendments.

Critical Audit Matter

The critical audit matter communicated below is a matter arising from the current period audit of the financial statements that was communicated or required to be communicated to the audit committee and that: (1) relates to accounts or disclosures that are material to the financial statements and (2) involved our especially challenging, subjective or complex judgments. The communication of the critical audit matter does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the accounts or disclosures to which it relates.

Accrued Research and Development Costs

Description of the Matter	The Company's accrual for research and development costs totaled $7.9 million at December 31, 2020. As discussed in Note 3 to the consolidated financial statements, expenses incurred for certain research and development activities, including expenses associated with particular activities performed by contract research organizations, investigative sites in connection with clinical trials and contract manufacturing organizations, are recognized based on an evaluation of the progress or completion of specific tasks using either time-based measures or data such as information provided to the Company by its vendors on 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. Auditing the Company's research and development accruals is especially complex due to the significant management judgement to estimate costs incurred and not yet billed at each reporting period as a result of the volume of clinical trials and the extent of third-party service providers utilized. Additionally, due to the duration of the clinical trials as well as the timing of invoices received from third parties, actual amounts incurred are not typically known as of the audit report date.
How We Addressed the Matter in Our Audit	We obtained an understanding, evaluated the design, and tested the operating effectiveness of internal controls over the Company's accounting for research and development costs, including controls over the completeness and valuation of accrued research and development expenses. To test the Company's research and development accrual, our audit procedures included, among others, evaluating the significant assumptions that are used by management to estimate the recorded accruals and testing the completeness and accuracy of the underlying data. To test the significant assumptions, we inspected the Company's contracts with third-party service providers and any related amendments, corroborated the progress of clinical trials and other research and development projects with the Company's research and development personnel that oversee these activities and obtained information received directly from third parties, which included the third parties' estimate of costs incurred to date. We also tested subsequent invoicing received from third parties to assess the completeness of the recorded accruals.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2018.

New York, New York
February 25, 2021

SpringWorks Therapeutics, Inc.
Consolidated Balance Sheets

(in thousands, except share and per-share data)	December 31, 2020	December 31, 2019
Assets		
Current assets:		
Cash and cash equivalents	$ 147,089	$ 327,652
Marketable securities	361,395	—
Prepaid expenses and other current assets	4,914	3,709
Total current assets	513,398	331,361
Long-term marketable securities	53,336	—
Property and equipment, net	1,075	795
Operating lease right-of-use assets	1,944	—
Equity investment	3,871	976
Restricted cash	565	540
Other assets	2,002	1,159
Total assets	$ 576,191	$ 334,831
Liabilities and Stockholders' equity		
Current liabilities:		
Accounts payable	$ 1,350	$ 2,654
Accrued expenses	14,885	8,953
Operating lease liabilities, current	1,375	—
Deferred rent	—	363
Total current liabilities	17,610	11,970
Operating lease liabilities, long-term	1,359	—
Long-term portion of deferred rent	—	789
Other long-term liabilities	164	—
Total liabilities	19,133	12,759
Commitments and contingencies		
Stockholders' equity:		
Preferred stock, $0.0001 par value, 10,000,000 shares authorized, no shares issued or outstanding at December 31, 2020 and December 31, 2019.	—	—
Common stock, $0.0001 par value, 150,000,000 shares authorized, 48,819,591 and 43,006,077 shares issued and outstanding at December 31, 2020 and December 31, 2019, respectively.	5	4
Additional paid-in capital	675,615	395,097
Accumulated other comprehensive income	41	—
Accumulated deficit	(118,603)	(73,029)
Total stockholders' equity	557,058	322,072
Total liabilities and stockholders' equity	$ 576,191	$ 334,831

See accompanying notes to consolidated financial statements.

SpringWorks Therapeutics, Inc.
Consolidated Statements of Operations

(in thousands, except share and per-share data)	Year Ended December 31, 2020	2019	2018
Licensing revenue	$ 35,000	$ —	$ —
Operating expenses:			
Research and development	51,859	42,545	9,898
General and administrative	29,465	16,694	8,593
Total operating expenses	81,324	59,239	18,491
Loss from operations	(46,324)	(59,239)	(18,491)
Other income:			
Other income	25	—	—
Interest income, net	1,330	3,547	678
Total other income	1,355	3,547	678
Equity investment loss	(605)	(2,614)	—
Net loss	$ (45,574)	$ (58,306)	$ (17,813)
Reconciliation of net loss to net loss attributable to common stockholders and unit holders:			
Net loss	$ (45,574)	$ (58,306)	$ (17,813)
Net gain attributable to extinguishment of Series A convertible preferred and Junior Series A convertible preferred units	—	7,729	—
Net loss attributable to common stockholders and unit holders, basic and diluted	$ (45,574)	$ (50,577)	$ (17,813)
Net loss per unit, basic and diluted	$ —	$ —	$ (52.24)
Net loss per share, basic and diluted	$ (1.05)	$ (3.81)	$ —
Weighted average common units outstanding, basic and diluted	—	—	341,014
Weighted average common shares outstanding, basic and diluted	43,300,063	13,274,836	—

See accompanying notes to consolidated financial statements.

SpringWorks Therapeutics, Inc.
Consolidated Statements of Comprehensive Loss

(in thousands)	Year Ended December 31, 2020	2019	2018
Net loss	$ (45,574)	$ (58,306)	$ (17,813)
Changes in other comprehensive income:			
Unrealized gain on marketable securities, net	41	—	—
Total changes in other comprehensive income	$ 41	$ —	$ —
Comprehensive loss	(45,533)	(58,306)	(17,813)
Net gain attributable to extinguishment of Series A convertible preferred and Junior Series A convertible preferred units	—	7,729	—
Comprehensive loss attributable to common stockholders	$ (45,533)	$ (50,577)	$ (17,813)

See accompanying notes to consolidated financial statements.

SpringWorks Therapeutics, Inc.
Consolidated Statement of Preferred Unit and Members'/Stockholders' Equity/(Deficit)

	Year ended December 31, 2018, 2019 and 2020									
	Series A & B Convertible Preferred		Junior Series A Convertible Preferred		Common		Additional Paid-In	Accumulated Other Comprehensive	Accumulated	
(in thousands, except share and unit data)	Shares	Amount	Shares	Amount	Shares	Amount	Capital	Income	Deficit	Total
Balance at December 31, 2017	13,200,001	12,554	6,437,500	2,014					(4,639)	(2,625)
Issuance of Series A convertible preferred units, net	50,399,999	50,376								—
Issuance of common units to founders					195,638		154			154
Issuance of incentive units, net of forfeitures					2,905,568		915			915
Net loss									(17,813)	(17,813)
Balance at December 31, 2018	63,600,000	62,930	6,437,500	2,014	3,101,206	—	1,069	—	(22,452)	(19,369)
Issuance of Series A convertible preferred shares, net	39,400,000	39,367								—
Issuance of Series B convertible preferred shares, net of $413 in legal costs	86,639,279	124,590								—
Series A convertible preferred extinguishment		(9,597)							9,597	9,597
Junior Series A convertible preferred extinguishment				1,868					(1,868)	—
Issuance of common stock upon closing of initial public offering, net of $16,570 in issuance cost					10,350,000	1	169,729			169,730
Stock-based compensation expense							3,109			3,109
Forfeitures of restricted stock awards					(248,568)					—
Conversion of convertible preferred stock into common stock	(189,639,279)	(217,290)	(6,437,500)	(3,882)	29,794,359	3	221,169			217,290
Exercise of stock options					9,080		21			21
Net loss									(58,306)	(58,306)
Balance at December 31, 2019	—	—	—	—	43,006,077	4	395,097	—	(73,029)	322,072
Exercise of stock options					190,484		893			893
Issuance of common stock upon closing of follow-on offering, net of $17,908 in issuance cost					5,637,254	1	269,591			269,592
Forfeitures of restricted stock awards					(14,224)					—
Stock-based compensation expense							10,034			10,034
Other comprehensive income, net of tax								41		41
Net Loss									(45,574)	(45,574)
Balance at December 31, 2020	—	—	—	—	48,819,591	5	675,615	41	(118,603)	557,058

See accompanying notes to consolidated financial statements.

SpringWorks Therapeutics, Inc.
Consolidated Statements of Cash Flows

(in thousands)	Year Ended December 31, 2020	2019	2018
Operating Activities			
Net loss	$ (45,574)	$ (58,306)	$ (17,813)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation expense	349	192	17
Non-cash operating lease expense	1,049	—	—
Stock compensation expense	10,034	3,109	1,069
Equity investment loss	605	2,614	—
Changes in Operating Assets and Liabilities			
Prepaid expenses and other current assets	(1,205)	(2,327)	(1,112)
Other assets	(843)	(656)	(503)
Accounts payable	(1,304)	1,880	491
Accrued expenses	5,945	6,385	2,198
Deferred rent	—	(335)	1,487
Lease Liability	(1,411)	—	—
Other long-term liabilities	164	—	—
Net cash used in operating activities	$ (32,191)	$ (47,444)	$ (14,166)
Investing Activities			
Capital expenditures	(642)	(670)	(293)
Equity investments	(3,500)	(3,590)	—
Purchases of marketable securities	(442,690)	—	—
Proceeds from sale and maturity of debt securities	28,000	—	—
Net cash used in investing activities	$ (418,832)	$ (4,260)	$ (293)
Financing Activities			
Proceeds from issuance of common stock, net of issuance costs	269,592	169,730	—
Proceeds from issuance of Series A convertible preferred shares, net of issuance costs	—	39,367	50,376
Proceeds from issuance of Series B convertible preferred shares, net of issuance costs	—	124,590	—
Proceeds from stock option exercises	893	21	—
Net cash provided by financing activities	$ 270,485	$ 333,708	$ 50,376
Net increase (decrease) in cash and cash equivalents	(180,538)	282,004	35,917
Cash and cash equivalents including Restricted cash, beginning of period	328,192	46,188	10,271
Cash and cash equivalents including Restricted cash, end of period	$ 147,654	$ 328,192	$ 46,188
Supplemental non-cash items not included above resulting from the adoption of ASC 842			
Initial recognition of operating lease right of use asset	$ 2,879	$ —	$ —
Initial recognition of lease liabilities	(4,030)	—	—

See accompanying notes to consolidated financial statements.

SpringWorks Therapeutics, Inc.
Notes to Consolidated Financial Statements

1. Nature of Operations

SpringWorks Therapeutics, Inc., or the Company, was formed in Delaware on August 18, 2017.

The Company is a clinical-stage biopharmaceutical company applying a precision medicine approach to acquiring, developing and commercializing life-changing medicines for underserved patient populations suffering from devastating rare diseases and cancer. The Company has a differentiated portfolio of small molecule targeted oncology product candidates and is advancing two potentially registrational clinical trials in rare tumor types, as well as several other programs addressing highly prevalent, genetically defined cancers. Two of the programs are late-stage clinical product candidates: nirogacestat and mirdametinib.

COVID-19 Pandemic

On March 11, 2020, the World Health Organization designated the outbreak of the disease associated with the novel strain of coronavirus known as COVID-19 as a global pandemic. Governments and businesses around the world have taken unprecedented actions to mitigate the spread of COVID-19, including, but not limited to, shelter-in-place orders, quarantines, significant restrictions on travel, as well as restrictions that prohibit many employees from going to work. Uncertainty with respect to the economic impacts of the pandemic has introduced significant volatility in the financial markets. The Company did not observe significant impacts on its business or results of operations for the year ended December 31, 2020 from the global emergence of COVID-19. While the extent to which COVID-19 impacts the Company’s future results will depend on future developments, the pandemic and associated economic impacts could result in a material impact to the Company’s future financial condition, results of operations and cash flows.

Follow-On Offering

On October 13, 2020, the Company completed the sale of 5,637,254 shares of common stock in an underwritten public offering, including 735,294 shares of common stock sold pursuant to the underwriter's full exercise of their option to purchase additional shares, at an offering price of $51.00 per share, resulting in net proceeds to the Company of $269.5 million.

Initial Public Offering

On September 12, 2019, the Company completed an initial public offering, or IPO, of its common stock. In connections with its IPO, the Company issued and sold 10,350,000 shares of its common stock at a price to the public of $18.00 per share. The net proceeds from the IPO were approximately $169.7 million after deducting underwriting discounts and commissions of $13.0 million and offering expenses of approximately $3.5 million.

At the closing of the IPO, 196,076,779 shares of outstanding convertible preferred stock were automatically converted into 29,794,359 shares of common stock at a conversion rate of 6.5810-for-one. Following the IPO, there were no shares of preferred stock outstanding.

Reverse Stock Split

In August 2019, the Company’s Board of Directors and stockholders approved a one-for-6.5810 reverse stock split of the Company’s common stock. The reverse stock split became effective on August 30, 2019. Stockholders entitled to a fractional share as a result of the reverse stock split received a cash payment in lieu of the fractional shares at the initial public offering price.

Series B convertible preferred

In March 2019, the Company authorized the sale and issuance of up to 86,639,279 shares of Series B convertible preferred stock. The Series B convertible preferred financing was closed in a single tranche at the original price of $1.4428 per share for gross proceeds of $125 million. Issuance costs totaled $0.4 million.

The liquidation preference terms of each of the Series A convertible preferred stock and Junior Series A convertible preferred stock changed in connection with the issuance of Series B convertible preferred. Specifically, after receiving one times its original issue price, the Series A convertible preferred does not participate in the distribution with the Junior Series A convertible preferred prior to final distribution to all stockholders, and the Junior Series A convertible preferred does not participate with all other stockholders in the final distribution. The Company concluded that the changes in the Series A convertible preferred and Junior Series A convertible preferred liquidation preferences are a significant change in the economics of those instruments and therefore were accounted for as an extinguishment. Immediately following the extinguishment of Series A convertible preferred and Junior Series A convertible preferred, the same number of shares was reissued at fair value. As a result, the difference between (1) the fair value of the consideration transferred to the holders of the preferred stock and (2) the carrying amount of the extinguished instruments (net of issuance costs) was recorded to retained earnings.

Reorganization

Prior to March 29, 2019, the Company conducted its business through SpringWorks Therapeutics, LLC, a Delaware limited liability company. On March 29, 2019, the Company completed a series of transactions pursuant to which SpringWorks MergerSub LLC, a wholly owned subsidiary of SpringWorks Therapeutics, Inc., merged with SpringWorks Therapeutics, LLC, with SpringWorks Therapeutics, LLC surviving the merger as a wholly owned subsidiary of SpringWorks Therapeutics, Inc., or the Reorganization.

Upon consummation of the Reorganization, the historical consolidated financial statements of SpringWorks Therapeutics, LLC became the historical consolidated financial statements of SpringWorks Therapeutics, Inc.

As part of the Reorganization:

Holders of Series A convertible preferred Units of SpringWorks Therapeutics, LLC received one share of Series A convertible preferred stock of SpringWorks Therapeutics, Inc. for each Series A convertible preferred unit held immediately prior to the Reorganization;

Holders of Junior Series A convertible preferred units of SpringWorks Therapeutics, LLC received one share of Junior Series A convertible preferred stock of Parent for each Junior Series A convertible preferred unit held immediately prior to the Reorganization;

Holders of common units received one share of common stock of SpringWorks Therapeutics, Inc. for each common unit held immediately prior to the Reorganization;

Each outstanding incentive unit converted into one share of common stock of SpringWorks Therapeutics, Inc. for each incentive unit held immediately prior to the Reorganization, and such common stock is subject to vesting in accordance with the vesting schedule applicable to such incentive units; and

Holders of options exercisable to purchase common units, or unit options, of SpringWorks Therapeutics, LLC received one stock option exercisable to purchase common stock of the Company for each unit option held immediately prior to the Reorganization, at the same exercise price of such unit option immediately prior to the Reorganization. Such stock options continue to be subject to vesting in accordance with the vesting schedule applicable to such unit options.

2. Risks and Liquidity

The Company has incurred losses and negative operating cash flows since inception and had an accumulated deficit of $118.6 million and $73.0 million, and working capital of $495.8 million and $319.4 million at December 31, 2020 and 2019, respectively. To date, we have derived all of our revenue from the nonrefundable upfront payment we received under the asset purchase and license agreement with Jazz Pharmaceuticals Ireland Limited, or Jazz. We do not have any products approved for commercial sale or sources of recurring revenue. The Company is subject to those risks associated with any biopharmaceutical company that has substantial expenditures for development. There can be no assurance that the Company's development projects will be successful, that products developed will obtain necessary regulatory approval, or that any approved product will be commercially viable. In addition, the Company operates in an environment of rapid technological change and is largely dependent on the services of its employees, advisors, consultants and vendors.

The Company had cash, cash equivalents and marketable securities of $561.8 million and $327.7 million as of December 31, 2020 and 2019, respectively. The increase in the cash balance of approximately $234.2 million was primarily driven by net proceeds of $269.5 million from the sale of shares of common stock in an underwritten public offering in October 2020; offset by normal operating activities. Based on the Company's cash, cash equivalents and marketable securities at December 31, 2020, management estimates that its current liquidity will enable it to meet operating expenses through at least twelve months after the date that these financial statements were issued.

3. Summary of Significant Accounting Policies

Basis of Presentation

These consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States, or U.S. GAAP.

Principles of Consolidation

The consolidated financial statements include the accounts of SpringWorks Therapeutics, Inc. and its subsidiaries. All intercompany transactions and balances have been eliminated in consolidation. Investments in business entities in which the Company lacks control but does have the ability to exercise significant influence over operating and financial policies are accounted for using the equity method of accounting.

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 in the financial statements and accompanying notes. Significant estimates and assumptions reflected in these consolidated financial statements include, but are not limited to, Research and Development expenses and the valuation of equity-based awards. The Company bases its estimates on historical experience, known trends and other market-specific or relevant factors that it believes to be reasonable under the circumstances. Actual results may differ from those estimates. On an ongoing basis, management evaluates its estimates, and adjusts those estimates and assumptions when facts or circumstances change. Changes in estimates are recorded in the period in which they become known.

Segment Information

Operating segments are defined as components of an entity about which separate discrete information is available for evaluation by the chief operating decision maker, or decision-making group, in deciding how to allocate resources and in assessing performance. The Company views its operations and manages its business in one operating segment operating exclusively in the United States.

SEC Filing Status

The Company became a large accelerated filer on December 31, 2020, based on the market value of the Company's common stock held by non-affiliates as of the last day of the second quarter in 2020. Prior to that, the Company was an emerging growth company, or EGC, as defined in the Jumpstart Our Business Startups Act, or the JOBS Act. Being an EGC allowed the Company to defer adoption of new or revised accounting pronouncements applicable to public companies until such pronouncements are made applicable to private companies. The Company had elected to use this extended transition period under the JOBS Act.

The Company lost the ability to defer adoption of new or revised accounting pronouncements when it became a large accelerated filer as of December 31, 2020. As a result, the financial statements included in this Annual Report reflect the adoption of new accounting standards effective for calendar year end public companies, including the adoption of Financial Accounting Standards Board Accounting Standards Codification Topic, or ASC, 842, Leases. Refer to the sections titled Recently Adopted Accounting Pronouncements in Footnote 3 and Footnote 7: *Leases* for more information.

Cash and Cash Equivalents

The Company considers all highly liquid instruments that have maturities of three months or less when acquired to be cash equivalents. The Company had cash and cash equivalents as of December 31, 2020 and 2019 of $147.1 million and $327.7 million, respectively.

Marketable Securities

Marketable debt securities are reported at fair value with unrealized gains and losses included in Accumulated other comprehensive income. Each reporting period, the Company evaluates whether there are declines in fair value below amortized cost and if these declines are due to credit losses, as well as the Company’s ability and intent to hold the investment until a forecasted recovery occurs. If both criteria regarding the intent or ability to hold are met, any decline in fair value due to credit losses is recorded as an allowance through Other income (expense), net on the Company’s consolidated statements of operations; limited by the amount that the fair value is less than the amortized costs basis. If either criteria is not met, any previously recorded allowance for credit losses and any excess amortized cost basis over fair value is recorded in Other income (expense), net on the Company’s consolidated statements of operations. As of, and for the year ended December 31, 2020, the Company did not have any allowance for credit losses or impairments of its marketable securities.

Concentration of Credit Risk

Financial instruments that potentially expose the Company to concentrations of credit risk consist primarily of cash, cash equivalents and available-for-sale marketable securities. The Company maintains each of its cash, cash equivalent balances and marketable securities balances with high quality, financial institutions and the Company’s marketable securities are invested in high-quality, highly liquid debt securities including corporate debt securities, U.S. government securities and commercial paper.

Property and Equipment

Property and equipment consist of computer equipment, furniture and leasehold improvements and are recorded at cost. Property and equipment are depreciated on a straight-line basis over their estimated useful lives.

Revenue

The Company recognizes revenue for consideration received related to the development and commercialization of medicines, which is conducted through various means, including in-house development by the Company, joint development or collaboration agreements with third parties, sale or out licensing of product rights, and others. The terms of these arrangements and agreements may contain multiple promised goods and services, which may include licenses,

know-how, drug product, related agreements and other deliverables. Payments to the Company under these arrangements may include one or more of the following: upfront license fees; milestone payments; and royalties on future product sales.

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

The Company recognizes revenue in accordance with ASC 606, which applies to all contracts with customers, except for contracts that are within the scope of other standards, such as collaboration arrangements and leases.

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

Once a contract is determined to be within the scope of ASC 606, the Company assesses the goods or services promised within the contract and determines those that are performance obligations.

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

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

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

Licenses of intellectual property: The terms of the Company's license agreements include the license of functional intellectual property, given the functionality of the intellectual property is not expected to change substantially as a result of the Company's ongoing activities. For licenses that are bundled with other promises (that is, for licenses that are not distinct from other promised goods and services in an arrangement), the Company utilizes judgment to assess the nature

of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue.

Up-front Fees: If a license agreement is determined to be distinct from the other performance obligations identified in the arrangement, the Company recognizes revenues from the transaction price allocated to the license when the license is transferred to the licensee and the licensee is able to use and benefit from the license. For licenses that are bundled with other promises, the Company utilizes judgment to assess the nature of the combined performance obligation to determine whether the license is deemed to be the predominant item and if the combined performance obligation is satisfied over time or at a point in time.

Milestone Payments: At the inception of each arrangement that includes milestone payments (variable consideration), the Company evaluates whether the milestones are considered probable of being reached and estimates the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments such as developmental and regulatory approval milestones, are generally not considered probable of being achieved until the related activity has been achieved, due to the uncertain nature of the success of clinical trials and obtaining regulatory approvals, which make it unlikely that a significant revenue reversal could be deemed not probable, until such time that the related event has occurred.

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

Reimbursement, cost-sharing and profit-sharing payments: Under certain arrangements, the Company has been reimbursed for a portion of its research and development expenses or participates in the cost-sharing of such research and development expenses. Such reimbursements and cost-sharing arrangements have been reflected as a reduction of research and development expense in the Company's consolidated statements of operations, as the Company does not consider performing research and development services for reimbursement to be a part of its ongoing major or central operations.

Research and Development

In accordance with ASC 730, "Research and Development", expenditures for clinical development, including upfront licensing fees and milestone payments associated with products that have not yet been approved by the U.S. Food and Drug Administration, are charged to research and development expense as incurred. These expenses consist of expenses incurred in performing development activities, including salaries and benefits, equity-based compensation expense, preclinical expenses, clinical trial and related clinical manufacturing expenses, contract services and other outside expenses. Expenses incurred for certain research and development activities, including expenses associated with particular activities performed by contract research organizations, investigative sites in connection with clinical trials and contract manufacturing organizations, are recognized based on an evaluation of the progress or completion of specific tasks using either time-based measures or data such as information provided to the Company by its vendors on actual costs incurred. Payments for these activities are based on the terms of the individual arrangements, which may differ from the pattern of expense recognition. Expenses for research and development activities incurred that have yet to be invoiced by the vendors that perform the related activities are reflected in the consolidated financial statements as accrued research and development expenses. Advance payments for goods or services to be received in the future for research and development activities are deferred and capitalized. The capitalized amounts are expensed as the related goods are delivered or the services are performed.

General and Administrative

General and administrative expenses consist primarily of payroll and employee related costs including salaries and benefits, equity-based compensation expense, rent and utilities, infrastructure, corporate insurance, office expenses and consulting and professional services, including legal, regulatory and compliance.

Equity-based compensation expense

The Company accounts for employee equity-based compensation in accordance with ASC 718, Compensation — Stock Compensation, which requires all equity-based awards to employees and non-employee directors be recognized as expense in the statement of operations based on the grant date fair value of the awards. The Company's equity-based awards generally vest over three or four years.

Stock compensation expense is recognized using the straight-line method, based on the grant date fair value, over the requisite service period of the award, which is generally the vesting term.

For awards subject to performance conditions, as well as awards containing both market and performance conditions, the Company recognizes equity award compensation expense using an accelerated recognition method over the remaining service period when management determines that achievement of the milestone is probable. Management evaluates when the achievement of a performance-based milestone is probable based on the expected satisfaction of the performance conditions as of the reporting date.

The Company recognizes forfeitures at the time of the actual forfeiture event in accordance with the adoption of the guidance per Accounting Standard Update, or ASU, No. 2016-09.

The grant-date fair value of performance-based awards with market conditions is estimated using a Monte Carlo simulation method that incorporates the probability of the performance conditions being met as of the grant date.

For stock options issued, the Company estimates the grant date fair value and the resulting stock-based compensation expense using the Black-Scholes option-pricing model.

The Black-Scholes option-pricing model requires the use of certain subjective assumptions which determine the fair value of stock-based awards, including the expected term and the price volatility of the underlying stock. Inputs used in the Black-Scholes option-pricing model are:

- Fair value of common stock, which is the current trading price of the Company's common stock.
- Expected term — The expected term represents the period that the equity-based awards are expected to be outstanding. The Company uses the simplified method to calculate the expected term due to the limited Company-specific historical information available for the Company.
- Expected volatility — The Company lacks Company-specific historical and implied volatility information. Therefore, it estimates its expected stock volatility based on the historical volatility of a publicly traded set of peer companies and expects to continue to do so until it has adequate historical data regarding the volatility of its own traded stock.
- Risk-free interest rate — The risk-free interest rate is based on the U.S. Treasury yield in effect at the time of grant for zero-coupon U.S. Treasury notes with maturities approximately equal to the expected term of the awards.
- Expected dividend — The Company has never paid dividends on its common units or stock and has no plans to pay dividends on its common stock. Therefore, the expected dividend yield is zero.

For equity-based compensation grants prior to the IPO, the Company estimated the fair value of equity awards granted using the special case of the market approach, including the guideline public company method and precedent transaction method which is known as a backsolve method. This option pricing model was utilized to solve for the implied total equity value that was consistent with the Company's Series A convertible preferred units "backsolves" to a preferred share price. The backsolve method derives the implied equity value for one type of equity security from a contemporaneous transaction involving another type of security to calculate the equity value. The use of these valuation approaches required management to make assumptions with respect to the expected volatility of its units and stock, time until a liquidity event and risk-free interest rates. Equity value was allocated to the common, incentive and convertible preferred units, and common, restricted and convertible preferred stock using an option-pricing method. Under this method, the common and incentive units and common stock would have had value only if the funds available for distribution exceeded the value of the convertible preferred units' liquidation preferences at the anticipated time of a liquidity event, such as a strategic sale, merger or IPO.

Net Loss per Unit and Share

Basic net loss per unit and per share is computed by dividing net loss by the weighted average number of common units and shares outstanding for the period. Diluted net loss per unit and share excludes the potential impact of convertible preferred units, unvested incentive units, convertible preferred stock, unvested restricted stock and stock options because their effect would be anti-dilutive due to the Company's net loss. Since the Company had a net loss in each of the periods presented, basic and diluted net loss per common unit and share are the same.

Income Taxes

Income taxes are accounted for using the asset-and-liability method. Deferred tax assets and liabilities are recognized for the future tax consequences attributable to differences between the financial statement carrying amounts of existing assets and liabilities and their respective tax basis and operating loss and tax credit carryforwards. Deferred tax assets and liabilities are measured using enacted tax rates expected to apply to taxable income in the years in which those temporary differences are expected to be recovered or settled. The effect on deferred tax assets and liabilities of a change in tax rates is recognized as income in the period that includes the enactment date. Changes in deferred tax assets and liabilities are recorded in the provision for income taxes.

The Company recognizes deferred tax assets to the extent that it believes that these assets are more likely than not to be realized. In making such a determination, management considers all available positive and negative evidence, including future reversals of existing taxable temporary differences, projected future taxable income, tax-planning strategies and results of recent operations. Valuation allowances are provided, if based upon the weight of available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized. If management determines that the Company would be able to realize its deferred tax assets in the future in excess of their net recorded amount, management would make an adjustment to the deferred tax asset valuation allowance, which would reduce the provision for income taxes.

The Company records uncertain tax positions in accordance with ASC 740 on the basis of a two-step process in which (1) management determines whether it is more likely than not that the tax positions will be sustained on the basis of the technical merits of the position and (2) for those tax positions that meet the more-likely-than-not recognition threshold, management recognizes the largest amount of tax benefit that is more than 50% likely to be realized upon ultimate settlement with the related tax authority.

The Company provides reserves for potential payments of tax to various tax authorities related to uncertain tax positions. These reserves are based on a determination of whether and how much of a tax benefit taken by the Company in its filings or positions is more likely than not to be realized following resolution of any potential contingencies related to the tax benefit. Potential interest related to the underpayment of income taxes will be classified as a component of income tax expense and any related penalties will be classified in income tax expenses in the statement of operations.

SpringWorks Therapeutics, LLC elected to be treated under the partnership provisions of the Internal Revenue Service Code prior to the reorganization on March 29, 2019. However, its five wholly owned subsidiaries, SpringWorks

Operating Company, SpringWorks Subsidiary 1, SpringWorks Subsidiary 2, SpringWorks Subsidiary 3, and SpringWorks Subsidiary 4, are taxable corporations.

Subsequent to the Reorganization, SpringWorks Therapeutics, Inc. became the 100% owner of SpringWorks Therapeutics, LLC, creating a new ultimate parent company, and a consolidated group for income tax reporting. The Reorganization and change in tax status of the reporting entity did not have an impact on the consolidated tax provision.

Recently Adopted Accounting Pronouncements

Leases

In February 2016, the FASB issued ASU 2016-02, Leases (Topic 842). This standard requires entities that lease assets to recognize on the balance sheet the assets and liabilities of the rights and obligations created by those leases. The Company utilized a package of practical expedients that allows it to not reassess: (1) whether any expired or existing contracts are or contain leases, (2) lease classification for any expired or existing leases, and (3) initial direct costs for any expired or existing leases. The Company adopted ASU 2016-02, as of January 1, 2020. Under ASC 842, the Company determines whether the arrangement contains a lease at the inception of an arrangement. If a lease is identified in an arrangement, the Company recognizes a right-of-use asset and liability on its consolidated balance sheet and determines whether the lease should be classified as a finance or operating lease. The Company does not recognize assets or liabilities for leases with lease terms of less than 12 months.

A lease qualifies as a finance lease if any of the following criteria are met at the inception of the lease: (i) there is a transfer of ownership of the leased asset to the Company by the end of the lease term, (ii) the Company holds an option to purchase the leased asset that it is reasonably certain to exercise, (iii) the lease term is for a major part of the remaining economic life of the leased asset, (iv) the present value of the sum of lease payments equals or exceeds substantially all of the fair value of the leased asset, or (v) the nature of the leased asset is specialized to the point that it is expected to provide the lessor no alternative use at the end of the lease term. All other leases are recorded as operating leases.

Finance and operating lease assets and liabilities are recognized at the lease commencement date based on the present value of the lease payments over the lease term using the discount rate implicit in the lease. If the rate implicit is not readily determinable, the Company utilizes its incremental borrowing rate at the lease commencement date. Operating lease assets are further adjusted for prepaid or accrued lease payments. Operating lease payments are expensed using the straight-line method as an operating expense over the lease term. Finance lease assets are amortized to depreciation expense using the straight-line method over the shorter of the useful life of the related asset or the lease term. Finance lease payments are bifurcated into (i) a portion that is recorded as imputed interest expense and (ii) a portion that reduces the finance liability associated with the lease.

The Company does not separate lease and non-lease components when determining which lease payments to include in the calculation of its lease assets and liabilities. Variable lease payments are expensed as incurred. If a lease includes an option to extend or terminate the lease, the Company reflects the option in the lease term if it is reasonably certain it will exercise the option.

Operating leases are recorded in “Operating lease right-of-use-assets,” “Operating lease liabilities, current” and “Operating lease liabilities, long-term” on the Company’s consolidated balance sheet. The Company had no finance lease obligations for the periods presented. Refer to Footnote 7 for additional lease disclosures.

The cumulative effect of applying ASC 842 on the Company’s consolidated balance sheet as of January 1, 2020 was as follows:

(in thousands)	Balance as of December 31, 2019 *	Adjustments	Balance as of January 1, 2020
Assets			
Operating lease right-of-use-assets	$ —	$ 2,848	$ 2,848
Total assets	$ —	$ 2,848	$ 2,848
Liabilities			—
Operating lease liabilities, current	$ —	$ 1,382	$ 1,382
Deferred rent	363	(363)	—
Operating lease liabilities, long-term	—	2,618	2,618
Long-term portion of deferred rent	789	(789)	—
Total liabilities	$ 1,152	$ 2,848	$ 4,000

*As reported in the Company's 2019 Annual Report on Form 10-K.

Internal-Use Software

In August 2018, the FASB issued ASU No. 2018-15, Intangibles—Goodwill and Other—Internal-Use Software (Subtopic 350-40): Customer’s Accounting for Implementation Costs Incurred in a Cloud Computing Arrangement That Is a Service Contract, or ASU 2018-15. The FASB issued ASU 2018-15 to align the requirements for capitalizing implementation costs incurred in a cloud-based hosting arrangement that is a service contract with the requirements for capitalizing implementation costs incurred to develop or obtain internal-use software. The Company adopted ASU 2018-15 as of January 1, 2020. The adoption of ASU 2018-15 did not have a significant impact on the Company’s consolidated financial statements.

Credit Losses

In 2016, the FASB issued ASU 2016-13, Financial Instruments—Credit Losses (Topic 326): Measurement of Credit Losses on Financial Instruments, which requires entities to record expected credit losses for certain financial instruments, including trade receivables, as an allowance that reflects the entity's current estimate of credit losses expected to be incurred. For available-for-sale debt securities with unrealized losses, the standard now requires allowances to be recorded instead of reducing the amortized cost of the investment with certain exceptions. ASU 2016-13 became effective on January 1, 2020. The adoption of ASU 2016-13 did not have a significant impact on the Company’s consolidated financial statements. The Company updated its accounting policy for evaluating impairment of its marketable securities.

Recently Issued Accounting Pronouncements

In 2019, the FASB issued ASU 2019-12, Income Taxes (Topic 740), which simplifies the accounting for income taxes. ASU 2019-12 will be effective for the Company on January 1, 2021 and is not expected to have a significant impact on the Company’s consolidated financial statements.

4. Marketable Securities

The following table summarizes the Company's available-for-sale marketable securities as of December 31, 2020 at net book value:

	As of December 31, 2020			
(in thousands)	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Marketable securities:				
Short-term investments:				
U.S. Government securities	$ 157,079	$ 24	$ (1)	$ 157,102
Corporate debt securities	74,773	2	(10)	74,765
Commercial paper	129,528	—	—	129,528
Long-term investments:				
U.S. Government securities	53,310	26	—	53,336
Total	$ 414,690	$ 52	$ (11)	$ 414,731

The Company's marketable securities are available-for-sale securities and consist of high-quality, highly liquid debt securities including corporate debt securities, U.S. government securities and commercial paper.

The Company's available-for-sale securities that are classified as short-term marketable securities in the consolidated balance sheet mature within one year or less of the balance sheet date. Marketable securities that mature greater than one year from the balance sheet date are classified as noncurrent. As of December 31, 2020, the Company did not hold any investments that matured beyond five years. As of December 31, 2019, the Company did not hold any marketable securities.

5. Fair Value Measurements

The fair value of the Company's financial assets measured on a recurring basis are classified based upon a fair value hierarchy consisting of the following three levels:

Level 1 — Unadjusted quoted prices in active markets that are accessible at the measurement date for identical, unrestricted assets, or liabilities.

Level 2 — Quoted prices for similar assets and liabilities in active markets, quoted prices in markets that are not active, or inputs which are observable, either directly or indirectly, for substantially the full term of the instrument.

Level 3 — Prices or valuation techniques that require inputs that are both significant to the fair value measurement and unobservable (i.e., supported by little or no market activity).

The fair value hierarchy is based on inputs to valuation techniques that are used to measure fair value that are either observable or unobservable. Observable inputs reflect assumptions market participants would use in pricing an asset or liability based on market data obtained from independent sources while unobservable inputs reflect a reporting entity's pricing based upon their own market assumptions.

The following table sets forth the fair value hierarchy of the Company's financial assets and liabilities measured on a recurring basis:

	As of December 31, 2020			
		Fair Value Hierarchy		
(in thousands)	Total	Level 1	Level 2	Level 3
Financial instruments carried at fair value (asset position):				
Cash equivalents:				
Money market funds	$ 107,723	$ 107,723	$ —	$ —
Short-term investments:				
U.S. Government securities	157,102	157,102	—	—
Corporate debt securities	74,765	—	74,765	—
Commercial paper	129,528	—	129,528	—
Long-term investments:				
U.S. Government securities	53,336	53,336	—	—
Total	$ 522,454	$ 318,161	$ 204,293	$ —

As of December 31, 2020, the Company's financial assets measured at fair value on a recurring basis included cash equivalents, which consist of money market funds, and marketable securities.

The Company's money market funds are readily convertible into cash and the net asset value of each fund on the last day of the quarter is used to determine fair value. The U.S. Government securities are classified as Level 1 and valued utilizing quoted market prices. The Company's corporate debt securities and commercial paper are classified as Level 2 and valued utilizing various market and industry inputs.

The Company had cash and cash equivalents at December 31, 2019 of $327.7 million. As of December 31, 2019, the Company had no other financial assets or liabilities that were measured at fair value on a recurring basis.

The Company considers all highly liquid instruments that have maturities of three months or less when acquired to be cash equivalents. The carrying amounts reflected in the Company's consolidated balance sheets for cash equivalents, accounts payable, and accrued expenses approximate fair value due to their short-term maturities.

6. Property and Equipment

Property and equipment, net consisted of the following:

	December 31,		
(in thousands)	2020	2019	Useful Life
Leasehold improvements	$ 1,184	$ 855	Length of lease or 5 years, whichever is shorter
Computer equipment	157	122	3 years
Furniture	97	31	5 years
Software	62	—	3 years
Construction in process	104	—	
	1,604	1,008	
Less accumulated depreciation	(529)	(213)	
	$ 1,075	$ 795	

Depreciation expense was $349,000, $192,000, and $17,000 for the years ended December 31, 2020, 2019 and 2018, respectively.

7. Leases

Operating Leases

The company's operating leases relate to real estate.

In October 2018, the Company entered into a lease for its corporate headquarters in Stamford, CT. The lease expires in November 2022. The Company received $1.5 million from the previous tenant in connection with the assumption of the lease. The lease payments increase by 2% in each of the subsequent years. The Company established a security deposit of $0.5 million in the form of a letter-of-credit.

In August 2018, the Company entered into a five-year operating lease in Durham, NC (the location of the Company's clinical development operations), with two five-year renewal options. The lease payments increase by 2.75% in each of the subsequent 4 years. Rental payments under the renewal period will be at current market rates for the premises.

In October 2019, the Company entered into a lease for office space in New York, NY. The Company executed an amendment in September 2020, which extended the lease to May 31, 2021.

Aggregate Lease Information Related to the Application of ASC 842

Prior to January 1, 2020, the Company accounted for leases under ASC 840. Refer to Footnote 3 for the cumulative effect of applying ASC 842 at adoption. The following information is disclosed in accordance with ASC 842, which was adopted as of January 1, 2020. The components of lease cost recorded in the Company's consolidated statement of operations were as follows:

(in thousands)	2020
Operating lease cost	
Fixed	$ 1,049
Variable	486
Total lease cost	$ 1,535

The Company's leases are included on its consolidated balance sheets as follows:

(in thousands)	As of December 31, 2020	As of December 31, 2019*
Operating leases		
Operating lease right-of-use-assets	$ 1,944	$ —
Total operating lease assets	$ 1,944	$ —
Operating lease liabilities, current	$ 1,375	$ —
Operating lease liabilities, long-term	1,359	—
Total operating lease liabilities	$ 2,734	$ —

*As reported in the Company's 2019 Annual Report on Form 10-K.

Maturities of the Company's operating lease liabilities in accordance with ASC 842 as of December 31, 2020 were as follows:

(in thousands)	Operating Leases
2021	$ 1,396
2022	1,298
2023	135
2024 and thereafter	—
Total lease payments	2,829
Less: imputed interest	(95)
Present value of lease liabilities	$ 2,734

The weighted-average remaining lease term and discount rate related to the Company's leases were as follows:

	As of December 31, 2020
Weighted-average remaining lease term (in years)	
Operating leases	2.0
Weighted-average discount rate	
Operating leases	3.45%

Supplemental cash flow information related to the Company's leases was as follows:

(in thousands)	December 31, 2020
Cash paid for amounts included in the measurement of lease liabilities:	
Operating cash flows from operating leases	$ 1,411
Right-of-use assets obtained in exchange for new operating lease liabilities	31

The Company recorded rent expense aggregating $1.5 million, $1.6 million and $0.5 million for the years ended December 31, 2020, December 31, 2019, and December 31, 2018, respectively.

8. Accrued Expenses

Accrued expenses consisted of the following:

(in thousands)	December 31, 2020	December 31, 2019
Accrued professional fees	$ 827	$ 793
Accrued compensation and benefits	5,834	3,147
Accrued research and development	7,922	4,447
Accrued other	302	566
Total accrued expenses	$ 14,885	$ 8,953

9. Equity Based Compensation

The Company recorded total equity-based compensation expense for the periods presented as follows:

(in thousands)	Year Ended December 31, 2020	2019	2018
Research and development	$ 3,055	$ 731	$ 164
General and administrative	6,979	2,378	905
Total equity compensation expense	$ 10,034	$ 3,109	$ 1,069

2019 Equity Incentive Plan

The 2019 Equity Incentive Plan provides for the grant of incentive stock options, nonqualified stock options, stock appreciation rights, restricted stock units, restricted stock awards, unrestricted stock awards and dividend equivalent rights to the Company's officers, employees, directors and other key persons (including consultants). The number of shares initially reserved for issuance under the 2019 Equity Incentive Plan was 3,537,225 shares and is cumulatively increased each January 1, through and including January 1, 2030, by 5% of the number of shares of the Company's common stock outstanding on the immediately preceding December 31 or such lesser number of shares determined by the Company's compensation committee. Effective January 1, 2020, the number of shares reserved for issuance under the 2019 Equity Incentive Plan was increased by 2,150,304 shares.

The terms of stock options and restricted stock awards, including vesting requirements, are determined by the Board of Directors or its delegates, subject to the provisions of the 2019 Equity Incentive Plan. Stock options and restricted stock awards granted by the Company to employees and directors generally vest over four years.

As of December 31, 2020, there were 4,256,747 shares available for future issuance under the 2019 Equity Incentive Plan.

2019 Private Company Plan

On March 29, 2019, the Company adopted the 2019 Stock Option and Incentive Plan, or the 2019 Private Company Plan, in connection with the Reorganization. The 2019 Private Company Plan originally had 5,292,355 shares available for issuance. In connection with the adoption of the 2019 Private Company Plan, all outstanding incentive units and unit options, granted under the 2018 Equity Plan, were exchanged for stock options and restricted stock under the 2019 Private Company Plan. The restricted common stock was issued with the same vesting terms as the unvested incentive units held immediately prior to the Reorganization. On June 4, 2019, the total shares available for issuance under the 2019 Private Company Plan was increased to 5,382,828 shares. On July 29, 2019, the total shares available for issuance was increased to 6,700,197.

In connection with the IPO no modification was triggered for the 2019 Private Company Plan and upon the effectiveness of the 2019 Public Company Plan no further grants can be made under the 2019 Private Company Plan. However, the shares of common stock underlying any awards that are forfeited, cancelled, held back upon exercise or settlement of an award to satisfy the exercise price or tax withholding, reacquired by the Company prior to vesting, satisfied without the issuance of stock, expire or are otherwise terminated (other than by exercise) under the 2019 Private Company Plan will be added back to the shares of common stock available for issuance under the 2019 Public Company Plan.

2018 Equity Plan

In January 2018, the Company adopted the 2018 Equity Incentive Plan, or the 2018 Equity Plan. There were 2,738,929 incentive units, or incentive units, initially available for issuance under the 2018 Equity Plan. The 2018 Plan was increased by 269,716 units for an aggregate of 3,008,645 as of December 31, 2018.

On March 19, 2019, the Company modified its operating agreement to allow for the award of unit options. In connection with the adoption of the 2019 Private Company Plan, as noted above, all outstanding awards were exchanged for identical awards under the 2019 Private Company Plan. No further grants can be made under the 2018 Equity Plan.

2019 Employee Stock Purchase Plan

On August 30, 2019, the Company's stockholders approved the 2019 Employee Stock Purchase Plan, or the ESPP, which became effective immediately preceding the effectiveness of the Company's registration statement on September 12, 2019 in connection with the IPO. A total of 442,153 shares of common stock were reserved for issuance under the ESPP. In addition, the number of shares of common stock that may be issued under the ESPP will automatically increase each January 1, through and including January 1, 2028, by the lesser of (i) 663,229 shares of common stock, (ii) 1% of the number of shares of the Company's common stock outstanding on the immediately preceding December 31 or (iii) such lesser number of shares determined by the administrator of the Company's ESPP. Effective January 1, 2020, the number of shares reserved for issuance under the ESPP was increased by 430,061 shares. No offering periods under the ESPP had been initiated as of December 31, 2020.

Stock Options

A summary of the changes in the Company's stock options from December 31, 2018 through December 31, 2020 is as follows:

	Shares	Weighted Average Exercise Price	Weighted Average Remaining Contractual Life (Years)	Aggregate Intrinsic Value
Outstanding at December 31, 2018	—	—	—	—
Granted	—	—	—	—
Outstanding at March 29, 2019	148,415	$ 1.65	—	—
Granted	3,177,233	5.21	—	—
Exercised	(9,080)	2.30	—	—
Forfeited/cancelled	(90,843)	2.18	—	—
Outstanding at December 31, 2019	3,225,725	5.08	9.4	107,771,472
Granted	1,580,788	35.90	—	—
Exercised	(190,484)	4.69	—	—
Forfeited/cancelled	(110,483)	23.49	—	—
Outstanding at December 31, 2020	4,505,546	15.51	8.7	256,860,405
Exercisable at December 31, 2020	1,402,718	8.25	8.5	90,150,057

Aggregate intrinsic value is calculated by subtracting the exercise price of the option from the closing price of the Company's common stock on closing date, multiplied by the number of shares per each option.

Assumptions used in determining the fair value of the stock options granted in 2020 include risk-free interest rate 0.31% – 1.73%, expected dividend yield of 0.00%, expected life in years of 5.50 - 6.08 and expected volatility of 70.0% - 75.0%.

2019 CEO Performance Award

In June 2019, the Company's CEO received an award of 176,411 stock options, or the 2019 CEO Performance Award. The 2019 CEO Performance Award can vest over 48 monthly installments based on four years of service, a performance condition (a liquidity event, such as an IPO) and market conditions, assuming continued employment and service through each vesting date. During the vesting period of four years, the 2019 CEO Performance Award is not earned unless the market condition is achieved on each vesting date. If the market condition is not achieved on a vesting date, but is achieved on a future vesting date, the award is earned for the entire period since the last date that such market condition was achieved. All or a portion of the award can be earned following the initial four-year service period if the market condition is next achieved after such four-year service period and Mr. Islam remains in continuous service. The market condition and performance condition are satisfied when the Company's common stock is listed on a U.S. national

securities exchange and achieves a 60-trading day average closing price of at least $28.49 per share (as adjusted for stock splits, recapitalizations, and similar events).

During the year ended December 31, 2020, 73,502 options of the CEO performance award became exercisable upon the satisfaction of the market condition applicable to this award.

At December 31, 2020, the total unrecognized compensation expense related to unvested stock options was $34.2 million, which the Company expects to recognize over a weighted-average remaining period of approximately 2.80 years. For the year ended December 31, 2020, total stock option compensation expense for outstanding stock options was $9.7 million.

Restricted Stock

A summary of the changes in the Company's restricted stock from December 31, 2018 through December 31, 2020 is as follows:

	Number of Shares	Weighted Average Grant Date Fair Value
Unvested and outstanding at December 31, 2018	2,503,744	$ 1.25
Vested	(228,209)	0.81
Forfeited	(12,570)	1.45
Unvested and outstanding at March 29, 2019	2,262,965	1.24
Vested	(737,530)	1.26
Forfeited	(235,998)	1.36
Unvested and outstanding at December 31, 2019	1,289,437	1.21
Vested	(588,345)	1.14
Forfeited	(14,224)	1.45
Unvested and outstanding at December 31, 2020	686,868	1.26

At December 31, 2020, the total unrecognized compensation expense related to unvested restricted stock was $0.3 million, which the Company expects to recognize over a weighted-average remaining period of approximately 0.86 years. For the year ended December 31, 2020, total restricted stock compensation expense was $0.3 million.

10. License and Collaboration Agreements

Pfizer Inc.

In August and October 2017, the Company entered into four license agreements with Pfizer Inc., or Pfizer, for rights to certain technologies, or the License Agreements. Under the License Agreements, the Company obtained from Pfizer the right to use research, develop, manufacture and commercialize certain products, including nirogacestat and mirdametinib. In connection with the License Agreements, the Company issued 6,437,500 units of Junior Series A convertible preferred units to Pfizer (see Note 1). No cash was received by the Company for these units.

The Company is required to pay Pfizer milestones payments of up to an aggregate of $232.5 million for nirogacestat and up to an aggregate of $229.8 million for mirdametinib, each upon achievement of certain commercial milestone events. Royalties are also payable under each License Agreement based on a specified percentage of net sales ranging from mid-single digit percentages to low 20s, Royalty payments under each License Agreement continue until the expiration of the last to expire licensed patent applicable to such product, but not less than ten years after the first commercial sale on a country-by-country basis.

BeiGene, Ltd.

In August 2018, the Company entered into a clinical collaboration agreement with BeiGene Ltd., or BeiGene to conduct a clinical study of the combination of mirdametinib and a BeiGene compound designated as lifirafenib. In accordance with the terms of the agreement, the Company and BeiGene share equally the costs associated with the clinical study. BeiGene is required to supply the BeiGene compound and the Company is required to supply mirdametinib to conduct the clinical study. The collaboration is guided by a joint steering committee. Specified areas of development require unanimous agreement among all members of the joint steering committee.

The Company recorded expense of $0.9 million and $1.0 million for the years ended December 31, 2020 and December 31, 2019, respectively, in connection with this collaboration agreement, which are classified as research and development expenses in the Company's statement of operations.

GSK clinical collaboration agreement

In June 2019, the Company entered into a clinical collaboration agreement with GlaxoSmithKline, or GSK, or the GSK Collaboration Agreement, to evaluate the safety, tolerability and preliminary efficacy of nirogacestat and belantamab mafodotin. Under the terms of the GSK Collaboration Agreement, GSK will sponsor and conduct the adaptive Phase 1b study of nirogacestat, in combination with GSK's B-cell maturation antigen, or BCMA antibody-drug conjugate, belantamab mafodotin, in patients with relapsed or refractory multiple myeloma. GSK will assume all development costs associated with the study. The Company agreed to manufacture and supply the Company compound for purposes of the study.

Pursuant to the GSK Collaboration Agreement, GSK is responsible for administering the clinical trial and is responsible for all costs associated with the direct conduct of the clinical trial, other than the manufacture and supply of nirogacestat and certain expenses related to intellectual property rights. The collaboration is managed by a joint development committee of equal representation by the Company and GSK. Following completion of the clinical trial, within a specified period of time, either party may propose new agreements for the purpose of performing one or more additional clinical trials of the combination therapy for the treatment of relapsed and refractory multiple myeloma. If a party proposes to conduct an additional clinical trial, the parties will negotiate in good faith, without obligation, the details of a definitive agreement to provide for the expansion of the clinical collaboration. If the parties do not reach an agreement, and only one party wishes to proceed with an additional clinical trial, it may do so if the other party does not object to the protocol based on safety concerns.

Allogene clinical collaboration agreement

In January 2020, the Company entered into a clinical trial collaboration and supply agreement with Allogene Therapeutics, or Allogene, to evaluate nirogacestat in combination with ALLO-715, Allogene's investigational allogeneic BCMA-targeted chimeric antigen receptor, or CAR, T cell product, in patients with relapsed or refractory multiple myeloma.

Allogene is responsible for administering the Phase 1 clinical trial and is responsible for all costs associated with the direct conduct of the clinical trial, other than the manufacture and supply of nirogacestat and certain expenses related to intellectual property rights. The collaboration is managed by a joint development committee of equal representation by the Company and Allogene.

Janssen clinical collaboration agreement

In September 2020, the Company entered into a clinical collaboration and supply agreement with Janssen Biotech, Inc., or Janssen, to evaluate the Company's investigational gamma secretase inhibitor, or GSI, nirogacestat, in combination with Janssen's bispecific antibody targeting BCMA, and CD3, teclistamab, in patients with relapsed or refractory multiple myeloma.

Janssen is responsible for administering the Phase 1 clinical trial and is responsible for all costs associated with the direct conduct of the clinical trial, other than the manufacture and supply of nirogacestat and certain expenses related to intellectual property rights. The collaboration is managed by a joint oversight committee of equal representation by the Company and Janssen.

Precision BioSciences clinical collaboration agreement

In September 2020, the Company entered into a clinical trial collaboration agreement with Precision BioSciences, Inc., or Precision, to evaluate nirogacestat in combination with PBCAR269A, an investigational allogeneic, or CAR-T cell therapy candidate targeting BCMA, in patients with relapsed or refractory multiple myeloma.

Precision is responsible for administering the Phase 1/2a clinical trial and is responsible for all costs associated with the direct conduct of the clinical trial, other than the manufacture and supply of nirogacestat and certain expenses related to intellectual property rights. The collaboration is managed by a joint steering committee of equal representation by the Company and Precision.

Pfizer clinical collaboration agreement

In October 2020, the Company entered into a clinical trial collaboration and supply agreement with Pfizer to evaluate nirogacestat in combination with Pfizer's bispecific antibody targeting BCMA and CD3, elranatamab, in patients with relapsed or refractory multiple myeloma.

Pfizer is responsible for administering the Phase 1b/2 clinical trial and is responsible for all costs associated with the direct conduct of the clinical trial, other than the manufacture and supply of nirogacestat and certain expenses related to intellectual property rights. The collaboration is managed by a joint development committee of equal representation by the Company and Pfizer.

Jazz Pharmaceuticals asset purchase and exclusive license agreement

In October 2020, the Company and Jazz announced an asset purchase and exclusive license agreement, pursuant to which Jazz acquired the Company's fatty acid amide hydrolase, or FAAH, inhibitor program including PF-04457845. The FAAH inhibitor program was obtained by the Company as part of the License Agreements in 2017. Jazz made an upfront payment of $35 million to the Company with potential future payments of up to $375 million based upon the achievement of certain clinical development, regulatory, and commercial milestones. In addition, Jazz is obligated to pay the Company tiered sales-based royalties on future net sales of PF-04457845 in the single-digit range.

Pursuant to the Jazz Agreement, Jazz is obligated to use commercially reasonable efforts to develop and seek regulatory approval for at least one product in the United States and if regulatory approval is obtained, to commercialize such product in the United States.

Consideration received under the Jazz Agreement

The Company evaluated the Jazz Agreement under ASC 606, and determined there was a single performance obligation and the license was the predominant item in a bundle of goods that was distinct. The Company transferred all items in the bundle of goods, including the license, in the period ended December 31, 2020. The license is functional intellectual property, given the functionality of the intellectual property is not expected to change substantially as a result of the Company's ongoing activities, and accordingly, revenue should be recognized at a point in time. The Company recognized the upfront payment as revenue in the period ended December 31, 2020. The Company will not recognize development or regulatory approval milestones until the related activity has been achieved; and royalties, including commercial milestone payments based on the level of sales, will be recognized at the later of (i) when the related sales occur, or (ii) when the performance obligation to which some or all the royalty has been allocated has been satisfied (or partially satisfied), which for the Jazz Agreement will be the period when the related sales occur.

11. Investments

MapKure

In June 2019, the Company announced the formation of MapKure, an entity jointly owned by the Company and BeiGene. BeiGene licensed to MapKure exclusive rights to BGB-3245, an oral, small molecule selective inhibitor of specific BRAF driver mutations and genetic fusions. MapKure is advancing BGB-3245 through clinical development for solid tumor patients harboring BRAF driver mutations and genetic fusions that were observed to be sensitive to the compound in preclinical studies. In addition to the Company's equity ownership in MapKure, the Company has appointed a member to each of MapKure's joint steering committee and board of directors. The Company also contributes to clinical development and other operational activities for BGB-3245 through a service agreement with MapKure.

In conjunction with the formation of MapKure in June 2019, the Company purchased 3,500,000 Series A preferred units of MapKure, or a 25% ownership interest, for $3.5 million, and BeiGene received 10,000,000 Series A preferred units as payment for its contributed intellectual property, or a 71.4% ownership interest. Two individuals each purchased 250,000 Series A preferred units, or 1.8% ownership interest each.

In June 2020, the Company purchased an additional 3,500,000 Series A preferred units of MapKure for $3.5 million, as required by the terms of the initial investment in MapKure. As of December 31, 2020, the Company's ownership interest in MapKure is 38.9%.

The Company determined that MapKure is a variable interest entity. The Company is not the primary beneficiary, as the Company does not have the power to direct the activities that most significantly impact the economic performance of MapKure. Accordingly, the Company does not consolidate the financial statements of this entity and accounts for this investment using the equity method of accounting. The Company reaffirmed its assessment as of December 31, 2020. In accordance with ASC 323-10-35-6, the Company records its portion of MapKure's earnings or losses based on a one quarter lag.

For the year ended December 31, 2020, the Company recognized a $0.6 million loss for its portion of MapKure's losses. The Company's investment in MapKure is included in "Equity method investments" in the consolidated balance sheet. The balance of the Company's investment was $3.9 million at December 31, 2020, representing the maximum exposure to loss as a result of the Company's involvement with MapKure.

12. Commitments and Contingencies

As of December 31, 2020, the Company had obligations consisting of operating leases for facilities. Refer to Footnote 7: *Leases* for more information.

The Company enters into contracts in the normal course of business for clinical trials, preclinical studies, manufacturing and other services and products for operating purposes. These contracts generally provide for termination following a certain period after notice and therefore the Company believes that non-cancelable obligations under these agreements are not material.

Additionally, the Company has excluded milestone or royalty payments or other contractual payment obligations as the timing and amount of such obligations are unknown or uncertain.

Contingencies

From time to time, the Company may be involved in disputes or regulatory inquiries that arise in the ordinary course of business. When the Company determines that a loss is both probable and reasonably estimable, a liability is recorded and disclosed if the amount is material to the financial statements taken as a whole. When a material loss contingency is only

reasonably possible, the Company does not record a liability, but instead discloses the nature and the amount of the claim, and an estimate of the loss or range of loss, if such an estimate can reasonably be made.

As of December 31, 2020, and December 31, 2019, there was no litigation or contingency that created at least a reasonable possibility of a material loss.

13. Income Taxes

Prior to the Reorganization, SpringWorks Therapeutics, LLC elected to be treated under the partnership provisions of the Internal Revenue Service code. However, its five wholly owned subsidiaries, SpringWorks Operating Company, SpringWorks Subsidiary 1, SpringWorks Subsidiary 2, SpringWorks Subsidiary 3, and SpringWorks Subsidiary 4, or Combined Subsidiaries, are taxable corporations.

Subsequent to the Reorganization, SpringWorks Therapeutics, Inc. became the 100% owner of SpringWorks Therapeutics, LLC, creating a new ultimate parent company, and a consolidated group for income tax reporting. The Reorganization and change in tax status of the reporting entity did not have an impact on the consolidated tax provision.

For the years ended December 31, 2020 and December 31, 2019, the Company did not have a current or deferred income tax expense or benefit as the Company has incurred losses since inception.

As of December 31, 2020, the Company has federal, state and city net operating loss carryforwards of $110.9 million, $0.6 million and $3.7 million, respectively, which are available to reduce future taxable income. Federal net operating loss carryforwards of $34.8 million, $55.9 million and $16.0 million reported in 2020, 2019 and 2018, will be available to offset 80% of taxable income for an indefinite period of time, until fully utilized. Federal net operating loss carryforwards of $4.3 million reported in 2017 and the state and city net operating loss carryforwards expire at various dates through 2038. The Company also has federal tax credits of $7.2 million, which may be used to offset future tax liabilities. These tax credit carryforwards will expire at various dates beginning in 2038.

The net operating loss and tax credit carryforwards are subject to review and possible adjustment by the Internal Revenue Service and state tax authorities. Net operating loss and tax credit carryforwards may become subject to an annual limitation in the event of certain cumulative changes in the ownership interest of significant shareholders over a three-year period in excess of 50%, as defined under Sections 382 and 383 of the Internal Revenue Code, respectively, as well as similar state provisions and other provisions within the Internal Revenue Code. This could limit the amount of tax attributes that can be utilized annually to offset future taxable income or tax liabilities. The amount of the annual limitation is determined based on the value of the Company immediately prior to an ownership change. Subsequent ownership changes may further affect the limitation in future years.

The Company has not recorded any reserves for uncertain tax positions as of December 31, 2020 or December 31, 2019. The Company has completed a study for the research and development credit carryforwards through December 31, 2019, and has not yet conducted a study of research and development credit carryforwards for the year ended December 31, 2020. The 2020 study, once completed, may result in an adjustment to the Company’s research and development credit carryforwards. A full valuation allowance has been provided against the Company’s research and development credits and, if an adjustment is required, this adjustment would be offset by an adjustment to the valuation allowance. Thus, there would be no impact to the balance sheets or statements of operations and comprehensive loss if an adjustment were required.

Interest and penalty charges, if any, related to unrecognized tax benefits will be classified as income tax expense in the accompanying statements of operations and comprehensive loss. As of December 31, 2020, the Company had no accrued interest or penalties related to uncertain tax positions.

Since the Company is in a loss carryforward position, it is generally subject to examination by the U.S. federal, state and local income tax authorities for all tax years in which a loss carryforward is available. The Company is not currently under examination by the Internal Revenue Service or any other jurisdictions for any tax years.

The principal components of the Subsidiaries deferred tax assets are as follows:

(in thousands)	As of December 31, 2020	2019
Deferred tax assets:		
Net operating loss carryforwards	$ 23,630	$ 16,252
Research and development credits	1,673	706
Orphan drug credit	5,519	71
Deferred rent	—	242
Accrued expenses	1,225	212
Depreciation	71	34
Stock compensation	1,972	496
Operating lease liabilities	574	—
Total deferred tax assets	34,664	18,013
Deferred tax liability:		
Operating lease right-of-use assets	(408)	—
Valuation allowance	(34,256)	(18,013)
Net deferred tax assets	$ —	$ —

ASC 740 requires a valuation allowance to reduce the deferred tax assets reported if, based on the weight of available evidence, it is more likely than not that some portion or all of the deferred tax assets will not be realized. After consideration of all the evidence, both positive and negative, the Company has recorded a full valuation allowance against its deferred tax assets at December 31, 2020 and December 31, 2019 because the Company's management has determined that it is more likely than not that these assets will not be realized. The increase in the valuation allowance of $16.2 million in 2020 primarily relates to the net loss incurred by the Company as well as federal research and orphan drug credits generated.

The effective tax rate for the Company for the years ended December 31, 2020, December 31, 2019 and December 31, 2018 was zero percent. A reconciliation of the income tax expense at the federal statutory tax rate to the Company's effective income tax rate follows:

	Year Ended December 31, 2020	2019	2018
Statutory tax rate	21.00 %	21.00 %	21.00 %
Federal and state return to provision adjustments	0.03	(0.01)	(1.08)
Stock-based compensation	0.55	—	—
Research and development credit	2.12	0.57	2.02
Orphan drug credit	11.95	—	—
Other	(0.01)	(0.03)	(0.04)
Change in valuation allowance	(35.64)	(21.53)	(21.90)
Effective tax rate	— %	— %	— %

14. 401(k) Plan

In 2017, the Company adopted a tax-qualified employee savings and retirement plan, or the 401(k) Plan, that covers all of its full-time employees who are at least 21 years of age. Pursuant to the 401(k) Plan, participants may elect to contribute up to the federally allowed maximum limits of their pretax earnings to the 401(k) Plan. As of December 31, 2020, the Company has not made any matching contributions.

15. Related Party Transactions

Pfizer is a significant shareholder of the Company and a former Pfizer employee is a member of the Board of Directors. See Note 9 for further details on transactions entered into with Pfizer.

Prior to the IPO, the Company regarded the Board of Directors, or BOD, as related parties. The Company recorded consulting and BOD expenses totaling $0.2 million for the period January 1, 2019 through the date of the IPO. For the year ended December 31, 2018, the Company recorded consulting and BOD expenses totaling $0.3 million.

16. Net Loss per Share

Basic and diluted net loss per unit and share is calculated as follows:

	Year Ended December 31,		
(In thousands, except share and per-share data)	**2020**	**2019**	**2018**
Numerator:			
Net loss	$ (45,574)	$ (58,306)	$ (17,813)
Net gain attributable to extinguishment of Series A convertible preferred and Junior Series A convertible preferred units	—	7,729	—
Net loss attributable to common stockholders	$ (45,574)	$ (50,577)	$ (17,813)
Denominator:			
Weighted average units outstanding, basic and diluted	—	—	341,014
Weighted average shares outstanding, basic and diluted	43,300,063	13,274,836	—
Net loss per unit, basic and diluted	$ —	$ —	$ 52.24
Net loss per share, basic and diluted	$ (1.05)	$ (3.81)	$ —

Potentially dilutive securities that were not included in the diluted per share calculations because they would be anti-dilutive were as follows:

	As of December 31,	
	2020	**2019**
Common stock options issued and outstanding	4,505,546	3,225,725
Restricted stock subject to future vesting	686,868	1,289,437
Total potentially dilutive securities	5,192,414	4,515,162

Item 9. Changes in and Disagreements With Accountants on Accounting and Financial Disclosure

None.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our Chief Executive Officer and Chief Financial Officer (our principal executive officer and principal financial officer, respectively), conducted an evaluation of the effectiveness of the design and operation of our disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, as of the end of the period covered by this report.

Based on our evaluation, our Chief Executive Officer and Chief Financial Officer concluded that, as of December 31, 2020, our disclosure controls and procedures were effective to provide reasonable assurance that the information we are required to disclose in reports that we file or submit under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in SEC rules and forms, and that such information is accumulated and communicated to our management, including our principal executive officer and principal financial officer, as appropriate, to allow timely decisions regarding required disclosures.

Internal Control Over Financial Reporting

Management's Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting, as such term is defined in Rule 13a-15(f) of the Exchange Act, as a process designed by, or under the supervision of, the company's principal executive and principal financial officers and effected by the company's board of directors, management and other personnel, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles and includes those policies and procedures that: (i) pertain to the maintenance of records that in reasonable detail accurately and fairly reflect the transactions and dispositions of the assets of the company; (ii) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of our company are being made only in accordance with authorizations of management and directors of the company; and (iii) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of our company's assets that could have a material effect on the financial statements.

In connection with the preparation of this Annual Report, our management, including our Chief Executive Officer and Chief Financial Officer, assessed the effectiveness of our internal control over financial reporting as of December 31, 2020 based on criteria established in *Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission* (2013 framework) (the "COSO criteria"). Based on its assessment, our management concluded that our internal control over financial reporting was effective as of December 31, 2020.

Attestation Report of Independent Registered Public Accounting Firm

The effectiveness of our internal control over financial reporting as of December 31, 2020 has been audited by Ernst & Young LLP, an independent registered public accounting firm, as stated in their report included elsewhere in this Annual Report on Form 10-K.

Limitations on the Effectiveness of Controls

Our management, including our Chief Executive Officer and Chief Financial Officer, does not expect that our disclosure controls and procedures or our internal control over financial reporting will prevent all error and all fraud. A

control system, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. Further, the design of a control system must reflect the fact that there are resource constraints, and the benefit of controls must be considered relative to their costs. Because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that all control issues and instances of fraud, if any, have been detected. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Changes in Internal Control over Financial Reporting

There was no change in our internal control over financial reporting (as defined in Rule 13a-15(f) of the Exchange Act) identified in connection with the evaluation required by paragraph (d) of Rule 13a-15 of the Exchange Act, which occurred during the fourth quarter of the year ended December 31, 2020 which has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

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

Opinion on Internal Control Over Financial Reporting

We have audited SpringWorks Therapeutics, Inc.'s internal control over financial reporting as of December 31, 2020, based on criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) (the COSO criteria). In our opinion, SpringWorks Therapeutics, Inc. ("the Company") maintained, in all material respects, effective internal control over financial reporting as of December 31, 2020, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the consolidated balance sheets of the Company as of December 31, 2020 and 2019, the related consolidated statements of operations, comprehensive loss, preferred unit and members'/stockholders' equity/(deficit), and cash flows for each of the three years in the period ended December 31, 2020, and the related notes of the Company and our report dated February 25, 2021 expressed an unqualified opinion thereon.

Basis for Opinion

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

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

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

Definition and Limitations of Internal Control Over Financial Reporting

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

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

/s/ Ernst & Young LLP

New York, New York
February 25, 2021

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 our definitive proxy statement with respect to our 2021 Annual Meeting of Shareholders to be filed with the SEC, and is incorporated herein by reference.

Item 11. Executive Compensation

The information required by this item will be included in our definitive proxy statement with respect to our 2021 Annual Meeting of Shareholders to be filed with the SEC, and is incorporated herein by reference.

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

The information required by this item will be included in our definitive proxy statement with respect to our 2021 Annual Meeting of Shareholders to be filed with the SEC, and is incorporated herein by reference.

Item 13. Certain Relationships and Related Transactions, and Director Independence

The information required by this item will be included in our definitive proxy statement with respect to our 2021 Annual Meeting of Shareholders to be filed with the SEC, and is incorporated herein by reference.

Item 14. Principal Accounting Fees and Services

The information required by this item will be included in our definitive proxy statement with respect to our 2021 Annual Meeting of Shareholders to be filed with the SEC, and is incorporated herein by reference.

PART IV

Item 15. Exhibits, Financial Statement Schedules

Financial Statements

The consolidated financial statements filed as part of this report are listed on the Index to Financial Statements on page 120.

Financial Statement Schedules

All schedules for which provision is made in the applicable accounting regulations of the Securities and Exchange Commission are not required under the related instructions or are inapplicable and, therefore, have been omitted.

Exhibits

The exhibits required by Item 601 of Regulation S-K and Item 15(b) of this Annual Report on Form 10-K are listed in the Exhibit Index immediately preceding the signature page of this Annual Report on Form 10-K. The exhibits listed in the Exhibit Index are incorporated by reference herein.

Item 16. Form 10-K Summary

The Company has elected not to include summary information.

EXHIBIT INDEX

Exhibit Number	Description
3.1	Amended and Restated Certificate of Incorporation, as amended, of the Registrant, as currently in effect. (Incorporated by reference to Exhibit 3.1 to the Registrant's Current Report on Form 8-K filed with the Securities and Exchange Commission on September 17, 2019).
3.2	Bylaws of the registrant, as currently in effect. (Incorporated by reference to Exhibit 3.2 to the Registrant's Current Report on Form 8-K filed with the Securities and Exchange Commission on September 17, 2019).
3.3	Amendment to Bylaws of the Registrant, as currently in effect. (Incorporated by reference to Exhibit 3.1 to the Registrant's Current Report on Form 8-K filed with the Securities and Exchange Commission on May 27, 2020).
4.1	Specimen Stock Certificate evidencing shares of common stock (Incorporated by reference to Exhibit 4.1 to the Registrant's Registration Statement on Form S-1/A (File No. 333-233351) filed with the Securities and Exchange Commission on September 12, 2019).
4.2	Amended and Restated Investors' Rights Agreement among the Registrant and certain of its stockholders, dated August 30, 2018 (Incorporated by reference to Exhibit 4.2 to the Registrant's Registration Statement on Form S-1 (File No. 333-233351) filed with the Securities and Exchange Commission on September 12, 2019).
4.3	Description of the Registrant's Securities (Incorporated by reference to Exhibit 4.3 to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2019, filed March 12, 2020.)
4.4*	Amendment to the Amended and Restated Investors' Rights Agreement, dated as of February 25, 2021.
10.1	2019 Stock Option and Incentive Plan and forms of award agreements thereunder (Incorporated by reference to Exhibit 10.1 to the Registrant's Registration Statement on Form S-1/A (File No. 333-233351) filed with the Securities and Exchange Commission on September 12, 2019).
10.2	2019 Stock Option and Equity Incentive Plan and forms of award agreements thereunder (Incorporated by reference to Exhibit 10.2 to the Registrant's Registration Statement on Form S-1/A (File No. 333-233351) filed with the Securities and Exchange Commission on September 12, 2019).
10.3	2019 Employee Stock Purchase Plan (Incorporated by reference to Exhibit 10.3 to the Registrant's Registration Statement on Form S-1/A (File No. 333-233351) filed with the Securities and Exchange Commission on September 12, 2019).
10.4	Senior Executive Cash Incentive Bonus Plan (Incorporated by reference to Exhibit 10.4 to the Registrant's Registration Statement on Form S-1/A (File No. 333-233351) filed with the Securities and Exchange Commission on September 12, 2019).
10.5*	Amended and Restated Non-Employee Director Compensation Policy.
10.6	Form of Indemnification Agreement, by and between the Registrant and each of its Directors (Incorporated by reference to Exhibit 10.6 to the Registrant's Registration Statement on Form S-1/A (File No. 333-233351) filed with the Securities and Exchange Commission on September 12, 2019).
10.7	Form of Indemnification Agreement, by and between the Registrant and each of its Officers (Incorporated by reference to Exhibit 10.7 to the Registrant's Registration Statement on Form S-1/A (File No. 333-233351) filed with the Securities and Exchange Commission on September 12, 2019).
10.8§	Amended and Restated License Agreement by and among the Registrant, Pfizer Inc., SpringWorks Subsidiary 2, Inc. and Pfizer Products, Inc., dated July 31, 2019 (Incorporated by reference to Exhibit 10.8 to the Registrant's Registration Statement on Form S-1/A (File No. 333-233351) filed with the Securities and Exchange Commission on September 12, 2019).
10.9§	Amended and Restated License Agreement by and among the Registrant, Pfizer Inc., SpringWorks Subsidiary 3, Inc. and Warner-Lambert Company LLC, dated August 7, 2019 (Incorporated by reference to Exhibit 10.9 to the Registrant's Registration Statement on Form S-1/A (File No. 333-233351) filed with the Securities and Exchange Commission on September 12, 2019).
10.10§	Clinical Collaboration Agreement by and among SpringWorks Subsidiary 3, PBC and BeiGene, Ltd., dated August 16, 2018 (Incorporated by reference to Exhibit 10.10 to the Registrant's Registration Statement on Form S-1/A (File No. 333-233351) filed with the Securities and Exchange Commission on September 12, 2019).

10.11§	Clinical Trial Collaboration and Supply Agreement by and between the Registrant and GlaxoSmithKline LLC, dated June 25, 2019 (Incorporated by reference to Exhibit 10.11 to the Registrant's Registration Statement on Form S-1/A (File No. 333-233351) filed with the Securities and Exchange Commission on September 12, 2019).
10.12§	Assignment and Assumption of Lease, dated as of October 10, 2018, by and between R&D Subsidiary and Structured Portfolio Management LLC (Incorporated by reference to Exhibit 10.12 to the Registrant's Registration Statement on Form S-1/A (File No. 333-233351) filed with the Securities and Exchange Commission on September 12, 2019).
10.13#	Employment Agreement between SpringWorks Therapeutics, Inc. and Saqib Islam, dated October 10, 2019 (Incorporated by reference to Exhibit 10.8 to the Registrant's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on November 12, 2019).
10.14#	Employment Agreement between SpringWorks Therapeutics, Inc. and Francis I. Perier, Jr., dated October 10, 2019 (Incorporated by reference to Exhibit 10.9 to the Registrant's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on November 12, 2019).
10.15#	Employment Agreement between SpringWorks Therapeutics, Inc. and Jens Renstrup, dated October 10, 2019 (Incorporated by reference to Exhibit 10.10 to the Registrant's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on November 12, 2019).
10.16#	Employment Agreement between SpringWorks Therapeutics, Inc. and Badreddin Edris, dated October 10, 2019 (Incorporated by reference to Exhibit 10.11 to the Registrant's Quarterly Report on Form 8-K filed with the Securities and Exchange Commission on November 12, 2019).
10.17#	Employment Agreement between SpringWorks Therapeutics, Inc and L. Mary Smith, dated October 10, 2019 (Incorporated by reference to Exhibit 10.12 to the Registrant's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on November 12, 2019).
21.1	Subsidiaries of the Registrant (Incorporated by reference to Exhibit 21.1 to the Registrant's Registration Statement on Form S-1/A (File No. 333-233351) filed with the Securities and Exchange Commission on September 12, 2019).
23.1*	Consent of Ernst & Young LLP, Independent Registered Public Accounting Firm.
24.1*	Power of Attorney (included on signature page to this Annual Report on Form 10-K).
31.1*	Certification of Principal Executive Officer pursuant to Rule 13a-14(a) or Rule 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2*	Certification of Principal Financial Officer pursuant to Rule 13a-14(a) or Rule 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1†	Certification of Principal Executive Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
32.2†	Certification of Principal Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to by Section 906 of the Sarbanes-Oxley Act of 2002.
101.INS	Inline XBRL Instance Document.
101.SCH	Inline XBRL Taxonomy Extension Schema Document.
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document.
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document.
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document.
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document.
104	Cover Page Interactive Data File (formatted as inline XBRL and contained in Exhibit 101)

* Filed herewith.

\# Indicates a management contract or any compensatory plan, contract or arrangement.

† This certification will not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or otherwise subject to the liability of that section. Such certification will not be deemed to be incorporated by reference into any filing under the Securities Act of 1933, as amended, except to the extent specifically incorporated by reference into such filing.

§ Confidential treatment has been granted with respect to redacted portions of this exhibit. Redacted portions of this exhibit have been filed separately with the Securities and Exchange Commission.

SIGNATURES

Pursuant to the requirements 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.

SPRINGWORKS THERAPEUTICS, INC.

Date: February 25, 2021

By: /s/ Saqib Islam
Saqib Islam
Chief Executive Officer

POWER OF ATTORNEY

Each person whose individual signature appears below hereby authorizes and appoints Saqib Islam and Francis I. Perier, Jr., and each of them, with full power of substitution and resubstitution and full power to act without the other, as his or her true and lawful attorney-in-fact and agent to act in his or her name, place and stead and to execute in the name and on behalf of each person, individually and in each capacity stated below, and to file any and all amendments to this annual report on Form 10-K and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing, ratifying and confirming all that said attorneys-in-fact and agents or any of them or their or his substitute or substitutes may lawfully do or cause to be done by virtue thereof.

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

Signature	Title	Date
/s/ Saqib Islam Saqib Islam, J.D.	Chief Executive Officer and Director (Principal Executive Officer)	February 25, 2021
/s/ Francis I. Perier, Jr. Francis I. Perier, Jr.	Chief Financial Officer (Principal Financial Officer)	February 25, 2021
/s/ Michael P. Nofi Michael P. Nofi	Chief Accounting Officer (Principal Accounting Officer)	February 25, 2021
/s/ Daniel S. Lynch Daniel S. Lynch, M.B.A.	Chairman	February 25, 2021
/s/ Alan Fuhrman Alan Fuhrman	Director	February 25, 2021
/s/ Julie Hambleton Julie Hambleton, M.D.	Director	February 25, 2021
/s/ Freda Lewis-Hall Freda Lewis-Hall, M.D, DFAPA	Director	February 25, 2021
/s/ Jeffrey Schwartz Jeffrey Schwartz, M.B.A.	Director	February 25, 2021
/s/ Stephen Squinto Stephen Squinto, Ph.D.	Director	February 25, 2021

Exhibit 4.4

SPRINGWORKS THERAPEUTICS, INC.

AMENDMENT TO THE
AMENDED AND RESTATED INVESTORS' RIGHTS AGREEMENT

This Amendment to the Amended and Restated Investors' Rights Agreement (this "Amendment") is made as of February 25, 2021 by and among SpringWorks Therapeutics, Inc., a Delaware corporation (the "Company"), and certain holders of outstanding Registrable Securities.

Reference is hereby made to that certain Amended and Restated Investor Rights Agreement, dated August 30, 2019, by and among the Company and the signatories thereto, as amended to date (the "Rights Agreement"). Capitalized terms used herein that are not otherwise defined shall have the meaning ascribed thereto in the Rights Agreement.

WHEREAS, Section 6.6 of the Rights Agreement provides that any term of the Rights Agreement may be amended, modified or terminated with the written consent of the Company and the holders of at least a majority of the Requisite Parties, provided that the written consent of any particular Investor need not be obtained in connection with such amendment, modification or termination of any term of the Rights Agreement so long as such amendment, modification or termination applies to all Investors in the same fashion;

NOW THEREFORE, for good and valuable consideration, the receipt of and sufficiency of which is hereby acknowledged, each of the Requisite Parties and the Company agree as follows:

1. The undersigned Investors, together comprising the Requisite Parties, hereby agree to amend and restate Section 2.13 of the Rights Agreement in its entirety, to read as follows:

"2.13 Termination of Registration Rights. The right of any Holder to request registration or inclusion of Registrable Securities in any registration pursuant to Subsections 2.1 or 2.2 shall terminate upon the earliest to occur of:

(a) immediately before the closing of a Deemed Liquidation Event, as such term is defined in the Company's Certificate of Incorporation;

(b) as to such Holder, such earlier time after the IPO at which all shares of Registrable Securities held or entitled to be held upon conversion by such Holder may immediately be sold under SEC Rule 144 without regard to time or volume limitations; and

(c) the fourth anniversary of the IPO.

2. Except as expressly amended, modified, supplemented or waived hereby, the provisions of the Rights Agreement are and will remain in full force and effect.

3. This Amendment may be executed in any number of counterparts, each of which shall constitute one agreement binding on all the parties to the Rights Agreement.

4. This Amendment shall be governed by, and construed and enforced in accordance with, the laws of the State of New York, exclusive of its choice of laws and conflicts of laws rules.

NO ANNOUNCEMENT HAS BEEN MADE CONCERNING THE FILING OF THE REGISTRATION STATEMENT OR THE OFFERING. ACCORDINGLY, THIS INFORMATION MUST BE KEPT STRICTLY CONFIDENTIAL.

[*Signature page follows*]

IN WITNESS WHEREOF, the undersigned have executed this Amendment as of the date first set forth above.

SPRINGWORKS THERAPEUTICS, INC.

By: /s/ Francis I. Perier, Jr.
Name: Francis I. Perier, Jr.
Title: Chief Financial Officer

IN WITNESS WHEREOF, the undersigned have executed this Amendment as of the date first set forth above.

ORBIMED PRIVATE INVESTMENTS VI, LP

By: OrbiMed Capital GP VI LLC, its General Partner

By: : OrbiMed Advisors LLC, its Managing Member

By: /s/ Carl Gordon

Name: Carl Gordon

Title: Member

BC SW, LP

By: Bain Capital Life Sciences Investors, LLC its general partner

By: /s/ Jeff Schwartz

Name: Jeff Schwartz

Title: Managing Director

PFIZER INC.

By: /s/ Barbara Dalton

Name: Barbara Dalton

Title: Vice President

PFIZER INC.

By: /s/ Barbara Dalton

Name: Barbara Dalton

Title: President

Exhibit 10.5

SPRINGWORKS THERAPEUTICS, INC.

AMENDED AND RESTATED

NON-EMPLOYEE DIRECTOR COMPENSATION POLICY

This Amended and Restated Non-Employee Director Compensation Policy (the "Policy") of dated February 23, 2021 (the "Effective Date") of SpringWorks Therapeutics, Inc., a Delaware corporation (the "Company") amends and restates the previous Non-Employee Director Compensation Policy which became effective as of the effective time of the registration statement for the Company's initial firm commitment underwritten public offering of equity securities on September 12, 2019. The purpose of the Policy is to provide a total compensation package that enables the Company to attract and retain, on a long-term basis, high-caliber directors who are not employees or officers of the Company. This Policy and will apply to all non-employee directors of the Board (such directors, the "Eligible Directors") of the Company (the "Board"). In furtherance of this purpose, except as otherwise provided in any written agreement between the Company and an Eligible Director, all Eligible Directors shall be paid compensation for services provided to the Company as set forth below:

Cash Retainers

Annual Retainer for Board Membership: $40,000 for general availability and participation in meetings and conference calls of our Board. No additional compensation for attending individual Board meetings.

Additional Annual Retainer for Non-Executive Chair of the Board: $30,000

Additional Annual Retainers for Committee Membership:

Audit Committee Chairperson:	$15,000
Audit Committee member:	$ 7,500
Compensation Committee Chairperson:	$10,000
Compensation Committee member:	$ 5,000
Nominating and Corporate Governance Committee Chairperson:	$ 8,000
Nominating and Corporate Governance Committee member:	$ 4,000
Research and Development Committee Chairperson	$10,000
Research and Development Committee member	$ 5,000

Note: Chair and committee member retainers are in addition to retainers for members of the Board of Directors.

All cash retainers will be paid quarterly, in arrears, or upon the earlier of resignation or removal of the Eligible Director. Cash retainers owing to Eligible Directors shall be annualized, meaning that with respect to Eligible Directors who join the Board during the calendar year.

For purposes of this Policy, "Value" means with respect to any award of stock options the grant date fair value of the option (i.e., Black-Scholes Value) determined in accordance with the reasonable assumptions and methodologies employed by the Company for calculating the fair value of options under ASC 718.

Equity Retainers

Initial Equity Grant: Upon the Effective Date, each Eligible Director serving as of such date shall receive a one-time equity grant of an option to purchase that number of shares of Common Stock that has a Value equivalent to $840,000, with 80% of such value to be provided in stock options for shares of the Company's common stock, par value $0.0001 per share ("Common Stock") and 20% of such value to be provided in restricted stock awards, representing shares of the Company's Common Stock. Such initial equity grant shall vest in equal annual installments for three years starting from the Eligible Director's commencement of service on the Board any of the above committees, as applicable, subject to the Eligible Director's continued service on the Board through each such date. For each Eligible Director joining the Board after the Effective Date, upon his or her initial appointment to the Board, each such Eligible Director shall receive a one-time equity grant of an option to purchase that number of shares of Common Stock that has a Value equivalent to $840,000. Such initial equity grant shall vest in equal annual installments for three years starting from the Eligible Director's commencement of service on the Board any of the above committees, as applicable, subject to the Eligible Director's continued service on the Board through each such date.

Annual Equity Grant: Immediately following each annual meeting of the Company's stockholders, each continuing Eligible Director will receive an annual equity grant of an option to purchase that number of shares of Common Stock that has a Value equivalent to $420,000, with 80% of such value to be provided in stock options for shares of the Company's Common Stock and 20% of such value to be provided in restricted stock awards, representing shares of the Company's Common Stock. Such annual equity grant shall vest on the earlier of the one-year anniversary of the grant date and the Company's next annual meeting of stockholders, subject to the Eligible Director's continued service on the Board through such date.

All of the foregoing option grants will become immediately exercisable upon the death, disability of an Eligible Director or upon a Sale Event (as defined in the Company's 2019 Stock Option and Incentive Plan). In addition, Eligible Directors will have until the earlier of one year following cessation of service as a director or the original expiration date of the option to exercise the option (to the extent vested at the date of such cessation), provided that the Eligible Director has not been removed for cause.

Any stock option granted to an Eligible Director pursuant to this Policy will be granted at an exercise price equal to the Fair Market Value of a share of Common Stock on the date of grant (as defined in the Company's 2019 Stock Option and Incentive Plan).

Expenses

The Company shall reimburse all reasonable out-of-pocket expenses incurred by Eligible Directors in attending Board and committee meetings.

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the Registration Statements:

(1) Registration Statement on Form S-3 No. 333-249339 of SpringWorks Therapeutics, Inc, and

(2) Registration Statements on Form S-8 Nos. 333- 237350 and 333-234365 pertaining to the 2019 Stock Option and Incentive Plan, 2019 Stock Option and Equity Incentive Plan and 2019 Employee Stock Purchase Plan of SpringWorks Therapeutics, Inc;

of our reports dated February 25, 2021, with respect to the consolidated financial statements of SpringWorks Therapeutics, Inc and the effectiveness of internal control over financial reporting of SpringWorks Therapeutics, Inc., included in this Annual Report (Form 10-K) for the year ended December 31, 2020.

/s/ Ernst & Young LLP

New York, New York
February 25, 2021

Exhibit 31.1

CERTIFICATION PURSUANT TO RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934, AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

CERTIFICATIONS

I, Saqib Islam, certify that:

1. I have reviewed this Annual Report on Form 10-K of SpringWorks 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) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

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

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

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

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

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

Date: February 25, 2021

By: /s/ Saqib Islam
Saqib Islam
Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATION PURSUANT TO RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934, AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

CERTIFICATIONS

I, Francis I. Perier, Jr., certify that:

1. I have reviewed this Annual Report on Form 10-K of SpringWorks 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) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

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

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

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

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

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

Date: February 25, 2021

By: /s/ Francis I. Perier, Jr.
Francis I. Perier, Jr.
Chief Financial Officer
(Principal Financial Officer)

Exhibit 32.1

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

AS ADOPTED PURSUANT TO

SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report on Form 10-K of SpringWorks Therapeutics, Inc. (the "Company") for the year ended December 31, 2020, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, Saqib Islam, Chief Executive Officer of the Company, hereby certifies, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to his knowledge:

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

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

Date: February 25, 2021

By: /s/ Saqib Islam
Saqib Islam
Chief Executive Officer
(Principal Executive Officer)

Exhibit 32.2

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

AS ADOPTED PURSUANT TO

SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report on Form 10-K of SpringWorks Therapeutics, Inc. (the "Company") for the year ended December 31, 2020, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, Francis I. Perier, Jr., Chief Financial Officer of the Company, hereby certifies, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to his knowledge:

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

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

Date: February 25, 2021

By: /s/ Francis I. Perier, Jr.
Francis I. Perier, Jr.
Chief Financial Officer
(Principal Financial Officer)