FOLLOWING IS THE COMPANY'S ANNUAL REPORT ON FORM 10-K
FOR THE FISCAL YEAR ENDED DECEMBER 31, 2021

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

FORM 10-K

(Mark One)

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

For the fiscal year ended: December 31, 2021

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

For the transition period from to

Commission file number: 000-31141

INFINITY PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**33-0655706**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**

1100 Massachusetts Avenue, Floor 4, Cambridge, Massachusetts 02138

(Address of principal executive offices) (zip code)

Registrant's telephone number, including area code: (617) 453-1000

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

Title of each class	**Trading Symbol**	**Name of each exchange on which registered**
Common Stock, $0.001 par value	**INFI**	**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 (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See 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 register 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 Common Stock held by non-affiliates of the registrant as of June 30, 2021 was $259,501,798 based on the last reported sale price of the registrant's Common Stock on the Nasdaq Global Select Market on that date.

Number of shares outstanding of the registrant's Common Stock as of March 25, 2022: 89,155,311

Documents incorporated by reference:

Portions of our definitive proxy statement to be filed with the Securities and Exchange Commission no later than April 30, 2022 in connection with our 2022 annual meeting of stockholders are incorporated by reference into Part III of this Annual Report on Form 10-K.

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Cautionary Note Regarding Forward-Looking Information

The following discussion of our financial condition and results of operations contained in this Annual Report on Form 10-K should be read in conjunction with our consolidated financial statements and related notes included elsewhere in this report. Some of the information contained in this discussion and analysis and set forth elsewhere in this report, including information with respect to our plans and strategies for our business, the possible achievement of clinical development goals and milestones in 2022 and beyond, our future development efforts, our collaborations, and our future operating results and financial position, includes forward-looking statements that involve risks and uncertainties. We often use words such as "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "target," "potential," "will," "would," "could," "should," "continue," and other words and terms of similar meaning to help identify forward-looking statements, although not all forward-looking statements contain these identifying words. You also can identify these forward-looking statements by the fact that they do not relate strictly to historical or current facts. There are a number of important risks and uncertainties that could cause actual results or events to differ materially from those indicated by forward-looking statements made herein. These risks and uncertainties include those inherent in pharmaceutical research and development, such as adverse results in our drug development activities, decisions made by the U.S. Food and Drug Administration, or FDA, and other regulatory authorities with respect to the development and commercialization of our product candidates, our ability to obtain, maintain and enforce intellectual property rights for our product candidates, our dependence on our alliance partners, competition, our ability to obtain any necessary financing to conduct our planned activities and other risk factors described herein. We have included important factors in the cautionary statements included in this Annual Report on Form 10-K, particularly the factors discussed below under the heading "Risk Factor Summary," and the risk factors detailed further in Part I, Item 1A, "Risk Factors," that could cause actual results to differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis. Unless required by law, we do not undertake any obligation to update any forward-looking statements.

Market and Industry Data

Unless otherwise indicated, information contained in this Annual Report on Form 10-K concerning our industry and the markets in which we operate, including our general expectations, market position and market opportunity, is based on our management's estimates and research, as well as industry and general publications and research, surveys and studies conducted by third parties. We believe that the information from these third-party publications, research, surveys and studies included in this report is reliable. Management's estimates are derived from publicly available information, their knowledge of our industry and their assumptions based on such information and knowledge, which we believe to be reasonable. This data involves a number of assumptions and limitations which are necessarily subject to a high degree of uncertainty and risk due to a variety of factors, including those described in "Risk Factors" in Part I, Item 1A of this of this Annual Report on Form 10-K. These and other factors could cause our future performance to differ materially from our assumptions and estimates.

Summary of Risk Factors

The risk factors described below are a summary of the principal risk factors associated with an investment in us. These are not the only risks we face. Additional risks and uncertainties not presently known to us or that we presently deem less significant may also impair our business operations. You should carefully consider these risk factors, together with the risk factors set forth in "Risk Factors" in Part I, Item 1A of this Annual Report on Form 10-K and the other reports and documents filed by us with the U.S. Securities and Exchange Commission, or the SEC. If any of the following risks occur, our business, financial condition, and results of operations and future growth prospects could be materially and adversely affected, and the actual outcomes of matters as to which forward-looking statements are made in this report could be materially different from those anticipated in such forward-looking statements.

- We will need substantial additional funding, and if we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate the development of eganelisib or future efforts to commercialize eganelisib, including the potential initiation of two new clinical trials in 2022. We cannot provide assurances that our estimates regarding expenses, future revenue, capital requirements and needs for additional financing are accurate.

- We have a history of operating losses, expect to incur significant and increasing operating losses in the future, and may never become profitable, or if we become profitable, we may not remain profitable.

- We cannot provide assurances that our plans with respect to our ongoing and potential future clinical trials for our product candidates will succeed, including the timing of these trials and of the anticipated results.

- We are dependent on the success of eganelisib. If we are unable to complete the clinical development of, obtain marketing approval for, or successfully commercialize eganelisib, either alone or with a collaborator, or if we experience significant delays in doing so, our business could be substantially harmed.
- If clinical trials of eganelisib fail to satisfactorily demonstrate safety and efficacy to the FDA and other regulators, we may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of eganelisib.
- Adverse events or undesirable side effects caused by, or other unexpected properties of, product candidates that we develop may be identified during development and could delay or prevent their marketing approval or limit their use.
- The immuno-oncology industry is characterized by a rapidly changing competitive landscape and a crowded competitive field. We may be unable to compete with larger, more established entities in the field.
- We are reliant on third parties, including collaborators, contract research organizations, manufacturers, and suppliers, to support our business. Should any such third party perform unsatisfactorily or unilaterally end our relationship, such outcome could have a material negative impact on our business and finances.
- Our success depends substantially upon our ability to obtain, maintain and enforce intellectual property rights for the protection of eganelisib. We cannot guarantee the success of our intellectual property position and strategy.
- The COVID-19 pandemic may materially and adversely affect our clinical trial operations, our future supply chain and our financial results.
- We need to attract and retain highly skilled personnel; we may be unable to effectively manage growth with our limited resources.
- Our common stock may have a volatile trading price and low trading volume.

PART I

Item 1. Business

Business Overview

We are a clinical-stage innovative biopharmaceutical company dedicated to developing novel medicines for people with cancer. We combine proven scientific expertise with a passion for developing novel small molecule drugs that target disease pathways for potential applications in oncology. We are focused on advancing eganelisib, also known as IPI-549, an orally administered, clinical-stage, immuno-oncology product candidate that reprograms macrophages through selective inhibition of the enzyme phosphoinositide-3-kinase-gamma, or PI3K-gamma. We have worldwide development and commercialization rights to eganelisib.

Selective inhibition of PI3K-gamma by eganelisib has been shown in preclinical studies to reprogram macrophages from a pro-tumor, immunosuppressive function, to an anti-tumor, immune activating function and to enhance the activity of, and overcome resistance to, checkpoint inhibitors. These preclinical findings indicate that eganelisib may have the potential to treat a broad range of solid tumors and represents a potentially additive or synergistic approach to restoring anti-tumor immunity in combination with other immunotherapies such as checkpoint inhibitors. Further, preclinical studies showed that eganelisib significantly inhibits the regrowth of tumors that can occur following treatment with chemotherapy.

Preclinical Rationale for Development of Eganelisib: Targeting the Immunosuppressive Microenvironment in Solid Tumors

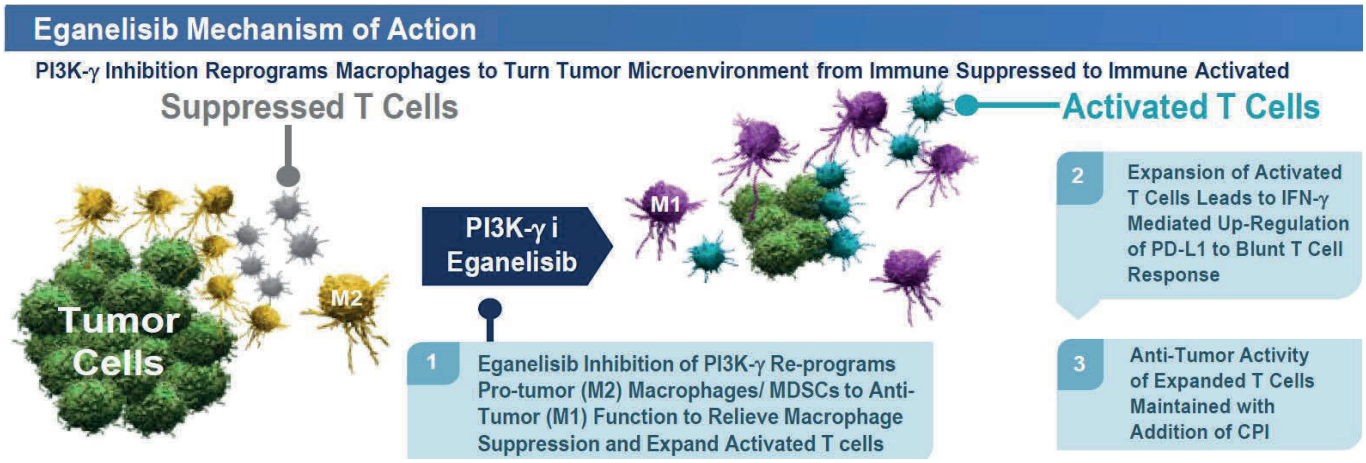
Role of PI3K-gamma in Cancer Growth and Survival

The body's immune system is responsible for fighting infections and disease, including cancer, and helping the body to heal. The immune system functions by identifying and destroying foreign cells and substances within the body. When confronted by pathogens or disease, an early response of the body's immune system comes in the form of macrophages, a type of white blood cell that produces pro-inflammatory proteins called cytokines. These cytokines activate T cells, another type of immune cell, to attack the threat to the body's health. The macrophages then transition to producing other types of cytokines that dampen T cell activation and promote tissue growth, which, in turn, stimulates repair of the affected tissue.

Cancer cells arise from normal cells that have changed in a way that allows them to grow in an unregulated manner. Cancer cells are not always recognized by the body's immune system as foreign cells that should be destroyed. However, even if cancer cells are recognized by the immune system, both normal homeostatic and cancer cell-induced mechanisms exist to dampen this immune response, including upregulation of "checkpoint proteins," such as programmed death receptor 1, or PD-1, on T cells and programmed-death ligand 1, or PD-L1, on tumor and immune cells. Additionally, in solid tumors there exists a tumor microenvironment, or TME, which refers to the non-cancerous cells present in the tumor. Cells within the TME, including macrophages, can suppress the body's immune response and provide signals to cancer cells that facilitate tumor growth. The presence of the pro-tumor, immunosuppressive TME is thought to be one reason why some cancer therapies, including checkpoint inhibitors, have shown limited efficacy and durability to date. PI3K-gamma expression is restricted to the myeloid cell compartment within the TME, including tumor-associated macrophages and myeloid-derived suppressor cells, or MDSCs, where it plays a key role in maintaining the immunosuppressive function of these cells. Targeting these pro-tumor, immunosuppressive cells represents an emerging approach within the field of cancer immunotherapy, and inhibition of PI3K-gamma by eganelisib represents a novel approach to targeting this immunosuppressive microenvironment that has the potential to be nonredundant and complementary to current approaches such as checkpoint inhibitor therapy.

Anti-Tumor Activity of Eganelisib in Preclinical Models

Our preclinical research has demonstrated that blockade of PI3K-gamma by treatment with eganelisib leads to a shift in the type of macrophages present in the TME from pro-tumor, immunosuppressive macrophages, known as M2 macrophages, to anti-tumor, immune activating macrophages, known as M1 macrophages. In preclinical studies, treatment with eganelisib in tumor models was shown to increase the ratio of M1 to M2 macrophages, the number of T cells that attack the tumor, and the production of pro-inflammatory, anti-tumor cytokines. The body's natural defense to prevent an over-active immune response involves upregulation of checkpoint proteins, including the upregulation of PD-L1 in response to T cell dependent interferon-gamma signaling. Preclinical data has shown that blocking the PD-1/PD-L1 axis with a checkpoint inhibitor in combination with eganelisib both expanded the number of anti-tumor T cells and enhanced the anti-tumor activity of expanded T cells in preclinical models.



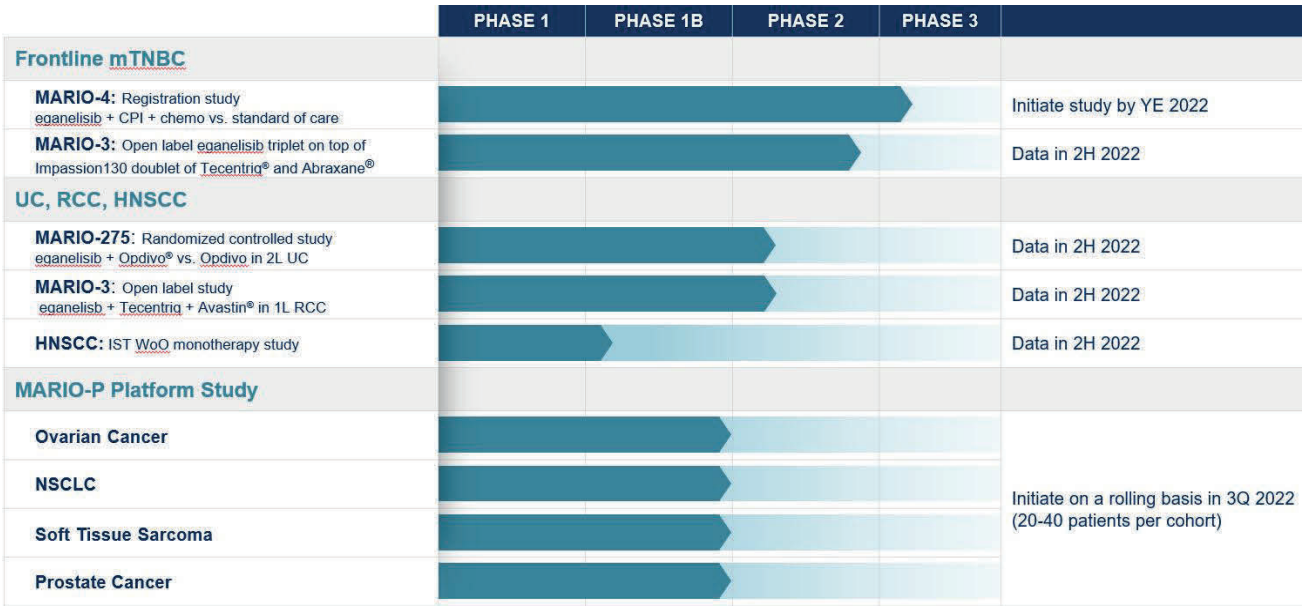
Preclinical studies to investigate the anti-tumor activity of eganelisib have demonstrated dose-dependent, single-agent anti-tumor activity in multiple solid tumor models, including syngeneic models of lung cancer, colon cancer and breast cancer. Additionally, in preclinical models, treatment with eganelisib in combination with a checkpoint inhibitor showed greater tumor growth inhibition and extended survival, including a greater number of complete tumor regressions, compared to treatment with either eganelisib or the checkpoint inhibitor alone. The combination treatment resulted in long-lasting anti-tumor immune memory as evidenced by the lack of tumor growth when animals were re-challenged post-treatment with the same tumor cells in the absence of any treatment.

Overcoming Resistance to Checkpoint Inhibition

In recent years, checkpoint inhibitors, or CPIs, have shown promising results as a treatment for multiple types of cancer, but most patients do not respond, and most who do respond eventually become resistant to and require treatment with an additional ***therapy***. Our preclinical studies in a number of tumor models demonstrated that resistance to checkpoint inhibition is associated with increased numbers of tumor-associated macrophages (TAMs) and is directly mediated by the immunosuppressive activity of these macrophages on T cells. Furthermore, the data demonstrated that inhibition of PI3K-gamma by eganelisib reprogrammed macrophages to a less immunosuppressive state, enhanced anti-tumor cytotoxic T cell activity, and restored sensitivity to checkpoint inhibitors. These data demonstrated that eganelisib treatment was able to reverse the lack of response to checkpoint inhibitors in models that were refractory to checkpoint inhibitor therapy due to the presence of enhanced numbers of immunosuppressive macrophage.

2022 Eganelisib Development Strategy: Advancing and Expanding MARIO Clinical Development Program

Building on data from our MARIO-3 (MAcrophage Reprogramming in Immuno-Oncology-3, or MARIO-3), MARIO-275, and MARIO-1 studies, described in more detail below, we expect to initiate two new studies in 2022. We are planning a randomized, double-blind, registration study in front-line metastatic triple-negative breast cancer, or mTNBC, which we refer to as MARIO-4. For the patients with tumors that test negative for programmed-death ligand 1, or PD-L1-negative patients, in the future MARIO-4 study, eganelisib in combination with chemotherapy and a checkpoint inhibitor (the eganelisib triplet) will be evaluated against chemotherapy. In the PD-L1-positive patients, the eganelisib triplet will be evaluated against the combination of chemotherapy and a checkpoint inhibitor. We expect MARIO-4 to include endpoints of progression-free survival (PFS) and overall survival (OS). Pending feedback from a MARIO-3 end-of-Phase 2 meeting with global regulatory authorities, we will finalize the MARIO-4 trial design. We also expect to initiate MARIO-P, a platform study to evaluate the clinical benefit of eganelisib in additional solid tumor indications, on a rolling basis in the third quarter of 2022.



Eganelisib Clinical Development Program

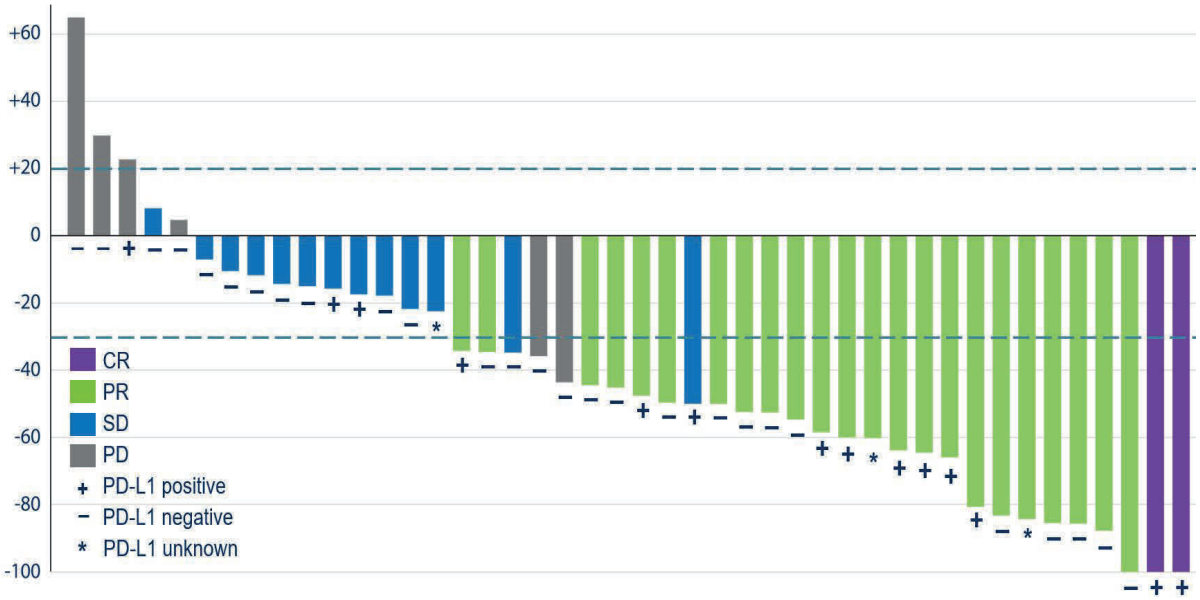
MARIO-3 (MAcrophage Reprogramming in Immuno-Oncology-3)

MARIO-3 is a multi-arm Phase 2 study designed to evaluate eganelisib in the front-line treatment for both metastatic triple negative breast cancer, or TNBC, and renal cell carcinoma, or RCC. The TNBC cohort is evaluating eganelisib in combination with atezolizumab, an anti-PD-L1 monoclonal antibody also known as Tecentriq®, and nab-paclitaxel, an albumin-bound chemotherapy drug also known as Abraxane®, in approximately 60 patients with unresectable locally advanced or metastatic TNBC. The RCC cohort is evaluating eganelisib in combination with atezolizumab and bevacizumab, also known as Avastin®, in approximately 30 patients with RCC. Using the same cutoff standard used in the F. Hoffmann-La Roche Ltd., or Roche, benchmark IMpassion130 study for PD-L1, we refer to patients with tumors that test below 1% PD-L1 at baseline as "PD-L1(-) patients" and those with tumors that test equal to or greater than 1% as "PD-L1(+) patients." We entered into clinical supply agreements with Roche, under which Roche has agreed to supply atezolizumab and bevacizumab for our use in MARIO-3. In August 2021, Roche voluntarily withdrew its accelerated approval in the United States for atezolizumab in combination with nab-paclitaxel for patients with PD-L1(+) metastatic TNBC after IMpassion131, Roche's post marketing study evaluating atezolizumab and paclitaxel in TNBC patients, did not meet its primary endpoint. Roche announced that its decision was made in consultation with the FDA, based on the agency's assessment of the current metastatic TNBC treatment landscape, and in accordance with the requirements of the accelerated approval program, and was unrelated to efficacy or safety associated with atezolizumab. Roche's decision does not alter our clinical rationale for MARIO-3, and we do not expect it to have any impact on the conduct of MARIO-3. The combination of atezolizumab and nab-paclitaxel for treatment of patients with PD-L1(+) metastatic TNBC remains approved in multiple countries outside of the U.S.

On December 10, 2021, we presented data at the 2021 San Antonio Breast Cancer Symposium, or SABCS, from the TNBC cohort of MARIO-3 study. As of the October 2, 2021 data cutoff date for the presentation, we had enrolled 44 evaluable patients and 50 patients total, with a median duration of follow up of 9.9 months. The MARIO-3 data presented at SABCS and an investor event following SABCS include the following findings:

- Of evaluable patients, tumor reduction was observed in 92.8% of patients with PD-L1(+) tumors and 85.2% of patients with PD-L1(-) tumors
- Disease control rate (DCR)
    - 92.8% (13/14) DCR in patients with PD-L1(+) tumors, complete response (CR) 14.3% (2/14), partial response (PR) 57.1% (8/14), stable disease (SD) 21.4% (3/14)
    - 81.4% (22/27) DCR in patients with PD-L1(-) tumors, CR 0% (0/27), PR 48.1% (13/27), SD 33.3% (9/27)
- Progression free survival (PFS)
    - In patients with PD-L1(+) tumors, median PFS in MARIO-3 was 11.0 months, a 47% improvement in median PFS compared to the 7.5 months reported for the atezolizumab and nab-paclitaxel doublet in IMpassion130
    - In patients with PD-L1(-) tumors, median PFS in MARIO-3 was 7.3 months, a 30% improvement compared to the 5.6 months reported for the atezolizumab and nab-paclitaxel doublet in IMpassion130
- 67% of the PD-L1(-) patients who reached the median PFS of 7.3 months remained on treatment

MARIO-3 TNBC Cohort: Best Percent Change in Target Lesion from Baseline

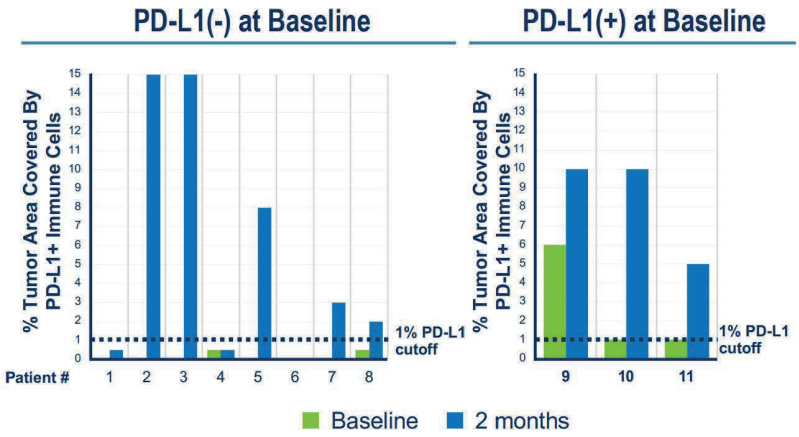


Cit: Soliman H. et al. 2021 San Antonio Breast Cancer Symposium.

MARIO-3 did not demonstrate any new safety signals compared to benchmark trials, and its safety profile was consistent with expectations for the three component drugs. The most common Grade 3 or higher treatment-related treatment emergent adverse events (TEAEs) were hepatic adverse events (AEs) (18%); neutropenia AEs (16%); skin AEs (12%); fatigue, diarrhea and peripheral sensory neuropathy (6% each); and vomiting and weight decreased (2% each). Seven patients (14%) discontinued treatment for treatment-related TEAEs and nine patients (18%) had treatment-related serious AEs. There was one Grade 4 and no Grade 5 treatment-related TEAEs.

Translational data presented at SABCS are supportive of eganelisib's immune modulation mechanism. Quantification across 11 paired tumor biopsies showing increased immune activation and decreased immune suppression, including an increase in CD8+ T cells, activated T cells, and anti-tumor M1 macrophages and a decrease in tumor cells and pro-tumor M2 macrophages resulting in an increase in the M1:M2 ratio. Further, paired tumor biopsy data show that treatment with eganelisib combination for two months led to increased expression of PD-L1 in 5 of 8 patients with PD-L1(-) tumors at baseline, reaching levels above the 1% PD-L1 cutoff of the standard PD-L1 biomarker assay used in MARIO-3 and the benchmark IMpassion130 study. PD-L1 expression also increased in the three patients with PD-L1(+) tumors.

MARIO-3 TNBC Cohort: Increased PD-L1 Expression in Paired Tumor Biopsies



Cit: Soliman H. et al. 2021 San Antonio Breast Cancer Symposium.

We expect to provide updated data from the MARIO-3 TNBC cohort in the second half of 2022.

The second MARIO-3 cohort is evaluating eganelisib in combination with atezolizumab and bevacizumab, also known as Avastin®, in up to 30 patients with front-line RCC. Enrollment has been completed in the RCC cohort and we expect to present data from the RCC cohort in the second half of 2022.

The Unmet Needs of Patients with Triple Negative Breast Cancer

There were estimated to be 281,550 new cases of breast cancer in 2021. Compared to other breast cancer subtypes, TNBC, which is so named because the cancer cells lack estrogen and progesterone receptors and do not make much of the protein called human epidermal growth factor receptor 2, or HER2, is aggressive and TNBC patients have limited treatment options. TNBC accounts for up to 15% of all breast cancer in women, and the 5-year survival rate of metastatic TNBC patients is only 12.2%. Available therapies for advanced front-line TNBC offer limited efficacy, particularly in PD-L1(-) patients.

MARIO-275

MARIO-275 is our global, randomized, placebo-controlled Phase 2 study evaluating the effect of adding eganelisib to nivolumab, also known as Opdivo®, in checkpoint-naïve advanced urothelial cancer, or UC, patients whose cancer has progressed or recurred following treatment with platinum-based chemotherapy. Nivolumab is an immune checkpoint inhibitor therapy commercialized by Bristol Myers Squibb Company, or BMS, that targets programmed death receptor 1, or PD-1, a checkpoint protein that helps regulate the body's immune system. We presented MARIO-275 data at the American Society of Clinical Oncology Genitourinary Cancers Symposium, or ASCO GU, in February 2021, and presented updates on overall survival data in July 2021 and January 2022. The data from the 49 patients enrolled in the trial include the following findings:

- Median overall survival (mOS) in the intent to treat population as of July 2021 was 15.4 months (6.2, NE) on the eganelisib plus nivolumab combination arm as compared to 7.9 months (2.3, NE) on the control arm of nivolumab alone with a hazard ratio (HR) 0.62 (0.28, 1.36), reflecting a 38% lower probability of death.
    - In a one-year landmark analysis of the ITT population, 59% of patients in the nivolumab combination were alive, compared to 32% in the nivolumab control arm.
- The mOS in PD-L1(-) patients, as updated in January 2022, was 15.3 months (4.7, NE) on the eganelisib plus nivolumab arm versus 7.9 months (1.9, NE) on the nivolumab control arm with an HR 0.58 (0.21, 1.66), reflecting a 42% lower probability of death.

- In a one-year landmark analysis of patients with PD-L1(-) tumors, 54% on the eganelisib plus nivolumab combination remained alive, compared to 17% in the nivolumab control arm.

The most common TEAEs for the eganelisib plus nivolumab combination arm across all doses, all causality, were pyrexia (33.3%), decreased appetite (30.3%), pruritus (27.3%), asthenia (27.3%), rash (27.3%), and increased alanine aminotransferase (24.2%); and the most common ≥Grade 3 TEAEs across all doses, all causality, were anemia (12.1%), and hepatic AEs including hepatotoxicity (15.2%), increased ALT (12.1%), and increased AST (12.1%) with no Hy's Law. No Grade 5 AEs were reported.

Data presented at ASCO GU demonstrated the greatest benefit of the combination of eganelisib and nivolumab was observed in the patient population (n=23) with tumors expressing low levels of PD-L1, with improvement over nivolumab monotherapy (n=7) in ORR (26% vs. 14%); DCR (57% vs. 14%); and best responses of CR (9% vs. 0%) and SD (30% vs. 0%). Of patients with PD-L1 low tumors in the combination arm, 58% (11 of 19) achieved a reduction in tumor burden, compared to 17% (1 of 6) in the nivolumab plus placebo arm.

The Unmet Needs of Patients with Urothelial Cancer

Approximately 95% of bladder cancers are urothelial cancer. According to SEER Cancer Statistics Review estimations of 2020 data as of the time of this filing, bladder cancer was estimated to be the sixth most common form of cancer in the U.S., with 81,400 new cases, or 4.5% of all new cancers, and 17,980 deaths, or 3% of all cancer deaths. According to a recent meta-analysis of clinical studies investigating PD-L1 status in metastatic UC, the ORR in PD-L1 high UC patients is approximately 25% in contrast to an overall response rate, or ORR, of 14% for patients with low levels of PD-L1 expression. The patients with low levels of PD-L1 expression have a poorer PFS and a poorer OS relative to the PD-L1 high patients. (Tan WP et al. Bladder Cancer. 2019;5(3):211-223.) Compounding these disparate outcomes, the majority of patients with metastatic UC are PD-L1 low. (Bellmunt J et al. Ann Oncol. 2015;26(4):812-817). Despite significant progress in the advancement of therapeutic options for UC in recent years, including the use of checkpoint inhibitors, there remains an opportunity to improve outcomes.

MARIO-1

Enrollment is complete in MARIO-1, our Phase 1/1b clinical study designed to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and activity for eganelisib — both as a monotherapy and in combination with nivolumab — in 224 patients with advanced solid tumors. The study included a dose escalation portion and a combination therapy expansion portion evaluating patients dosed at 40 mg daily, or QD, of eganelisib in combination with the standard regimen of nivolumab in the following forms of cancer: non-small cell lung cancer, melanoma, squamous cell carcinoma of the head and neck, or SCCHN, TNBC, mesothelioma, adrenocortical carcinoma, and those with high baseline blood levels of MDSCs.

Safety data demonstrated that eganelisib combined with nivolumab was well tolerated at all doses tested, up to the recommended combination therapy expansion dose of eganelisib at 40 mg QD plus the standard regimen of nivolumab. No maximum tolerated dose was determined, and there were no treatment-related deaths. The pharmacokinetic/pharmacodynamic profile of eganelisib (up to the recommended combination expansion dose of 40 mg QD) was unaffected by nivolumab co-administration, and eganelisib in combination with nivolumab reduced immune suppression and increased immune activation, as indicated by analyses of peripheral blood. Additional data demonstrated that eganelisib as a monotherapy was well tolerated at all doses studied up to the recommended dose for monotherapy expansion of 60 mg QD, and that eganelisib as a monotherapy reduced immune suppression and increased immune activation, as indicated by analyses of peripheral blood and paired tumor biopsies.

We provided updated data for the melanoma cohort and SCCHN cohort at the 2020 Annual Meeting of the Society for Immunotherapy of Cancers. Data from both cohorts demonstrate clinical activity of the combination therapy in patients not expected to benefit from checkpoint inhibitor alone, or CPI, having progressed on an immediate prior CPI therapy prior to entering MARIO-1. Safety data from both cohorts indicates the combination therapy was generally well tolerated and associated with a favorable safety profile.

The melanoma cohort achieved a DCR of 52.6% (10 of 19 patients) and an ORR of 21.1% (4 of 19 patients) in patients with immediate prior progression on CPI therapy and two or fewer prior lines of therapies, and reversal of progressive disease in patients with immediate prior treatment with anti-PD1/PD-L1 therapy was observed. Translational data validate the on-mechanism eganelisib effect of decreased immune suppression as measured by MDSC levels, and increased immune activation.

The SCCHN cohort achieved a DCR of 40% (4 of 10 patients) and an ORR of 20% (2 of 10 patients) in patients with immediate prior progression on CPI therapy and two or fewer prior lines of therapy, and reversal of progressive disease in patients with immediate prior treatment with anti-PD1/PD-L1 therapy was observed.

Alliances, Collaborations, and Other Arrangements

Since our inception, corporate alliances, license agreements and other strategic arrangements, as well as the sale of securities, have been integral to our strategy. Many of these arrangements have provided access to breakthrough science, significant research and development support and funding, supply of clinical trial materials, and innovative drug development programs, all intended to help us realize the full potential of our product pipeline. For more information related to the arrangements described below, please see Note 9 (Liability Related to Sales of Future Royalties) and Note 11 (Strategic Agreements) to our Consolidated Financial Statements in this Annual Report on Form 10-K.

Mundipharma and Purdue

We are obligated to pay Mundipharma International Corporation Limited, or Mundipharma, and Purdue Pharmaceutical Products L.P., or Purdue, a 4% royalty in the aggregate on worldwide net sales of eganelisib, duvelisib, or Copiktra®, a product we out-licensed in 2016; and IPI-926, or patidegib, a product we out-licensed in 2013. After a threshold is met the royalty will be reduced to a 1% royalty on net sales in the United States of such products.

Verastem, Secura Bio, and HCR

In 2016, we and Verastem Inc., or Verastem, entered into a license agreement, or the Verastem Agreement, under which we granted to Verastem an exclusive worldwide license for the research, development, commercialization, and manufacture of duvelisib, and products containing duvelisib, which we refer to as the Licensed Products, in each case in oncology indications. In September 2020, Verastem completed a disposition of its rights, title, and interest in and to duvelisib to Secura Bio, Inc., or Secura Bio, wherein Secura Bio assumed all liabilities and obligations under the Verastem Agreement, including obligations to pay us royalties on worldwide net sales of Licensed Products ranging from the mid-single digits to the high-single digits, a portion of which we are obligated to share with Takeda as described in the section below entitled "Takeda." We now refer to the Verastem Agreement as the Secura Bio Agreement.

In 2019, we and HealthCare Royalty Partners III, L.P., or HCR, entered into a purchase and sale agreement, or the HCR Transaction, providing for the acquisition by HCR of our interest in certain royalty payments, or the Purchased Assets, based on worldwide annual net sales of Licensed Products pursuant to the Secura Bio Agreement. See Note 9 of the notes to our consolidated financial statements included in Part II, Item 8, "Financial Statements and Supplementary Data" of this Annual Report on Form 10-K for details of the HCR transaction.

Secura Bio is obligated to pay us a royalty of 4% on worldwide net sales of Licensed Products to cover the obligations owed by us to Mundipharma and Purdue, which will reduce to a 1% royalty of net sales in the United States after a certain threshold is met.

Takeda

In 2010, we entered into a development and license agreement with Intellikine, Inc., or Intellikine, under which we obtained rights to discover, develop and commercialize pharmaceutical products targeting the gamma and/or delta isoforms of PI3K, including eganelisib and duvelisib. In January 2012, Intellikine was acquired by Takeda. In December 2012, we amended and restated our development and license agreement with Takeda and further amended the agreement in July 2014, September 2016, July 2017, and March 2019. We refer to the amended and restated development and license agreement, as amended, as the Takeda Agreement.

Eganelisib

Pursuant to the Takeda Agreement, we are obligated to pay Takeda the remaining $3.0 million success-based development milestone and up to $165.0 million in remaining success-based regulatory and commercial milestones for one product candidate other than duvelisib that inhibits the PI3K pathway, which could be eganelisib.

The Takeda Agreement expires on the later of the expiration of certain patents and the expiration of the royalty payment terms for the products, unless earlier terminated in accordance with its terms. Either party may terminate the Takeda Agreement on 75 days' prior written notice if the other party materially breaches the agreement and fails to cure such breach within the applicable notice period, provided that the notice period is reduced to 30 days where the alleged breach is non-payment. Takeda may also terminate the Takeda Agreement if we are not diligent in developing or commercializing the licensed products and do not, within three months after notice from Takeda, demonstrate to Takeda's reasonable satisfaction that we have not failed to be diligent. The foregoing periods are subject to extension in certain circumstances. Additionally, Takeda may terminate the Takeda Agreement upon 30 days' prior written notice if we or a related party bring an action challenging the validity of any of the licensed patents, provided that we have not withdrawn such action before the end of the

30-day notice period. We may terminate the agreement at any time upon 180 days' prior written notice. The Takeda Agreement also provides for customary reciprocal indemnification obligations of the parties.

Intellectual Property

Our intellectual property consists of patents, trademarks, trade secrets and know-how. Our ability to compete effectively depends in large part on our ability to obtain patents and trademarks for our technologies and products, maintain trade secrets, operate without infringing the rights of others and prevent others from infringing our proprietary rights. We will be able to protect our proprietary technologies from unauthorized use by third parties only to the extent that they are covered by valid and enforceable patents, or are effectively maintained as trade secrets. As a result, patents or other proprietary rights are an essential element of our business.

We have fifteen issued or allowed U.S. patents related to our PI3K-gamma program, which expire on various dates between 2033 and 2037, excluding any potential patent term extension. In addition, we have approximately 100 patents and patent applications pending worldwide related to our PI3K-gamma program. Any patents that may issue from our pending patent applications would expire between 2033 and 2041, excluding any potential patent term extension. These patents and patent applications disclose compositions of matter, pharmaceutical compositions, methods of use and synthetic methods.

The term of individual patents depends upon the legal term for patents in the countries in which they are obtained. In most countries, including the United States, the patent term is 20 years from the earliest filing date of a non-provisional patent application. In the United States, a patent's term may be extended by patent term adjustment, which compensates a patentee for administrative delays by the United States Patent and Trademark Office, or USPTO, in examining and granting a patent, or may be shortened if a patent is terminally disclaimed over an earlier filed patent. The term of a patent that covers a drug or biological product may also be eligible for patent term extension when FDA approval is granted, provided statutory and regulatory requirements are met. In the future, if and when our product candidates receive approval by the FDA or foreign regulatory authorities, we expect to apply for patent term extensions on issued patents covering those drugs, depending upon the length of the clinical trials for each drug and other factors. There can be no assurance that any of our pending patent applications will issue or that we will benefit from any patent term extension or favorable adjustment to the term of any of our patents.

As with other biotechnology and pharmaceutical companies, our ability to maintain and solidify our proprietary and intellectual property position for our product candidates and technologies will depend on our success in obtaining effective patent claims and enforcing those claims, if granted. However, our pending patent applications, and any patent applications that we may in the future file or license from third parties may not result in the issuance of patents. We also cannot predict the breadth of claims that may be allowed or enforced in our patents. Any issued patents that we may receive in the future may be challenged, invalidated or circumvented. For example, we cannot be certain of the priority of inventions covered by pending third-party patent applications. If third parties prepare and file patent applications in the United States that also claim technology or therapeutics to which we have rights, we may have to participate in interference proceedings in the USPTO to determine priority of invention, which could result in substantial costs to us, even if the eventual outcome is favorable to us, which is highly unpredictable. In addition, because of the extensive time required for clinical development and regulatory review of a product candidate we may develop, it is possible that, before any of our product candidates can be commercialized, any related patent may expire or remain in force for only a short period following commercialization, thereby limiting protection such patent would afford the respective product and any competitive advantage such patent may provide.

Our policy is to obtain and enforce the patents and proprietary technology rights that are commercially important to our business, and we intend to continue to file patent applications to protect such technology and compounds in countries where we believe it is commercially reasonable and advantageous to do so. We also rely on trade secrets to protect our technology where patent protection is deemed inappropriate or unobtainable. We seek to protect our proprietary information, in part, by executing confidentiality agreements with our collaborators and scientific advisors, and non-competition, non-solicitation, confidentiality, and invention assignment agreements with our employees and consultants. We have also executed agreements requiring assignment of inventions with selected scientific advisors and collaborators. The confidentiality agreements we enter into are designed to protect our proprietary information, and the agreements or clauses requiring assignment of inventions to us are designed to grant us ownership of technologies that are developed through our relationship with the respective counterparty. We cannot guarantee, however, that these agreements will afford us adequate protection of our intellectual property and proprietary information rights.

Competition

The pharmaceutical and biotechnology industries are intensely competitive, including the field of immuno-oncology, or IO, within which we are competing directly. Many companies are actively engaged in the research and development of drugs for the treatment of the same diseases and conditions as our current and potential future product candidates, and many have substantially greater financial and other resources, larger research and development staffs, and more extensive marketing and manufacturing organizations than we do. In addition, some of them have considerably more experience than us in preclinical testing, clinical trials and other regulatory approval procedures. There are also academic institutions, governmental agencies and other research organizations that are conducting research in areas in which we are working. They may also develop products that may be competitive with our product candidates, either on their own or through collaborative efforts.

We expect to encounter significant competition for any drugs we develop. Companies that complete clinical trials, obtain required regulatory approvals and commence commercial sales of their products before their competitors may achieve a significant competitive advantage. We are aware that many other companies or institutions are pursuing the development of drugs in the areas in which we are currently seeking to develop our own product candidates, and there may be other companies working on competitive projects of which we are not aware.

Our competitors may commence and complete clinical testing of their product candidates, obtain regulatory approvals and begin commercialization of their products sooner than we may for our own product candidates. These competitive products may have superior safety or efficacy, or be manufactured less expensively, than our product candidates. If we are unable to compete effectively against these companies on the basis of safety, efficacy or cost, then we may not be able to commercialize our product candidates or achieve a competitive position in the market. This would adversely affect our business.

Selective inhibition of PI3K-gamma by eganelisib has been shown in preclinical studies to reprogram macrophages from a pro-tumor, immunosuppressive function, to an anti-tumor, immune activating function and to enhance the activity of, and overcome resistance to, checkpoint inhibitors. We believe the following competitors are also investigating drug or product candidates targeting one or more aspects of macrophage biology: Arcus Biosciences, Inc. (PI3K-gamma inhibitor, pre-clinical); AstraZeneca plc (PI3K-gamma, pre-clinical); Jounce Therapeutics, Inc.; Macomics Ltd; Merck & Co.; Nanjing Zenshine Pharmaceuticals, Co. Ltd. (PI3K-gamma, clinical); Pathios Therapeutics Ltd; Pionyr Immunotherapeutics, Inc., Verseau Therapeutics, Inc.

We expect our MARIO-4 study to be a registration-focused study in front-line mTNBC in PD-L1(+) patients and PD-L1(-) patients. Currently, pembrolizumab (a PD-1 inhibitor developed and commercialized by Merck, Inc.) in combination with chemotherapy is the standard of care therapy in the United States for PD-L1(+) mTNBC patients, while chemotherapy alone remains the standard of care in the United States in PD-L1(-) mTNBC patients. Many additional companies have therapies in clinical development in mTNBC including but not limited to: AstraZeneca, Daiichi-Sankyo, G1 Therapeutics, Gilead Sciences, Inc., Novartis, Roche, and SeaGen.

Further, the broader field of IO is crowded with innovative therapies that may compete with eganelisib, including checkpoint inhibitor therapies, including: PD-1 inhibitors such as nivolumab, pembrolizumab, and cemiplimab; PD-L1 inhibitors such as atezolizumab, avelumab, and durvalumab; CTLA-4 inhibitors such as ipilimumab, and tremelimumab; and LAG3 inhibitors such as relatlimab. Many of these checkpoint inhibitor therapies are being evaluated in combination with other non-checkpoint inhibitor IO product candidates. For instance, in February 2020 the FDA granted breakthrough therapy designation to pembrolizumab in combination with enfortumab vedotin, Seagen's antibody-drug conjugate, for the treatment of patients with advanced urothelial cancer who are unable to receive cisplatin-based chemotherapy in the first-line setting. Additionally, nivolumab, which we are currently testing in combination with eganelisib, is being evaluated by others in multiple clinical trials in combination with non-checkpoint inhibitor candidates such as sitravatinib, a small-molecule inhibitor of tyrosine kinases including Tyro3, MER, AXL, VEGFR, and KIT; linrodostat, a small-molecule inhibitor of IDO; elotuzumab, a CD319 antibody; urelumab, a CD137 antibody; and cabiralizumab, an anti-CSF1R antibody. In January 2021, the FDA approved the combination of nivolumab and cabozantinib, Exelixis, Inc's small-molecule inhibitor of tyrosine kinases, including MET, AXL, VEGFR, and RET, as first-line treatment for patients with advanced RCC. The success of competing IO therapies may limit the number of patients available for enrollment in our clinical trials.

Research and Development

As of March 20, 2022, our research and development group consisted of 19 employees, of whom eight hold Ph.D. or M.D. degrees and seven hold a master's degree. Our research and development group is focused on preclinical research, translational medicine, clinical trials and manufacturing technologies. In addition, we rely on several consultants to fill strategic and tactical roles that support our research and development group.

Manufacturing and Supply

We rely on third parties and, in some instances, we rely on only one third party, to manufacture critical raw materials, drug substance and final drug product for our research, preclinical development and clinical trial activities. Commercial quantities of any drugs we seek to develop will have to be manufactured in facilities and by processes that comply with regulations of the FDA and other foreign regulatory authorities, and we plan to rely on third parties to manufacture commercial quantities of any products we successfully develop.

Despite the ongoing COVID-19 pandemic, our manufacturing processes have continued uninterrupted, and we have established contingency strategies intended to prevent potential supply chain interruptions related to the pandemic. To date, we believe we have enough eganelisib drug product to conduct our current clinical trials. Further, we believe that we have enough drug substance and drug product intermediates for additional drug product manufacturing necessary to support our clinical development program and potential preclinical studies. We expect the COVID-19 pandemic to have limited impact to existing manufacturing operations because all eganelisib drug product necessary to conduct our current clinical trials has been manufactured or is scheduled to be manufactured with sufficient lead times to accommodate potential delays. However, variants of the SARS-COV-2 virus have continued to develop, and potential future variants could be more virulent or more contagious than variants to date. Such variants may worsen or prolong the impact of the COVID-19 pandemic, and may be so extreme that we cannot fully mitigate their impact on our manufacturing timeline.

Sales and Marketing

We currently have no marketing, commercial sales, or distribution capabilities. We do, however, currently have worldwide commercialization rights for eganelisib. In order to commercialize eganelisib, if and when it is approved for sale, we will need to develop the necessary marketing, sales and distribution capabilities or establish a collaboration with a company that has commercial capabilities.

Government Regulation and Product Approvals

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

Approval and Regulation of Drugs in the United States

In the United States, drug products are regulated under the Federal Food, Drug and Cosmetic Act, or FDCA, and applicable implementing regulations and guidance. A company, institution, or organization which takes responsibility for the initiation and management of a clinical development program for such products, and for their regulatory approval, is typically referred to as a sponsor. The failure of a sponsor to comply with the applicable regulatory requirements at any time during the product development process, including non-clinical testing, clinical testing, the approval process or post-approval process, may result in delays to the conduct of a study, regulatory review and approval and/or administrative or judicial sanctions.

A sponsor seeking approval to market and distribute a new drug in the United States generally must satisfactorily complete each of the following steps before the product candidate will be approved by the FDA:

- preclinical testing including laboratory tests, animal studies and formulation studies, which must be performed in accordance with the FDA's good laboratory practice, or GLP, regulations and standards;
- design of a clinical protocol and submission to the FDA of an investigational new drug, or IND, for human clinical testing, which must become effective before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, representing each clinical site before each clinical trial may be initiated;
- performance of adequate and well-controlled human clinical trials to establish the safety, potency and purity of the product candidate for each proposed indication, in accordance with current good clinical practices, or GCP;
- preparation and submission to the FDA of a new drug application, or NDA, for a drug product which includes not only the results of the clinical trials, but also, detailed information on the chemistry, manufacture and quality controls for the product candidate and proposed labeling for one or more proposed indication(s);

- review of the product candidate by an FDA advisory committee, where appropriate or if applicable;
- satisfactory completion of any FDA audits of the non-clinical and clinical trial sites to assure compliance with GCP and the integrity of clinical data in support of the NDA;
- compliance with any post-approval requirements, including the potential requirement to implement a Risk Evaluation and Mitigation Strategy, or REMS, and the potential requirement to conduct any post-approval studies required by the FDA;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities, including those of third parties, at which the product candidate or components thereof are manufactured to assess compliance with current good manufacturing practices, or cGMP, requirements and to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality and purity; and
- payment of user fees and securing FDA approval of the NDA to allow marketing of the new drug product.

Preclinical Studies and Investigational New Drug Application

Before a sponsor begins testing a product candidate with potential therapeutic value in humans, the product candidate enters the preclinical testing stage. Preclinical tests include laboratory evaluations of product chemistry, formulation and stability, as well as other studies to evaluate, among other things, the toxicity of the product candidate. The conduct of the preclinical tests and formulation of the compounds for testing must comply with federal regulations and requirements, including GLP regulations and standards and the United States Department of Agriculture's Animal Welfare Act, if applicable. The results of the preclinical tests, together with manufacturing information and analytical data, are submitted to the FDA as part of an IND. Some long-term preclinical testing, such as animal tests of reproductive adverse events and carcinogenicity, and long-term toxicity studies, may continue after the IND is submitted.

The IND and IRB Processes

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include, among other things, the requirement that all research subjects provide their voluntary informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under written study protocols detailing, among other things, the inclusion and exclusion criteria, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND.

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

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

A sponsor may choose, but is not required, to conduct a foreign clinical study under an IND. When a foreign clinical study is conducted under an IND, all FDA IND requirements must be met unless waived. When a foreign clinical study is not conducted under an IND, the sponsor must ensure that the study complies with certain regulatory requirements of the FDA in order to use the study as support for an IND or application for marketing approval. The FDA's regulations are intended to help ensure the protection of human subjects enrolled in non-IND foreign clinical studies, as well as the quality and integrity of the resulting data. They further help ensure that non-IND foreign studies are conducted in a manner comparable to that required for IND studies.

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

Additionally, some trials are overseen by an independent group of qualified experts organized by the trial sponsor, known as a data safety monitoring board or committee, or DSMB. This group provides authorization as to whether or not a trial may move forward at designated check points based on access that only the group maintains to available data from the study. Suspension or termination of development during any phase of clinical trials can occur if it is determined that the participants or patients are being exposed to an unacceptable health risk. Other reasons for suspension or termination may be made by us based on evolving business objectives and/or competitive climate.

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

Expanded Access to an Investigational Drug for Treatment Use

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

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

There is no obligation for a sponsor to make its drug products available for expanded access; however, as required by the 21st Century Cures Act, or Cures Act, passed in 2016, sponsors are required to make policies for evaluating and responding to requests for expanded access for patients publicly available upon the earlier of initiation of a Phase 2 or Phase 3 clinical trial, or 15 days after the investigational drug or biologic receives designation as a breakthrough therapy, fast track product, or regenerative medicine advanced therapy.

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

Human Clinical Trials in Support of an NDA

Clinical trials involve the administration of the investigational product candidate to human subjects under the supervision of a qualified investigator in accordance with GCP requirements which include, among other things, the requirement that all research subjects provide their informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under written clinical trial protocols detailing, among other things, the objectives of the study, inclusion and exclusion criteria, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated.

Human clinical trials are typically conducted in three sequential phases, but the phases may overlap or be combined. Additional studies may also be required after approval.

Phase 1 clinical trials are initially conducted in a limited population to test the product candidate for safety, including adverse effects, dose tolerance, absorption, metabolism, distribution, excretion and pharmacodynamics in healthy humans or in patients. During Phase 1 clinical trials, information about the investigational drug product's pharmacokinetics and pharmacological effects may be obtained to permit the design of well-controlled and scientifically valid Phase 2 clinical trials.

Phase 2 clinical trials are generally conducted in a limited patient population to identify possible adverse effects and safety risks, evaluate the efficacy of the product candidate for specific targeted indications and determine dose tolerance and optimal dosage. Multiple Phase 2 clinical trials may be conducted by the sponsor to obtain information prior to beginning larger and more costly Phase 3 clinical trials. Phase 2 clinical trials are well controlled, closely monitored and conducted in a limited patient population.

Phase 3 clinical trials proceed if the Phase 2 clinical trials demonstrate that a dose range of the product candidate is potentially effective and has an acceptable safety profile. Phase 3 clinical trials are undertaken within an expanded patient population to further evaluate dosage, provide substantial evidence of clinical efficacy and further test for safety in an expanded and diverse patient population at multiple, geographically dispersed clinical trial sites. A well-controlled, statistically robust Phase 3 clinical trial may be designed to deliver the data that regulatory authorities will use to decide whether or not to approve, and, if approved, how to appropriately label a drug. Such Phase 3 studies are referred to as "pivotal."

A clinical trial may combine the elements of more than one phase and the FDA often requires more than one Phase 3 trial to support marketing approval of a product candidate. A company's designation of a clinical trial as being of a particular phase is not necessarily indicative that the study will be sufficient to satisfy the FDA requirements of that phase because this determination cannot be made until the protocol and data have been submitted to and reviewed by the FDA. Moreover, as noted above, a pivotal trial is a clinical trial that is believed to satisfy FDA requirements for the evaluation of a product candidate's safety and efficacy such that it can be used, alone or with other pivotal or non-pivotal trials, to support regulatory approval. Generally, pivotal trials are Phase 3 trials, but they may be Phase 2 trials if the design provides a well-controlled and reliable assessment of clinical benefit, particularly in an area of unmet medical need.

In some cases, the FDA may approve an NDA for a product candidate but require the sponsor to conduct additional clinical trials to further assess the product candidate's safety and effectiveness after approval. Such post-approval trials are typically referred to as Phase 4 clinical trials. These studies are used to gain additional experience from the treatment of a larger number of patients in the intended treatment group and to further document a clinical benefit in the case of drugs approved under accelerated approval regulations. Failure to exhibit due diligence with regard to conducting Phase 4 clinical trials could result in withdrawal of approval for products.

In March 2022, the FDA released a draft guidance entitled "Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics," which outlines how sponsors can utilize an adaptive trial design in the early stages of oncology product development (i.e., the first-in-human clinical trial) to compress the first two traditional phases of trials into one continuous trial called an expansion cohort trial. Information to support the design of individual expansion cohorts are included in IND applications and assessed by FDA. Expansion cohort trials can potentially bring efficiency to product development and reduce developmental costs and time.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. In addition, IND safety reports must be submitted to the FDA for any of the following: serious and unexpected suspected adverse reactions; findings from other studies or animal or *in vitro* testing that suggest a significant risk in humans exposed to the product; and any clinically important increase in the case of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. The FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the clinical data submitted.

Finally, sponsors of clinical trials are required to register and disclose certain clinical trial information on a public registry (clinicaltrials.gov) maintained by the U.S. National Institutes of Health, or NIH. In particular, information related to the product, patient population, phase of investigation, study sites and investigators and other aspects of the clinical trial is made public as part of the registration of the clinical trial. The failure to submit clinical trial information to clinicaltrials.gov, as required, is a prohibited act under the FDCA with violations subject to potential civil monetary penalties of up to $10,000 for each day the violation continues.

Manufacturing and Other Regulatory Requirements

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

The FDA's regulations also require that pharmaceutical products be manufactured in specific approved facilities and in accordance with cGMPs. The cGMP regulations include requirements relating to organization of personnel, buildings and facilities, equipment, control of components and product containers and closures, production and process controls, packaging and labeling controls, holding and distribution, laboratory controls, records and reports and returned or salvaged products. Manufacturers and other entities involved in the manufacture and distribution of approved pharmaceuticals are required to register their establishments with the FDA and some state agencies, and they are subject to periodic unannounced inspections by the FDA for compliance with cGMPs and other requirements. Inspections must follow a "risk-based schedule" that may result in certain establishments being inspected more frequently. Manufacturers may also have to provide, on request, electronic or physical records regarding their establishments. Delaying, denying, limiting, or refusing inspection by the FDA may lead to a product being deemed to be adulterated. Changes to the manufacturing process, specifications or container closure system for an approved product are strictly regulated and often require prior FDA approval before being implemented. The FDA's regulations also require, among other things, the investigation and correction of any deviations from cGMP and the imposition of reporting and documentation requirements upon the sponsor and any third-party manufacturers involved in producing the approved product.

Pediatric Studies

Under the Pediatric Research Equity Act of 2003, or PREA, a BLA or supplement thereto must contain data that are adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. Sponsors must also submit pediatric study plans prior to the assessment data. Those plans must contain an outline of the proposed pediatric study or studies the sponsor plans to conduct, including study objectives and design, any deferral or waiver requests, and other information required by regulation. The sponsor, the FDA, and the FDA's internal review committee must then review the information submitted, consult with each other, and agree upon a final plan. The FDA or the sponsor may request an amendment to the plan at any time.

The FDA may, on its own initiative or at the request of the sponsor, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. A deferral may be granted for several reasons, including a finding that the product or therapeutic candidate is ready for approval for use in adults before pediatric trials are complete or that additional safety or effectiveness data needs to be collected before the pediatric trials begin. The law now requires the FDA to send a PREA Non-Compliance letter to sponsors who have failed to submit their pediatric assessments required under PREA, have failed to seek or obtain a deferral or deferral extension or have failed to request approval for a required pediatric formulation. It further requires the FDA to publicly post the PREA Non-Compliance letter and sponsor's response. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation, although FDA has recently taken steps to limit what it considers abuse of this statutory exemption.

Review and Approval of an NDA

In order to obtain approval to market a drug product in the United States, a marketing application must be submitted to the FDA that provides sufficient data establishing the safety, purity and potency of the proposed drug product for its intended indication. The application includes all relevant data available from pertinent preclinical and clinical trials, including negative or ambiguous results as well as positive findings, together with detailed information relating to the product's chemistry, manufacturing, controls and proposed labeling, among other things. Data can come from company-sponsored clinical trials intended to test the safety and effectiveness of a use of a product, or from a number of alternative sources, including studies initiated by investigators. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety and efficacy of the drug product to the satisfaction of the FDA.

The NDA is a vehicle through which sponsors formally propose that the FDA approve a new product for marketing and sale in the United States for one or more indications. Every new drug product candidate must be the subject of an approved NDA before it may be commercialized in the United States. Under federal law, the submission of most NDAs is subject to an application user fee, which for federal fiscal year 2022 is $3,117,218 for an application requiring clinical data. The sponsor of an approved NDA is also subject to an annual program fee, which for federal fiscal year 2022 is $369,413. Certain exceptions and waivers are available for some of these fees, such as an exception from the application fee for products with orphan designation and a waiver for certain small businesses.

Following submission of an NDA, the FDA conducts a preliminary review of the application within 60 calendar days of its receipt and it must inform the sponsor by that time or before as to whether the application is sufficiently complete to permit substantive review. In the event that the FDA determines that an application does not satisfy this standard, it will issue a Refuse to File, or RTF, determination to the sponsor. The FDA may request additional information rather than accept the application for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA has agreed to specified performance goals in the review process of NDAs. Under that agreement, 90% of applications seeking approval of New Molecular Entities, or NMEs, are meant to be reviewed within ten months from the date on which the FDA accepts the application for filing, and 90% of applications for NMEs that have been designated for "priority review" are meant to be reviewed within six months of the filing date.

In connection with its review of an application, the FDA typically will inspect the facility or facilities where the product is or will be manufactured. These pre-approval inspections may cover all facilities associated with an NDA submission, including component manufacturing, finished product manufacturing and control testing laboratories. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP. Under the FDA Reauthorization Act of 2017, the FDA must implement a protocol to expedite review of responses to inspection reports pertaining to certain applications, including applications for products in shortage or those for which approval is dependent on remediation of conditions identified in the inspection report.

In addition, as a condition of approval, the FDA may require a sponsor to develop a REMS. REMS use risk minimization strategies beyond the professional labeling to ensure that the benefits of the product outweigh the potential risks. To determine whether a REMS is needed, the FDA will consider the size of the population likely to use the product, seriousness of the disease, expected benefit of the product, expected duration of treatment, seriousness of known or potential adverse events and whether the product is a new molecular entity.

The FDA may refer an application for a novel product to an advisory committee or explain why such referral was not made. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Expedited Review Programs

The FDA is authorized to expedite the review of NDAs in several ways. Under the Fast Track program, the sponsor of a product candidate may request the FDA to designate the product for a specific indication as a Fast Track product concurrent with or after the filing of the IND. Candidate products are eligible for Fast Track designation if they are intended to treat a serious or life-threatening condition and demonstrate the potential to address unmet medical needs for the condition. Fast Track designation applies to the combination of the product candidate and the specific indication for which it is being studied. In

addition to other benefits, such as the ability to have greater interactions with the FDA, the FDA may initiate review of sections of a Fast Track application before the application is complete, a process known as rolling review.

Any product candidate submitted to the FDA for marketing, including under a Fast Track program, may be eligible for other types of FDA programs intended to expedite development and review, such as breakthrough therapy designation, priority review and accelerated approval.

- *Breakthrough therapy designation.* To qualify for the breakthrough therapy program, product candidates must be intended to treat a serious or life-threatening disease or condition and preliminary clinical evidence must indicate that such product candidates may demonstrate substantial improvement on one or more clinically significant endpoints over existing therapies. The FDA will seek to ensure the sponsor of a breakthrough therapy product candidate receives intensive guidance on an efficient drug development program, intensive involvement of senior managers and experienced staff on a proactive, collaborative and cross-disciplinary review and rolling review.
- *Priority review.* A product candidate is eligible for priority review if it treats a serious condition and, if approved, it would be a significant improvement in the safety or effectiveness of the treatment, diagnosis or prevention compared to marketed products. FDA aims to complete its review of priority review applications within six months as opposed to 10 months for standard review.
- *Accelerated approval.* Drug or biologic products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may receive accelerated approval. Accelerated approval means that a product candidate may be approved on the basis of adequate and well controlled clinical trials establishing that the product candidate has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity and prevalence of the condition and the availability or lack of alternative treatments. As a condition of approval, the FDA may require that a sponsor of a drug or biologic product candidate receiving accelerated approval perform adequate and well controlled post-marketing clinical trials. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials.
- *Regenerative advanced therapy.* With passage of the 21st Century Cures Act, or the Cures Act, in December 2016, Congress authorized the FDA to accelerate review and approval of products designated as regenerative advanced therapies. A product is eligible for this designation if it is a regenerative medicine therapy that is intended to treat, modify, reverse or cure a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product candidate has the potential to address unmet medical needs for such disease or condition. The benefits of a regenerative advanced therapy designation include early interactions with the FDA to expedite development and review, benefits available to breakthrough therapies, potential eligibility for priority review and accelerated approval based on surrogate or intermediate endpoints.

None of these expedited programs change the standards for approval but they may help expedite the development or approval process of product candidates.

The FDA's Decision on an NDA

After evaluating the application and all related information, including the advisory committee recommendations, if any, and inspection reports of manufacturing facilities and clinical trial sites, the FDA will issue either a Complete Response Letter, or CRL, or an approval letter. To reach this determination, the FDA must determine that the drug is effective and that its expected benefits outweigh its potential risks to patients. This "benefit-risk" assessment is informed by the extensive body of evidence about the product's safety and efficacy in the NDA. This assessment is also informed by other factors, including: the severity of the underlying condition and how well patients' medical needs are addressed by currently available therapies; uncertainty about how the premarket clinical trial evidence will extrapolate to real-world use of the product in the post-market setting; and whether risk management tools are necessary to manage specific risks.

A CRL indicates that the review cycle of the application is complete, and the application will not be approved in its present form. The CRL generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

An approval letter, on the other hand, authorizes commercial marketing of the product with specific prescribing information for specific indications. The agency may require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms such as risk evaluation and mitigation strategies, or REMS, to help ensure that the benefits of the product outweigh the potential risks. REMS can include medication guides, communication plans for health care 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 patent registries. The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs. After approval, many types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Post-Approval Regulation

If regulatory approval for marketing of a product or new indication for an existing product is obtained, the sponsor will be required to comply with all regular post-approval regulatory requirements as well as any post-approval requirements that the FDA may have imposed as part of the approval process. The sponsor will be required to report, among other things, certain adverse reactions and manufacturing problems to the FDA, provide updated safety and efficacy information and comply with requirements concerning advertising and promotional labeling requirements. Manufacturers and certain of their subcontractors are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with ongoing regulatory requirements, including cGMP regulations, which impose certain procedural and documentation requirements upon manufacturers. Accordingly, the sponsor and its third-party manufacturers must continue to expend time, money and effort in the areas of production and quality control to maintain compliance with cGMP regulations and other regulatory requirements.

A product may also be subject to official lot release, meaning that the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official release, the manufacturer must submit samples of each lot, together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot, to the FDA. The FDA may in addition perform certain confirmatory tests on lots of some products before releasing the lots for distribution. Finally, the FDA will conduct laboratory research related to the safety, purity, potency and effectiveness of pharmaceutical products.

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

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

The FDA strictly regulates the marketing, labeling, advertising and promotion of prescription drug products placed on the market. This regulation includes, among other things, standards and regulations for direct-to-consumer advertising, communications regarding unapproved uses, industry-sponsored scientific and educational activities, and promotional activities involving the Internet and social media. Promotional claims about a drug's safety or effectiveness are prohibited before the drug is approved. After approval, a drug product generally may not be promoted for uses that are not approved by the FDA, as reflected in the product's prescribing information. In the United States, health care professionals are generally permitted to prescribe drugs for such uses not described in the drug's labeling, known as off-label uses, because the FDA does not regulate the practice of medicine. However, FDA regulations impose rigorous restrictions on manufacturers' communications, prohibiting the promotion of off-label uses. In September 2021, the FDA published final regulations which describe the types of evidence that the agency will consider in determining the intended use of a drug product.

If a company is found to have promoted off-label uses, it may become subject to adverse public relations and administrative and judicial enforcement by the FDA, the DOJ, or the Office of the Inspector General of the Department of Health and Human Services, as well as state authorities. This could subject a company to a range of penalties that could have a significant commercial impact, including civil and criminal fines and agreements that materially restrict the manner in which a company promotes or distributes drug products. The federal government has levied large civil and criminal fines against companies for alleged improper promotion, and has also requested that companies enter into consent decrees or permanent injunctions under which specified promotional conduct is changed or curtailed.

Pediatric Exclusivity

Pediatric exclusivity is another type of non-patent marketing exclusivity in the United States and, if granted, provides for the attachment of an additional six months of regulatory exclusivity to the term of any existing patent or regulatory exclusivity, including orphan exclusivity. This six-month exclusivity may be granted if an NDA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of requested pediatric studies are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patent protection cover the product are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot approve another application.

Orphan Drug Designation and Exclusivity

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

If a product with orphan designation receives the first FDA approval for the disease or condition for which it has such designation or for a select indication or use within the rare disease or condition for which it was designated, the product generally will receive orphan drug exclusivity. Orphan drug exclusivity means that the FDA may not approve another sponsor's marketing application for the same drug for the same condition for seven years, except in certain limited circumstances. Orphan exclusivity does not block the approval of a different product for the same rare disease or condition, nor does it block the approval of the same product for different conditions. If a drug designated as an orphan drug ultimately receives marketing approval for an indication broader than what was designated in its orphan drug application, it may not be entitled to exclusivity.

Orphan drug exclusivity will not bar approval of another product under certain circumstances, including if the company with orphan drug exclusivity is not able to meet market demand or the subsequent product with the same drug for the same condition is shown to be clinically superior to the approved product on the basis of greater efficacy or safety, or providing a major contribution to patient care. This is the case despite an earlier court opinion holding that the Orphan Drug Act unambiguously required the FDA to recognize orphan drug exclusivity regardless of a showing of clinical superiority. Under Omnibus legislation signed by President Trump on December 27, 2020, the requirement for a product to show clinical superiority applies to drugs and biologics that received orphan drug designation before enactment of FDARA in 2017, but have not yet been approved or licensed by FDA.

In September 2021, the Court of Appeals for the 11th Circuit held that, for the purpose of determining the scope of market exclusivity, the term "same disease or condition" in the statute means the designated "rare disease or condition" and could not be interpreted by the FDA to mean the "indication or use." Thus, the court concluded, orphan drug exclusivity applies to the entire designated disease or condition rather than the "indication or use." It is unclear how this court decision will be implemented by the FDA.

Section 505(b)(2) NDAs

NDAs for most new drug products are based on two full clinical studies which must contain substantial evidence of the safety and efficacy of the proposed new product for the proposed use. These applications are submitted under Section 505(b)(1) of the FDCA. The FDA is, however, authorized to approve an alternative type of NDA under Section 505(b)(2) of the FDCA. This type of application allows the sponsor to rely, in part, on the FDA's previous findings of safety and efficacy for a similar

product, or published literature. Specifically, Section 505(b)(2) applies to NDAs for a drug for which the investigations made to show whether or not the drug is safe for use and effective in use and relied upon by the sponsor for approval of the application "were not conducted by or for the sponsor and for which the sponsor has not obtained a right of reference or use from the person by or for whom the investigations were conducted."

Section 505(b)(2) thus authorizes the FDA to approve an NDA based on safety and effectiveness data that were not developed by the sponsor. NDAs filed under Section 505(b)(2) may provide an alternate and potentially more expeditious pathway to FDA approval for new or improved formulations or new uses of previously approved products. If the 505(b)(2) sponsor can establish that reliance on the FDA's previous approval is scientifically appropriate, the sponsor may eliminate the need to conduct certain preclinical or clinical studies of the new product. The FDA may also require companies to perform additional studies or measurements to support the change from the approved product. The FDA may then approve the new drug candidate for all or some of the label indications for which the referenced product has been approved, as well as for any new indication sought by the Section 505(b)(2) sponsor

Abbreviated New Drug Applications for Generic Drugs

In 1984, with passage of the Hatch-Waxman Amendments to the FDCA, Congress established an abbreviated regulatory scheme authorizing the FDA to approve generic drugs that are shown to contain the same active ingredients as, and to be bioequivalent to, drugs previously approved by the FDA pursuant to NDAs.

In order for an ANDA to be approved, the FDA must find that the generic version is identical to the drug product previously approved under an NDA (the reference-listed drug, or RLD), with respect to the active ingredients, the route of administration, the dosage form, the strength of the drug and the conditions of use of the drug. At the same time, the FDA must also determine that the generic drug is "bioequivalent" to the innovator drug. Under the statute, a generic drug is bioequivalent to a RLD if "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug." Upon approval of an ANDA, the FDA indicates whether the generic product is "therapeutically equivalent" to the RLD in its publication "Approved Drug Products with Therapeutic Equivalence Evaluations," also referred to as the "Orange Book." Physicians and pharmacists consider a therapeutic equivalent generic drug to be fully substitutable for the RLD.

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

Hatch-Waxman Patent Certification and the 30-Month Stay

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

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

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

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

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

Patent Term Restoration and Extension

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

Health Care Law and Regulation

Health care providers and third-party payors play a primary role in the recommendation and prescription of drug products that are granted marketing approval. Arrangements with providers, consultants, third-party payors and customers are subject to broadly applicable fraud and abuse, anti-kickback, false claims laws, patient privacy laws and regulations and other health care laws and regulations that may constrain business and/or financial arrangements.

Restrictions under applicable federal and state health care laws and regulations include the federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, paying, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made, in whole or in part, under a federal health care program such as Medicare and Medicaid; the federal civil and criminal false claims laws, including the civil False Claims Act, and civil monetary penalties laws, which prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false, fictitious or fraudulent or knowingly making, using or causing to made or used a false record or statement to avoid, decrease or conceal an obligation to pay money to the federal government; HIPAA, which prohibits, among other things, executing or attempting to execute a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters; the Foreign Corrupt Practices Act, or FCPA, which prohibits companies and their intermediaries from making, or offering or promising to make, improper payments to non-U.S. officials for the purpose of obtaining or retaining business or otherwise seeking favorable treatment; and the federal transparency requirements known as the federal Physician Payments Sunshine Act, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report annually to the Centers for Medicare & Medicaid Services, or CMS, within the United States Department of Health and Human Services, information related to payments and other transfers of value made by that entity to physicians (as defined under the Sunshine Act), other healthcare providers and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members.

Further, some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures. Additionally, some state and local laws require the registration of pharmaceutical sales representatives in the jurisdiction. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, which also imposes obligations, including

mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information, thus complicating compliance efforts.

Pharmaceutical Insurance Coverage and Health Care Reform

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

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

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

In March 2010, the United States Congress enacted the ACA, which, among other things, includes changes to the coverage and payment for drug products under government health care programs. Other legislative changes have been proposed and adopted since the ACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. These changes included aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2030 under the Coronavirus Aid, Relief, and Economic Security Act, or the CARES Act. These Medicare sequester reductions have been suspended through the end of March 2022. From April 2022 through June 2022 a 1% sequester cut will be in effect, with the full 2% cut resuming thereafter. The American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used.

Since enactment of the ACA, there have been, and continue to be, numerous legal challenges and Congressional actions to repeal and replace provisions of the law. For example, with enactment of the Tax Cuts and Jobs Act of 2017, which was signed by President Trump on December 22, 2017, Congress repealed the "individual mandate." The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, became effective in 2019. On December 14, 2018, a U.S. District Court judge in the Northern District of Texas ruled that the individual mandate portion of the PPACA is an essential and inseverable feature of the PPACA, and therefore because the mandate was repealed as part of the Tax Act, the remaining provisions of the PPACA are invalid as well. The U.S. Supreme Court heard this case on November 10, 2020 and, on June 17, 2021, dismissed this action after finding that the plaintiffs do not have standing to challenge the

constitutionality of the ACA. Litigation and legislation over the PPACA are likely to continue, with unpredictable and uncertain results.

The Trump Administration also took executive actions to undermine or delay implementation of the ACA, including directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. On January 28, 2021, however, President Biden rescinded those orders and issued a new Executive Order which directs federal agencies to reconsider rules and other policies that limit Americans' access to health care, and consider actions that will protect and strengthen that access. Under this Order, federal agencies are directed to re-examine: policies that undermine protections for people with pre-existing conditions, including complications related to COVID-19; demonstrations and waivers under Medicaid and the ACA that may reduce coverage or undermine the programs, including work requirements; policies that undermine the Health Insurance Marketplace or other markets for health insurance; policies that make it more difficult to enroll in Medicaid and the ACA; and policies that reduce affordability of coverage or financial assistance, including for dependents.

The prices of prescription pharmaceuticals have also been the subject of considerable discussion in the United States. There have been several recent U.S. congressional inquiries, as well as proposed and enacted state and federal legislation designed to, among other things, bring more transparency to pharmaceutical pricing, review the relationship between pricing and manufacturer patient programs, and reduce the costs of pharmaceuticals under Medicare and Medicaid. In 2020, President Trump issued several executive orders intended to lower the costs of prescription products and certain provisions in these orders have been incorporated into regulations. These regulations include an interim final rule implementing a most favored nation model for prices that would tie Medicare Part B payments for certain physician-administered pharmaceuticals to the lowest price paid in other economically advanced countries, effective January 1, 2021. That rule, however, has been subject to a nationwide preliminary injunction and, on December 29, 2021, CMS issued a final rule to rescind it. With issuance of this rule, CMS stated that it will explore all options to incorporate value into payments for Medicare Part B pharmaceuticals and improve beneficiaries' access to evidence-based care.

In addition, in October 2020, HHS and the FDA published a final rule allowing states and other entities to develop a Section 804 Importation Program, or SIP, to import certain prescription drugs from Canada into the United States. The final rule is currently the subject of ongoing litigation, but at least six states (Vermont, Colorado, Florida, Maine, New Mexico, and New Hampshire) have passed laws allowing for the importation of drugs from Canada with the intent of developing SIPs for review and approval by the FDA. Further, on November 20, 2020, HHS finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a new safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers. The implementation of this rule has been delayed by the Biden administration until January 1, 2026.

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

Review and Approval of Medicinal Products in the European Union

In order to market any product outside of the United States, a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of products. Whether or not it obtains FDA approval for a product, a sponsor will need to obtain the necessary approvals by the comparable non-U.S. regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions. Specifically, the process governing approval of medicinal products in the EU generally follows the same lines as in the United States. It entails satisfactory completion of preclinical studies and adequate and well-controlled clinical trials to establish the safety and efficacy of the product for each proposed indication. It also requires the submission to the relevant competent authorities of a marketing authorization application, or MAA, and granting of a marketing authorization by these authorities before the product can be marketed and sold in the EU.

Clinical Trial Approval

On January 31, 2022, the new Clinical Trials Regulation (EU) No 536/2014 became effective in the European Union and replaced the prior Clinical Trials Directive 2001/20/EC. The new regulation aims at simplifying and streamlining the authorization, conduct and transparency of clinical trials in the European Union. Under the new coordinated procedure for the approval of clinical trials, the sponsor of a clinical trial to be conducted in more than one Member State of the European Union, or EU Member State, will only be required to submit a single application for approval. The submission will be made through the Clinical Trials Information System, a new clinical trials portal overseen by the EMA and available to clinical trial sponsors, competent authorities of the EU Member States and the public.

The new regulation did not change the preexisting requirement that a sponsor must obtain prior approval from the competent national authority of the EU Member State in which the clinical trial is to be conducted. If the clinical trial is conducted in different EU Member States, the competent authorities in each of these EU Member States must provide their approval for the conduct of the clinical trial. Furthermore, the sponsor may only start a clinical trial at a specific study site after the applicable ethics committee has issued a favorable opinion.

As in the United States, similar requirements for posting clinical trial information are present in the European Union (EudraCT) website: https://eudract.ema.europa.eu/ and other countries.

Pediatric Studies

Prior to obtaining a marketing authorization in the European Union, sponsors must demonstrate compliance with all measures included in an EMA-approved PIP covering all subsets of the pediatric population, unless the EMA has granted a product-specific waiver, a class waiver, or a deferral for one or more of the measures included in the PIP. The respective requirements for all marketing authorization procedures are laid down in Regulation (EC) No 1901/2006, the so-called Paediatric Regulation. This requirement also applies when a company wants to add a new indication, pharmaceutical form or route of administration for a medicine that is already authorized. The Paediatric Committee of the EMA, or PDCO, may grant deferrals for some medicines, allowing a company to delay development of the medicine for children until there is enough information to demonstrate its effectiveness and safety in adults. The PDCO may also grant waivers when development of a medicine for children is not needed or is not appropriate, such as for diseases that only affect the elderly population. Before an MAA can be filed, or an existing marketing authorization can be amended, the EMA determines that companies actually comply with the agreed studies and measures listed in each relevant PIP.

PRIME Designation in the EU

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

Marketing Authorization

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

The centralized procedure provides for the grant of a single marketing authorization by the European Commission that is valid across the European Economic Area (i.e. the EU as well as Iceland, Liechtenstein and Norway). Pursuant to Regulation (EC) No 726/2004, the centralized procedure is compulsory for specific products, including for medicines produced by certain biotechnological processes, products designated as orphan medicinal products, advanced therapy medicinal products, and products with a new active substance indicated for the treatment of certain diseases, including products for the treatment of cancer. For products with a new active substance indicated for the treatment of other diseases and products that are highly innovative or for which a centralized process is in the interest of patients, the centralized procedure may be optional. The centralized procedure may at the request of the sponsor also be used in certain other cases. We anticipate that the centralized procedure will be mandatory for the product candidates we are developing.

Under the centralized procedure, the CHMP is also responsible for several post-authorization and maintenance activities, such as the assessment of modifications or extensions to an existing marketing authorization. Under the centralized procedure in the EU, the maximum timeframe for the evaluation of an MAA is 210 days, excluding clock stops, when additional information or written or oral explanation is to be provided by the sponsor in response to questions of the CHMP. Accelerated evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation. If the CHMP accepts such request, the time limit of 210 days will be reduced to 150 days but it is possible that the CHMP can revert to the standard time limit for the centralized procedure if it considers that it is no longer appropriate to conduct an accelerated assessment. At the end of this period, the CHMP provides a scientific opinion on whether or not a marketing authorization should be granted in relation to a medicinal product. Within 15 calendar days of receipt of a final opinion from the CHMP, the European Commission must prepare a draft decision concerning an application for marketing authorization. This draft decision must take the opinion and any relevant provisions of EU law into account. Before arriving at a final decision on an application for centralized authorization of a medicinal product the European Commission must consult the Standing Committee on Medicinal Products for Human Use. The Standing Committee is composed of representatives of the EU member states and chaired by a non-voting European Commission representative. The European Parliament also has a related "droit de regard". The European Parliament's role is to ensure that the European Commission has not exceeded its powers in deciding to grant or refuse to grant a marketing authorization.

The European Commission may also grant a so-called "conditional marketing authorization" prior to obtaining the comprehensive clinical data required for an application for a full marketing authorization. Such conditional marketing authorizations may be granted for product candidates (including medicines designated as orphan medicinal products), if (i) the risk-benefit balance of the product candidate is positive, (ii) it is likely that the sponsor will be in a position to provide the required comprehensive clinical trial data, (iii) the product fulfills an unmet medical need and (iv) the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required. A conditional marketing authorization may contain specific obligations to be fulfilled by the marketing authorization holder, including obligations with respect to the completion of ongoing or new studies, and with respect to the collection of pharmacovigilance data. Conditional marketing authorizations are valid for one year, and may be renewed annually, if the risk-benefit balance remains positive, and after an assessment of the need for additional or modified conditions and/or specific obligations. The timelines for the centralized procedure described above also apply with respect to the review by the CHMP of applications for a conditional marketing authorization.

The EU medicines rules expressly permit the EU member states to adopt national legislation prohibiting or restricting the sale, supply or use of any medicinal product containing, consisting of or derived from a specific type of human or animal cell, such as embryonic stem cells. While the products we have in development do not make use of embryonic stem cells, it is possible that the national laws in certain EU member states may prohibit or restrict us from commercializing our products, even if they have been granted an EU marketing authorization.

Unlike the centralized authorization procedure, the decentralized marketing authorization procedure requires a separate application to, and leads to separate approval by, the competent authorities of each EU Member State in which the product is to be marketed. This application is identical to the application that would be submitted to the EMA for authorization through the

centralized procedure. The reference EU Member State prepares a draft assessment and drafts of the related materials within 120 days after receipt of a valid application. The resulting assessment report is submitted to the concerned EU member states who, within 90 days of receipt, must decide whether to approve the assessment report and related materials. If a concerned EU Member State cannot approve the assessment report and related materials due to concerns relating to a potential serious risk to public health, disputed elements may be referred to the European Commission, whose decision is binding on all EU member states.

The mutual recognition procedure similarly is based on the acceptance by the competent authorities of the EU member states of the marketing authorization of a medicinal product by the competent authorities of other EU member states. The holder of a national marketing authorization may submit an application to the competent authority of an EU Member State requesting that this authority recognize the marketing authorization delivered by the competent authority of another EU Member State.

Regulatory Data Protection in the EU

In the EU, innovative medicinal products approved on the basis of a complete independent data package qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity pursuant to Directive 2001/83/EC. Regulation (EC) No 726/2004 repeats this entitlement for medicinal products authorized in accordance the centralized authorization procedure. Data exclusivity prevents sponsors for authorization of generics of these innovative products from referencing the innovator's data to assess a generic (abridged) application for a period of eight years. During an additional two-year period of market exclusivity, a generic marketing authorization application can be submitted and authorized, and the innovator's data may be referenced, but no generic medicinal product can be placed on the EU market until the expiration of the market exclusivity. The overall ten-year period will be extended to a maximum of 11 years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies. Even if a compound is considered to be a new chemical entity so that the innovator gains the prescribed period of data exclusivity, another company nevertheless could also market another version of the product if such company obtained marketing authorization based on an MAA with a complete independent data package of pharmaceutical tests, preclinical tests and clinical trials.

Periods of Authorization and Renewals

A marketing authorization has an initial validity for five years in principle. The marketing authorization may be renewed after five years on the basis of a re-evaluation of the risk-benefit balance by the EMA or by the competent authority of the EU Member State. To this end, the marketing authorization holder must provide the EMA or the competent authority with a consolidated version of the file in respect of quality, safety and efficacy, including all variations introduced since the marketing authorization was granted, at least six months before the marketing authorization ceases to be valid. The European Commission or the competent authorities of the EU member states may decide, on justified grounds relating to pharmacovigilance, to proceed with one further five-year period of marketing authorization. Once subsequently definitively renewed, the marketing authorization shall be valid for an unlimited period. Any authorization which is not followed by the actual placing of the medicinal product on the EU market (in case of centralized procedure) or on the market of the authorizing EU Member State within three years after authorization ceases to be valid.

Orphan Drug Designation and Exclusivity

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

Once authorized, orphan medicinal products are entitled to 10 years of market exclusivity in all EU member states and a range of other benefits during the development and regulatory review process, including scientific assistance for study protocols, authorization through the centralized marketing authorization procedure covering all member countries and a reduction or elimination of registration and marketing authorization fees. However, marketing authorization may be granted to a similar medicinal product with the same orphan indication during the 10-year period with the consent of the marketing authorization holder for the original orphan medicinal product or if the manufacturer of the original orphan medicinal product is unable to supply sufficient quantities. Marketing authorization may also be granted to a similar medicinal product with the same orphan indication if this product is safer, more effective or otherwise clinically superior to the original orphan medicinal

product. The period of market exclusivity may, in addition, be reduced to six years if it can be demonstrated on the basis of available evidence that the original orphan medicinal product is sufficiently profitable not to justify maintenance of market exclusivity.

Pediatric Exclusivity

If a sponsor obtains a marketing authorization in all EU Member States, or a marketing authorization granted in the centralized procedure by the European Commission, and the study results for the pediatric population are included in the product information, even when negative, the medicine is then eligible for an additional six-month period of qualifying patent protection through extension of the term of the Supplementary Protection Certificate, or SPC.

Regulatory Requirements after a Marketing Authorization has been Obtained

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

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

Brexit and the Regulatory Framework in the United Kingdom

The United Kingdom's withdrawal from the EU took place on January 31, 2020. The EU and the U.K. reached an agreement on their new partnership in the Trade and Cooperation Agreement, or the Agreement, which was applied provisionally beginning on January 1, 2021 and which entered into force on May 1, 2021. The Agreement focuses primarily on free trade by ensuring no tariffs or quotas on trade in goods, including healthcare products such as medicinal products. Thereafter, the EU and the U.K. will form two separate markets governed by two distinct regulatory and legal regimes. As such, the Agreement seeks to minimize barriers to trade in goods while accepting that border checks will become inevitable as a consequence that the U.K. is no longer part of the single market. As of January 1, 2021, the Medicines and Healthcare products Regulatory Agency, or the MHRA, became responsible for supervising medicines and medical devices in Great Britain, comprising England, Scotland and Wales under domestic law whereas Northern Ireland continues to be subject to EU rules under the Northern Ireland Protocol. The MHRA will rely on the Human Medicines Regulations 2012 (SI 2012/1916) (as amended), or the HMR, as the basis for regulating medicines. The HMR has incorporated into the domestic law the body of EU law instruments governing medicinal products that pre-existed prior to the U.K.'s withdrawal from the EU.

As with other issues related to Brexit, there are open questions about how personal data will be protected in the UK and whether personal information can transfer from the EU to the UK. Following the withdrawal of the U.K. from the EU, the U.K. Data Protection Act 2018 applies to the processing of personal data that takes place in the U.K. and includes parallel obligations to those set forth by GDPR. While the Data Protection Act of 2018 in the United Kingdom that "implements" and complements the European Union General Data Protection Regulation, or GDPR, has achieved Royal Assent on May 23, 2018 and is now effective in the United Kingdom, it is still unclear whether transfer of data from the European Economic Area, or EEA, to the United Kingdom will remain lawful under GDPR. The United Kingdom government has already determined that it considers all European Union and EEA member states to be adequate for the purposes of data protection, ensuring that data flows from the United Kingdom to the European Union/EEA remain unaffected. In addition, a recent decision from the European Commission appears to deem the UK as being "essentially adequate" for purposes of data transfer from the EU to the UK, although this decision may be re-evaluated in the future. We may, however, incur liabilities, expenses, costs, and other operational losses under GDPR and applicable EU Member States and the United Kingdom privacy laws in connection with any measures we take to comply with them.

Data Privacy Regulation

U.S. Privacy Law

There are multiple privacy and data security laws that may impact our business activities, in the United States and in other countries where we conduct trials or where we may do business in the future. These laws are evolving and may increase both our obligations and our regulatory risks in the future. In the health care industry generally, for example, under the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, the U.S. Department of Health and Human Services, or HHS, has issued regulations to protect the privacy and security of protected health information, or PHI, used or disclosed by specific covered entities including certain healthcare providers, health plans and healthcare clearinghouses. HIPAA also imposes certain obligations on the business associates of covered entities that obtain protected health information in providing services to or on behalf of covered entities. HIPAA may apply to us in certain circumstances and may also apply to our business partners in ways that may impact our relationships with them. Our clinical trials are or will be regulated by the Common Rule, which also includes specific privacy-related provisions. In addition to federal privacy regulations, there are a number of state laws governing confidentiality and security of health information that may be applicable to our business. In addition to possible federal civil and criminal penalties for HIPAA violations, state attorneys general are authorized to file civil actions for damages or injunctions in federal courts to enforce HIPAA and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, state attorneys general (along with private plaintiffs) have brought civil actions seeking injunctions and damages resulting from alleged violations of HIPAA's privacy and security rules. State attorneys general also have authority to enforce state privacy and security laws. Moreover, new laws and regulations governing privacy and security may be adopted in the future as well.

There have been several developments in recent years with respect to U.S. state data privacy laws. In 2018, California passed into law the California Consumer Privacy Act, or the CCPA, which took effect on January 1, 2020 and imposed many requirements on businesses that process the personal information of California residents. The CCPA's requirements include requiring businesses to provide notice to data subjects regarding the information collected about them and how such information is used and shared, and providing data subjects the right to request access to such personal information and, in certain cases, request the erasure of such personal information. The CCPA also affords California residents the right to opt-out of "sales" of their personal information. The CCPA contains significant penalties for companies that violate its requirements. It also provides California residents a private right of action in certain circumstances, including the ability to seek statutory damages, in the event of a breach involving their personal information. Compliance with the CCPA is a rigorous and time-intensive process that may increase the cost of doing business or require companies to change their business practices to ensure full compliance. On November 3, 2020, California voters passed a ballot initiative for the California Privacy Rights Act, or the CPRA, which will significantly expand the CCPA to incorporate additional provisions including requiring that the use, retention and sharing of personal information of California residents be reasonably necessary and proportionate to the purposes of collection or processing, granting additional protections for sensitive personal information, and requiring greater disclosures related to notice to residents regarding retention of information. The CPRA will also expand personal information rights of California residents, including creating a right to opt out of sharing of personal information with third parties for advertising, expanding the lookback period for the right to know about personal information held by businesses, and expanding the right to erasure for information held by third parties. Most CPRA provisions will take effect on January 1, 2023, though the obligations will apply to any personal information collected after January 1, 2022. These provisions may apply to some of our business activities. In addition, other states, including Virginia and Colorado, already have passed state privacy laws. Other states will be considering these laws in the future. These laws may impact our business activities, including our identification of research subjects, relationships with business partners and ultimately the marketing and distribution of our products.

General Data Protection Regulation

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

There are ongoing concerns about the ability of companies to transfer personal data from the EU to other countries. In July 2020, the Court of Justice of the European Union, or the CJEU, invalidated the EU-U.S. Privacy Shield framework, one of the mechanisms used to legitimize the transfer of personal data from the EEA to the United States. The CJEU decision also drew into question the long-term viability of an alternative means of data transfer, the standard contractual clauses, for transfers of personal data from the EEA to the United States. This CJEU decision may lead to increased scrutiny on data transfers from the EU to the U.S. generally and increase our costs of compliance with data privacy legislation as well as our costs of negotiating appropriate privacy and security agreements with our vendors and business partners.

As a result of these uncertainties, there is increased scrutiny on the extent to which clinical trial sites located in the EEA should apply the GDPR to transfers of personal data from such sites to countries that are considered to lack an adequate level of data protection, such as the United States. The GDPR also permits data protection authorities to require destruction of improperly gathered or used personal information and/or impose substantial fines for violations of the GDPR, which can be up to four percent of global revenues or 20 million Euros, whichever is greater, and it also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. In addition, the GDPR provides that EU member states may make their own further laws and regulations limiting the processing of personal data, including genetic, biometric or health data.

Beyond GDPR, there are privacy and data security laws in a growing number of countries around the world. While many loosely follow GDPR as a model, other laws contain different or conflicting provisions. These laws will impact our ability to conduct our business activities, including both our clinical trials and any eventual sale and distribution of commercial products. These laws also impose compliance obligations and related costs and may complicate both our business activities overall and our relationships with our business partners and service providers.

For these laws, both now and in the future, there is a wide range of enforcement agencies at the state, federal and international levels that can review companies for privacy and data security concerns based on general consumer protection laws. The Federal Trade Commission and state Attorneys General all are aggressive in reviewing privacy and data security protections for consumers. New laws also are being considered at both the state and federal levels. For example, the California Consumer Privacy Act, or CCPA, which went into effect on January 1, 2020, is creating similar risks and obligations as those created by GDPR, though the Act does exempt certain information collected as part of a clinical trial subject to the Federal Policy for the Protection of Human Subjects (the Common Rule). Many other states are considering similar legislation. A broad range of legislative measures also have been introduced at the federal level. Accordingly, failure to comply with federal and state laws (both those currently in effect and future legislation) regarding privacy and security of personal information could expose us to fines and penalties under such laws. There also is the threat of consumer class actions related to these laws and the overall protection of personal data. Even if we are not determined to have violated these laws, government investigations into these issues typically require the expenditure of significant resources and generate negative publicity, which could harm our reputation and our business.

In addition to the foregoing, any breach of privacy laws or data security laws, particularly resulting in a significant security incident or breach involving the misappropriation, loss or other unauthorized use or disclosure of sensitive or confidential patient or consumer information, could have a material adverse effect on our business, reputation and financial condition. As a data controller, we will be accountable for any third-party service providers we engage to process personal data on our behalf, including our CROs. There is no assurance that privacy and security-related safeguards we implement will protect us from all risks associated with the third-party processing, storage and transmission of such information. In certain situations, both in the United States and in other countries, we also may be obligated as a result of a security breach to notify individuals and/or government entities about these breaches.

New privacy and security legislation continues to be proposed or enacted across the United States. These laws impose, or have the potential to impose, additional obligations on companies that collect, store, use, retain, disclose, transfer and otherwise process confidential, sensitive and personal information, and will continue to shape the data privacy environment nationally. State laws are changing rapidly and there is discussion in Congress of a new federal data protection and privacy law to which we would become subject if it is enacted. There is also discussion of an executive order on cybersecurity that could affect how we collect and process information. All of these evolving compliance and operational requirements impose significant costs that are likely to increase over time, may require us to modify our data processing practices and policies, divert resources from other initiatives and projects, and could restrict the way products and services involving data are offered, all of which could significantly harm our business, financial condition, results of operations and prospects. Further, certain state laws may be more stringent or broader in scope, or offer greater individual rights, with respect to confidential, sensitive and personal information than federal, international or other state laws, and such laws may differ from each other, which may complicate compliance efforts.

Given the breadth and depth of changes in data protection obligations, preparing for and complying with such requirements is rigorous and time intensive and requires significant resources and a review of our technologies, systems and practices, as well as those of any third-party collaborators, service providers, contractors or consultants that process or transfer personal data. The GDPR and other changes in laws or regulations associated with the enhanced protection of certain types of sensitive data, such as healthcare data or other personal information from our clinical trials, could require us to change our business practices and put in place additional compliance mechanisms, may interrupt or delay our development, regulatory and commercialization activities and increase our cost of doing business, and could lead to government enforcement actions, private litigation and significant fines and penalties against us and could have a material adverse effect on our business, financial condition or results of operations.

Pricing Decisions for Approved Products

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

Employees

As of March 20, 2022, we had 33 full-time employees, 19 of whom were engaged in research and development and 14 of whom were engaged in general business management, administration and finance. Approximately 73% of our employees hold advanced degrees, including nine that hold Ph.D. or M.D. degrees and fifteen that hold a master's degree. Our success depends, in part, on our ability to recruit and retain talented and trained scientific and business personnel and senior leadership, as well as our ability to leverage key consultants in supporting strategic and tactical roles. We believe that we have been successful to date in obtaining and retaining these individuals, but we do not know whether we will be successful in doing so in the future. None of our employees are represented by a labor union or covered by a collective bargaining agreement, nor have we experienced work stoppages.

Corporate Information

We were incorporated in California on March 22, 1995 under the name IRORI and, in 1998, we changed our name to Discovery Partners International, Inc., or DPI. In July 2000, we reincorporated in Delaware. On September 12, 2006, DPI completed a merger with Infinity Pharmaceuticals, Inc., or IPI, pursuant to which a wholly owned subsidiary of DPI merged with and into IPI. IPI, the surviving corporation in the merger, changed its name to Infinity Discovery, Inc., or IDI, and became a wholly owned subsidiary of DPI. In addition, we changed our corporate name from Discovery Partners International, Inc. to Infinity Pharmaceuticals, Inc., and our ticker symbol on the Nasdaq Global Market to "INFI." Our common stock currently trades on the Nasdaq Global Select Market.

Our principal executive offices are located at 1100 Massachusetts Avenue, Floor 4, Cambridge Massachusetts 02138, and our telephone number is (617) 453-1000.

The Infinity logo and all other Infinity product names are trademarks of Infinity Pharmaceuticals, Inc. or its subsidiaries in the United States and in other select countries. We may indicate U.S. trademark registrations and U.S. trademarks with the symbols "®" and "™", respectively. Other third-party logos and product/trade names are registered trademarks or trade names of their respective owners.

Information about our Executive Officers

The following table lists the positions, names and ages of our executive officers as of March 25, 2022:

Name	Age	Position
Adelene Q. Perkins	62	Chief Executive Officer
Lawrence E. Bloch, M.D., J.D.	56	President and Treasurer
Robert Ilaria, Jr., M.D.	61	Chief Medical Officer
Stéphane Peluso, Ph.D.	52	Chief Scientific Officer
Seth A. Tasker, J.D.	43	Senior Vice President, Chief Business Officer, General Counsel, and Secretary

Adelene Q. Perkins has served as our Chief Executive Officer since January 2010. She previously served as our President between October 2008 and January 2017, our Chief Business Officer from October 2008 through December 2009 and our Executive Vice President and Chief Business Officer between September 2006 and October 2008. Ms. Perkins served as Executive Vice President of IPI from February 2006 until its merger with DPI in September 2006 and Chief Business Officer of IPI from June 2002 until the DPI merger. Prior to joining IPI, Ms. Perkins served as Vice President of Business and Corporate Development of TransForm Pharmaceuticals, Inc., a private pharmaceutical company, from 2000 to 2002. From 1992 to 1999, Ms. Perkins held various positions at Genetics Institute, most recently serving as Vice President of Emerging Business and General Manager of the DiscoverEase® business unit. Ms. Perkins has served on the board of directors for the Biotechnology Industry Organization since 2012; the Bruker Corporation, a publicly traded manufacturer of analytic instruments, since 2017; Massachusetts General Hospital since 2017; the Massachusetts Biotechnology Council, a not-for-profit organization, since 2014; and Project Hope, a not-for-profit social services company, since 2013. From 1985 to 1992, Ms. Perkins held a variety of positions at Bain & Company, a strategy consulting firm. Ms. Perkins received a B.S. in Chemical Engineering from Villanova University and an M.B.A. from Harvard Business School.

Lawrence E. Bloch, M.D., J.D., has served as our President since January 2017. He previously served as our Executive Vice President, Chief Financial Officer and Chief Business Officer from July 2012 to January 2017. Prior to joining Infinity, Dr. Bloch served as Chief Executive Officer of NeurAxon, Inc., a privately held biopharmaceutical company, from 2007 to 2011. Previously, he served as Chief Financial Officer and Chief Business Officer of NitroMed, Inc., a publicly held biopharmaceutical company, from 2004 to 2006. From 2000 to 2004, Dr. Bloch served as Chief Financial Officer, and from 1999 to 2002 as Vice President, Business Development, of Applied Molecular Evolution, Inc., a publicly held biopharmaceutical company. Dr. Bloch began his career as an emergency medicine resident physician at Massachusetts General Hospital and Brigham and Woman's Hospital. He holds a J.D. from Harvard Law School, an M.D. from Harvard Medical School and an M.B.A. from Harvard Business School.

Robert Ilaria, Jr., M.D., has served as our Chief Medical Officer since September 2021. Dr. Ilaria joined Infinity from Bristol Myers Squibb and Celgene, where he worked from 2017 to 2021 and focused on immune-oncology drug development, serving leadership roles on the CTLA-4 and PD-1 inhibitor drug development teams, respectively. Prior to joining Celgene, Dr. Ilaria was at Eli Lilly from 2005 to 2017 in leadership roles of increasing responsibility in both Early and Late Phase drug development. During his time at Eli Lilly, Dr. Ilaria was responsible for the clinical strategy of multiple assets ranging from pre-clinical development through regulatory approval. Prior to joining the pharmaceutical industry, Dr. Ilaria had academic clinical and basic science research careers at UT Southwestern and Harvard Medical School. He holds a BA in biology and philosophy from Rice University and an MD from UT Southwestern Medical School. He did his internal medicine and hematology and medical oncology training at Brigham and Women's Hospital and the Dana Farber Cancer Institute. Dr. Ilaria has remained clinically active during his pharmaceutical career through volunteer oncology staff service at academic teaching institutions.

Stéphane Peluso, Ph.D., has served as our Chief Scientific Officer since August 2021. Dr. Peluso returns to Infinity from Ipsen Bioscience where he was most recently Vice President, Global Head of Oncology External Innovation. Prior to Ipsen, Dr. Peluso worked at Infinity where he held positions of increasing responsibility in medicinal chemistry and drug discovery from 2006 to August 2016, ultimately leading the Company's early drug discovery and pipeline expansion efforts through both internal R&D and business development. Dr. Peluso started his career as a medicinal chemist at Millennium Pharmaceuticals. He graduated from the Ecole Supérieure de Chimie Industrielle de Lyon (ESCIL), France, obtained his Ph.D. from the University of Lausanne, Switzerland, and completed postdoctoral studies at the Massachusetts Institute of Technology.

Seth A. Tasker, J.D., has served as our Senior Vice President, Chief Business Officer, General Counsel, and Secretary since December 2019. Mr. Tasker previously served as our Vice President, General Counsel and Secretary between July 2016 and December 2019, our Deputy General Counsel between March 2015 and July 2016, our Associate General Counsel between March 2013 and March 2015, our Assistant General Counsel between March 2010 and March 2013, and our Corporate Counsel between March 2008 and March 2010. Prior to joining Infinity, Mr. Tasker served in varying levels of responsibility in the legal function at Surface Logix, Inc., a privately held biopharmaceutical company, from 2001 to 2008. Mr. Tasker holds a B.S. in Microbiology from the University of Vermont, a J.D. from Suffolk University Law School, and an M.B.A. from Suffolk University Sawyer School of Management.

Available Information

Our Internet website is http://www.infi.com. We make available free of charge through our website our annual report on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and amendments to those reports filed or furnished pursuant to Sections 13(a) and 15(d) of the Securities Exchange Act of 1934, as amended. We make these reports available through our website as soon as reasonably practicable after we electronically file such reports with, or furnish such reports to, the U.S. Securities and Exchange Commission. In addition, we regularly use our website to post information regarding our business, product development programs and governance, and we encourage investors to use our website, particularly the information in the section entitled "Investors/Media," as a source of information about us.

Our Code of Conduct and Ethics and the charters of the Audit, Compensation, Nominating & Corporate Governance and Research & Development Committees of our Board of Directors are all available on our website at http://www.infi.com at the "Investors/Media" section under "Corporate Governance." Stockholders may request a free copy of any of these documents by writing to Investor Relations, Infinity Pharmaceuticals, Inc., 1100 Massachusetts Avenue, Floor 4, Cambridge, Massachusetts 02138, U.S.A.

The foregoing references to our website are not intended to, nor shall they be deemed to, incorporate information on our website into this report by reference.

Item 1A. RISK FACTORS

The following risk factors and other information included in this Annual Report on Form 10-K, including the Management's Discussion and Analysis of Financial Condition and Results of Operations section and the consolidated financial statements and related notes, should be carefully considered in evaluating our business. The risks and uncertainties described below are not the only risks and uncertainties we face. Additional risks and uncertainties not presently known to us or that we presently deem less significant may also impair our business operations. Therefore, historical operating results, financial and business performance, events and trends are often not a reliable indicator of future operating results, financial and business performance, events or trends. Please see the Cautionary Note Regarding Forward-Looking Information and Industry Data in this Annual Report on Form 10-K for a discussion of some of the forward-looking statements that are qualified by these risk factors. If any of the following risks occur, our business, financial condition, results of operations and future growth prospects could be materially and adversely affected.

Risks Related to Our Financial Position and Need for Additional Capital

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

We may seek additional funding through public or private financings of equity or debt securities, but such financing may not be available on acceptable terms, if at all. If we raise additional funds through the issuance of additional debt or equity securities, as we did in 2020 under our common stock sales facility as well as in February 2021 through a public offering of our common stock, we may not be able to raise capital at the price we desire, and any public offering could result in dilution to our existing stockholders, increased fixed payment obligations and the existence of securities with rights that may adversely affect the rights of our existing stockholders including liquidation or other preferences and anti-dilution protections.

In addition, securing financing could require a substantial amount of time and attention from our management and may divert a disproportionate amount of their attention away from day-to-day activities, which may adversely affect our management's ability to oversee the development of our product candidates.

We may also seek additional funds through arrangements with collaborators or other third parties, or through project financing. These arrangements would generally require us to relinquish or encumber valuable rights to our technologies, future revenue streams, or product candidates, and we may not be able to enter into such agreements on acceptable terms, if at all.

If we are unable to obtain additional funding on a timely basis, we may be required to curtail, terminate, sell or license rights to develop and market eganelisib that we would otherwise prefer to develop and market ourselves, or to scale back, suspend, or terminate our business operations.

We have a history of operating losses, expect to incur significant and increasing operating losses in the future, and may never become profitable, or if we become profitable, we may not remain profitable.

We have no approved products, have generated no product revenue from sales, and have primarily incurred operating losses. As of December 31, 2021, we had an accumulated deficit of $811.6 million. We expect to continue to spend significant resources to fund eganelisib, our selective inhibitor of phosphoinositide-3-kinase, or PI3K-gamma. While we may have net income in some periods as the result of non-recurring collaboration revenue, we expect to incur substantial operating losses over the next several years as our clinical trial and drug manufacturing activities continue. In addition, if we proceed to seek and possibly obtain regulatory approval of eganelisib, we would expect to incur significant commercialization expenses for product sales, marketing, manufacturing and distribution, to the extent such sales, marketing, manufacturing and distribution are not the responsibility of a future collaborator. As a result, we expect that our accumulated deficit would also increase significantly.

Eganelisib is under clinical development and may never be approved for sale or generate any revenue. We will not be able to generate product revenue unless and until eganelisib successfully completes clinical trials and receives regulatory approval. We do not expect to generate revenue from product sales for the foreseeable future. Even if we eventually generate revenues, we may never be profitable, and 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, expand our business, and maintain our research and development efforts, and cause a decline in the value of our common stock.

We will need substantial additional funding, and if we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate the development of eganelisib or future efforts to commercialize eganelisib.

Developing pharmaceutical products, including conducting preclinical studies and clinical trials, is a time consuming, expensive and uncertain process that takes years to complete. We will need substantial additional funds to support our planned operations. We believe that our existing cash and cash equivalents balance as of December 31, 2021, which was $80.7 million, will be adequate to satisfy our current operating plans for at least the next twelve months from the issuance date of these financial statements.

Our estimate as to how long we expect our existing cash and cash equivalents to be able to continue to fund our operations will depend on many factors, which assumptions may prove to be wrong, and we could use our available capital resources sooner than we currently expect. Further, changing circumstances, some of which may be beyond our control, could cause us to consume capital significantly faster than we currently anticipate, and we may need to seek additional funds sooner than planned. Our future funding requirements, both short-term and long-term, will depend on many factors, including, but not limited to, the scope, progress, results and costs of developing and marketing eganelisib, including costs of acquiring raw materials and manufacturing, as well as the impact of delays as a result of the COVID-19 pandemic. Our funding requirements will further depend on the timing and amount of additional revenues, if any, received from commercial sales of eganelisib and from collaboration agreements and funding arrangements, including milestone payments from entities affiliated with BVF, regulatory and commercial-based milestone payments from PellePharm related to patidegib, and additional royalty and milestone payments owed to Takeda.

We have broad discretion in the use of our available cash and other sources of funding and may not use them effectively.

Our management has broad discretion in the use of our available cash and other sources of funding and could spend those resources in ways that do not improve our results of operations or enhance the value of our common stock. The failure by our management to apply these funds effectively could result in financial losses that could cause the price of our common stock to decline and delay the development of eganelisib or any future product candidate. We may invest our available cash pending its use in a manner that does not produce income or that loses value.

Risks Related to the Development and Commercialization of Eganelisib and Any Future Product Candidate

We are dependent on the success of eganelisib, our only product candidate, which remains subject to clinical testing and regulatory approval. If we are unable to initiate or complete clinical development of, obtain marketing approval for or successfully commercialize eganelisib, either alone or with a collaborator, or if we experience significant delays in doing so, our business could be substantially harmed.

We currently have no products approved for sale and are investing substantially all of our efforts and financial resources in the development of eganelisib. The success of eganelisib will depend on our ability to generate product revenue, which will heavily depend on the successful clinical development and eventual commercialization of eganelisib. We also expect that the success of eganelisib will depend primarily on its therapeutic potential in combination with other therapeutics, such as checkpoint inhibitor therapies, and not as a monotherapy.

To date, we have not obtained approval from the FDA or any comparable foreign regulatory authority to market or sell eganelisib or any other product candidates. Rigorous preclinical testing, testing in clinical trials, and an extensive regulatory approval process are required in the United States and in many foreign jurisdictions prior to the commercial sale of medicinal products. If our current clinical trials for eganelisib are successful, we will need to conduct further clinical trials and will need to apply for regulatory approval before we may market or sell any products based on eganelisib. Satisfaction of these and other regulatory requirements is costly, time consuming, uncertain and subject to unanticipated delays. It is possible that eganelisib will not obtain marketing approval. Even if eganelisib has a beneficial effect, that effect may not be detected during clinical evaluation as a result of one or more of a variety of factors, including the size, duration, design, measurements, conduct or analysis of our clinical trials. Conversely, as a result of the same factors, our clinical trials may indicate an apparent positive effect of eganelisib that is greater than the actual positive effect, if any. Similarly, in our clinical trials we may fail to detect toxicity of or intolerability caused by eganelisib or mistakenly believe that eganelisib is toxic or not well tolerated when that is not in fact the case.

We cannot predict whether we will encounter problems with any of our ongoing or planned clinical trials that will cause us or regulatory authorities to delay, suspend, or discontinue clinical trials or to delay the analysis of data from ongoing clinical trials. Moreover, we, or any collaborators, may experience any of a number of possible unforeseen adverse events in connection with clinical trials, many of which are beyond our control, including:

- insufficient or inadequate supply, delays in distribution or deficient quality of, or inability to purchase or manufacture drug product, combination drugs, comparator drugs or other materials necessary to conduct our or any collaborators' clinical trials. For example, in 2021 BMS experienced a temporary global manufacturing-related supply shortage of nab-paclitaxel, or Abraxane®, a drug used in the MARIO-3 combination study of patients with unresectable locally advanced or metastatic front-line TNBC;
- unfavorable results of discussions with the FDA or comparable foreign authorities regarding the scope or design of our, or any collaborators', clinical trials or our or their interpretation of data from preclinical studies and clinical trials;
- delays in receiving, or the inability to obtain, required approvals from institutional review boards or other reviewing entities at clinical sites selected for participation in our clinical trials;
- delays in enrolling patients into clinical trials;
- a lower than anticipated retention rate of patients in clinical trials due to, among other reasons, patients that enroll in a clinical trial misrepresenting their eligibility to do so or otherwise not complying with the clinical trial protocol, resulting in the need to drop the patients from the clinical trial, increase the needed enrollment size for the clinical trial or extend the clinical trial's duration and cost;
- the number of patients required for clinical trials of eganelisib, the speed of patient enrollment and the rate of participant drop outs may differ from the expectations of us or our collaborators;
- the cost of planned clinical trials of eganelisib may be greater than we anticipate;
- comparator or combination drugs, or components or ingredients thereof or conducting clinical trials on our behalf or on behalf of any collaborators, to comply with regulatory requirements or meet their contractual obligations to us or any collaborators in a timely manner or at all;
- the requirement by regulators or institutional review boards that we, or any collaborators, or our or their investigators, suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or their standards of conduct, a finding that the participants are being exposed to unacceptable health risks, undesirable side effects or other unexpected characteristics of eganelisib, or findings of undesirable effects caused by a chemically or mechanistically similar product or product candidate;
- the need to repeat or discontinue clinical trials as a result of inconclusive or negative results or unforeseen complications in testing, or because the results of later trials may not confirm positive results from earlier preclinical studies or clinical trials;
- unfavorable FDA or other foreign regulatory inspection and review of a clinical trial site, us, or a vendor of ours, or records of any clinical or preclinical investigation;
- delays or failures by us or any collaborators in reaching agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites;
- failures by the FDA or comparable foreign regulatory authorities to approve the manufacturing processes or facilities of third-party manufacturers with which we, or any collaborators, enter into agreements for clinical and commercial supplies, or subsequent findings of fault with such processes or facilities;
- insufficient or inadequate supply or quality of raw materials, manufactured product candidates, combination or comparator drugs or other materials necessary to conduct clinical trials of eganelisib, or the inability to acquire such materials at acceptable cost, which may result in interruptions in supply;
- significant changes in the approval policies or regulations of the FDA or comparable foreign regulatory authorities, which may rendering our clinical data insufficient to obtain marketing approval;
- serious and unexpected drug-related side effects experienced by participants in our or any collaborators' clinical trials, which may occur even if they were not observed in earlier trials or only observed in a limited number of participants;
- a finding that the trial participants are being exposed to unacceptable health risks, undesirable side effects or other unexpected characteristics of eganelisib;
- the placement by the FDA or a foreign regulatory authority of a clinical hold on a trial;
- outcomes of third party trials of drugs and drug candidates that we also use in our combination trials, such as Roche's decision to voluntarily withdraw its accelerated approval in the United States for atezolizumab in combination with nab-paclitaxel for patients with PD-L1(+) metastatic TNBC after IMpassion131, Roche's post marketing study evaluating atezolizumab and paclitaxel in TNBC patients, did not meet its primary endpoint; and
- any restrictions on, or post-approval commitments with regard to, any regulatory approval we ultimately obtain that render the product candidate not commercially viable.

The delay, suspension or discontinuation of any of our or any collaborators' clinical trials, or a delay in the analysis of clinical data for eganelisib, for any of the foregoing reasons, could adversely affect our ability to obtain regulatory approval for and to commercialize eganelisib, increase our operating expenses and have a material adverse effect on our financial results.

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

Adverse events or undesirable side effects caused by, or other unexpected properties of, eganelisib, alone or in combination with other agents, may be identified during clinical development and could delay or prevent eganelisib marketing approval or limit its use.

Adverse events or undesirable side effects caused by, or other unexpected properties of, eganelisib, alone or in combination with other agents, could cause us, any collaborators, an institutional review board or regulatory authorities to interrupt, delay or halt clinical trials of eganelisib and could result in a more restrictive label or the delay or denial of marketing approval by the FDA or comparable foreign regulatory authorities. If eganelisib is associated with adverse events or undesirable side effects or has properties that are unexpected, we, or any collaborators, may need to abandon or delay development of eganelisib, or limit its development to certain uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective. Even though eganelisib has initially shown promise in earlier stage testing, it may later be found to cause undesirable or unexpected side effects that prevent its further development. Combining two or more agents may increase the instances of or severity of adverse events or undesirable effects.

Interim top-line and preliminary results from our clinical trials that we announce or publish from time to time may change as more patient data become available and are subject to audit and verification procedures, which could result in material changes in the final data.

From time to time, we may publish interim top-line or preliminary results from our clinical trials. Interim results 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. Preliminary or top-line results 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 and preliminary data should be viewed with caution until the final data are available. 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.

Even assuming approval of a drug candidate, our business may suffer if the market opportunities for eganelisib or product candidates we may develop in the future are smaller than we believe them to be.

Our projections of both the number of people who are affected by disease within our target indications, as well as the subset of these people who have the potential to benefit from treatment with eganelisib or product candidates we may develop in the future, are based on our beliefs and estimates. These estimates have been derived from a variety of sources, including the scientific literature, healthcare utilization databases and market research, and may prove to be incorrect. Further, new studies may change the estimated incidence or prevalence of these diseases. The potentially addressable patient population for eganelisib may be limited or may not be amenable to treatment with eganelisib, and new patients may become increasingly difficult to identify or gain access to, which would adversely affect our results of operations and our business.

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

MARIO-275, our Phase 2 global study, is being conducted, and we may choose to conduct future clinical trials, at trial sites located in the United States and Europe. Although the FDA may accept data from clinical trials conducted outside the United States, acceptance of these data is subject to certain conditions imposed by the FDA, such as the clinical trial must be well designed and conducted and performed by qualified investigators in accordance with good clinical practices; the FDA must

be able to validate the data from the trial through an onsite inspection if necessary; the trial population must also have a similar profile to the U.S. population; and the data must be applicable to the U.S. population and U.S. medical practice in ways that the FDA deems clinically meaningful, except to the extent the disease being studied does not typically occur in the United States. In addition, while these clinical trials are subject to the applicable local laws, FDA acceptance of the data will be dependent upon its determination that the trials also complied with all applicable U.S. laws and regulations. There can be no assurance that the FDA will accept data from trials conducted outside of the United States. If the FDA does not accept the data from any trial that we conduct outside the United States, it would likely result in the need for additional trials, which would be costly and time-consuming and delay or permanently halt our development of eganelisib or any future product candidates.

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

- clinical practice patterns and standards of care that vary widely among countries;
- non-U.S. regulatory authority requirements that could restrict or limit our ability to conduct our clinical trials;
- administrative burdens of conducting clinical trials under multiple non-U.S. regulatory authority schema;
- foreign exchange fluctuations;
- diminished protection of intellectual property in some countries; and
- geopolitical actions, including war and terrorism, disease outbreak, such as the COVID-19 pandemic, or natural disasters including earthquakes, typhoons, floods and fires.

Results of preclinical studies and early clinical trials may not be predictive of results of future late-stage clinical trials.

The outcome of preclinical studies and early clinical trials may not be predictive of the success of later clinical trials, and interim results of clinical trials do not necessarily predict success in future clinical trials. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials after achieving positive results in earlier development, and we could face similar setbacks. In some instances, there can be significant variability in safety or efficacy results between different clinical trials of the same product candidate due to numerous factors, including changes in trial procedures set forth in protocols, differences in the size and type of the patient populations, changes in and adherence to the dosing regimen and other clinical trial protocols and the rate of dropout among clinical trial participants. If we fail to receive positive results in clinical trials of eganelisib, the development timeline and regulatory approval and commercialization prospects for eganelisib and, correspondingly, our business and financial prospects, would be negatively impacted.

Our inability to enroll sufficient numbers of patients in our clinical trials, or any delays in patient enrollment, could result in increased costs and longer development periods for our product candidates.

Clinical trials require sufficient patient enrollment. Our failure to enroll patients in a clinical trial could delay the initiation or completion of the clinical trial beyond current expectations. In addition, the FDA or other comparable foreign regulatory authorities could require us to conduct clinical trials with a larger number of patients than has been projected for eganelisib or any product candidates we may develop in the future. As a result of these factors, we may not be able to enroll a sufficient number of patients in a timely or cost-effective manner. Furthermore, enrolled patients may drop out of a clinical trial for reasons such as being included in a placebo or comparator arm in a trial, the occurrence of adverse side effects, whether or not related to our product candidate, or low or no activity of our product candidate at one or more dose levels being testes, which could impair the validity or statistical significance of the clinical trial. Please refer to "Risks Related to COVID-19 Pandemic" for a further discussion of the impact of COVID-19 on enrollment in our clinical trials. A delay in our clinical trial activities could adversely affect our ability to obtain regulatory approval for and to commercialize our product candidates, increase our operating expenses, and have a material adverse effect on our financial results.

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

Even if we receive regulatory approval for a product candidate, we will have tested it in only a small number of patients in carefully defined subsets and over a limited period of time during our clinical trials, such as is the case for eganelisib. If any future applications for marketing are approved and more patients begin to use our products, or patients use such products for a longer period of time, such products might be less effective than indicated by our clinical trials. Furthermore, new risks and side effects associated with such products may be discovered or previously observed risks and side effects may become more prevalent and/or clinically significant.

In addition, supplemental clinical trials that may be conducted on a drug following its initial approval may produce findings that are inconsistent with the trial results previously submitted to regulatory authorities. As a result, regulatory authorities may revoke their approvals, or we may be required to conduct additional clinical trials, make changes in labeling of a product (including a "black box" warning or a contraindication) or the manner in which it is administered, reformulate such product or make changes to and obtain new approvals for our and our suppliers' manufacturing facilities. We also might have to withdraw or recall such product from the marketplace, and regulators might seize such product. We might be subject to fines, injunctions, or the imposition of civil or criminal penalties. Any of these results could decrease or prevent any sales of our approved product or substantially increase the costs and expenses of commercializing and marketing our product, harm our reputation, business and operations, result in our and our collaborators' becoming subject to lawsuits, including class actions and could negatively impact our stock price.

Even if a product candidate 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, in which case we may not be able to generate significant revenues from product sales to become profitable.

Even if a product candidate obtains regulatory approval, it may not gain market acceptance among physicians, patients, managed care organizations, third-party payors, and the medical community for a variety of reasons including:

- timing of our receipt of any marketing approvals, the terms of any such approvals and the countries in which any such approvals are obtained;
- timing of market introduction of competitive products;
- lower demonstrated clinical safety or efficacy, or less convenient or more difficult route of administration, compared to competitive products;
- lack of cost-effectiveness;
- lack of reimbursement from government payors, managed care plans and other third-party payors;
- prevalence and severity of side effects;
- potential advantages of alternative treatment methods;
- whether it is designated under physician treatment guidelines as a first, second or third line therapy;
- changes in the standard of care for targeted indications;
- limitations or warnings, including distribution or use restrictions, contained in the product's approved labeling;
- safety concerns with similar products marketed by others;
- the reluctance of the target population to try new therapies and of physicians to prescribe those therapies;
- the lack of success of our physician education programs; and
- ineffective sales, marketing and distribution support.

If any product candidate we develop, such as eganelisib, received marketing approval but fails to achieve market acceptance, we would not be able to generate significant revenue, which may adversely impact our ability to become profitable.

If we obtain approval to commercialize a product candidate outside of the United States, a variety of risks associated with international operations could materially adversely affect our business.

We expect that we will be subject to additional risks in commercializing any product candidate outside the United States, including:

- different regulatory requirements for approval of drugs and biologics in foreign countries;
- reduced protection for intellectual property rights;
- unexpected changes in tariffs, trade barriers and regulatory requirements;
- economic weakness, including inflation, or political instability in particular foreign economies and markets;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenue, and other obligations incident to doing business in another country;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geopolitical actions, including war and terrorism, disease outbreak, or natural disasters including earthquakes, typhoons, floods and fires.

Even if we receive regulatory approvals for marketing any product candidates we may develop, we could lose our regulatory approvals and our business would be adversely affected if we, our collaborators, or our contract manufacturers fail to comply with continuing regulatory requirements.

The FDA and other regulatory agencies continue to review products even after they receive initial approval. If we receive approval to commercialize any product candidates, the manufacturing, marketing and sale of these drugs will be subject to continuing regulation, including compliance with quality systems regulations, the FDA's current good manufacturing practices, or cGMPs, adverse event requirements and prohibitions on promoting a product for unapproved uses. Enforcement actions resulting from our failure to comply with government and regulatory requirements could result in fines, suspension of approvals, withdrawal of approvals, product recalls, product seizures, mandatory operating restrictions, criminal prosecution, civil penalties and other actions that could impair the manufacturing, marketing and sale of any product candidates and our ability to conduct our business.

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

We have no experience in the sale, marketing or distribution of pharmaceutical products and do not currently have the necessary infrastructure to do so. To achieve commercial success for any approved product, we must either develop a sales and marketing organization or outsource these functions to third parties. The development of sales, marketing and distribution capabilities would require substantial resources, would be time consuming and could delay any product launch. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing and distribution capabilities is delayed or does not occur for any reason, we could have prematurely or unnecessarily incurred these commercialization costs, and our investment could be lost if we cannot retain or reposition our sales and marketing personnel. In addition, we may not be able to hire or retain a sales force that is sufficient in size or has adequate expertise in the medical markets that we choose to target. If we are unable to establish or retain a sales force and marketing and distribution capabilities, our operating results may be adversely affected. We may seek to collaborate with potential partners if we believe they have development or commercialization expertise relevant to one or more of our products, even if we believe we could otherwise develop and commercialize the product independently. As a result of entering into these arrangements, our product revenues or the profitability of these product revenues may be lower, perhaps substantially lower, than if we were to directly market and sell our products in those markets. Furthermore, we may be unsuccessful in entering into the necessary arrangements with third parties or may be unable to do so on terms that are favorable to us. In addition, we may have little or no control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our products effectively.

Our competitors and potential competitors may develop products that make eganelisib less attractive or obsolete.

Immuno-oncology, or IO, is a highly competitive and rapidly changing segment of the pharmaceutical industry. Many large pharmaceutical and biotechnology companies, academic institutions, governmental agencies and other public and private research organizations are pursuing the development of novel drugs that target various oncology diseases. We currently face, and expect to continue to face, intense and increasing competition as new products enter the market and advanced technologies become available. We believe eganelisib is the only PI3K-gamma selective inhibitor in clinical trials, but also believe that there are competitors in pre-clinical development of their PI3K-gamma selective inhibitors and that other competitors are developing or commercializing therapies targeting macrophage biology. For more information on our competitors, please see Part I, Item 1 "Business Overview – Competition" to this Annual Report on Form 10-K.

Our competitors may commence and complete clinical testing of their product candidates, obtain regulatory approvals and begin commercialization of their products sooner than we and/or our collaborators may for eganelisib. These competitive products may have superior safety or efficacy, have more attractive pharmacologic properties, or be manufactured less expensively than eganelisib. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller or early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, the development of eganelisib or future product candidates we may develop. If we are unable to compete effectively against these companies on the basis of safety, efficacy or cost, then we may not be able to commercialize eganelisib or achieve a competitive position in the market. This would adversely affect our ability to generate revenues.

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

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

The extent to which patients have third-party payor coverage that could in principle cover treatment with eganelisib may be affected by legislative and regulatory changes relating to the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act, or collectively the ACA. For instance, the so-called "individual mandate" provisions of the ACA require most individuals to carry acceptable insurance for themselves and their family, whether through the government or a private insurer, or else incur a penalty. However, the tax reform legislation signed into law on December 22, 2017, eliminated the penalty for failure to comply with the individual mandate, effective for periods beginning after December 31, 2018. This change and other legislative or regulatory actions in relation to the ACA may increase the pool of patients lacking third-party payor coverage. There is significant uncertainty related to third-party payor coverage and reimbursement of newly approved drugs. Marketing approvals, pricing and reimbursement for new drug products vary widely from country to country. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we, or any future collaborators, might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay commercial launch of the product, possibly for lengthy time periods, or prevent it altogether, which may negatively impact the revenues we are able to generate from the sale of the product in that country. Adverse pricing limitations may hinder our ability or the ability of any future collaborators to recoup our or their investment in eganelisib, even if eganelisib obtains marketing approval.

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

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

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

If the FDA or comparable foreign regulatory authorities grant marketing approval for generic versions of eganelisib, or such authorities do not grant eganelisib appropriate periods of data exclusivity before approving generic versions of eganelisib, sales of eganelisib could be adversely affected.

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

The FDA may not approve an ANDA for a generic product until any applicable period of non-patent exclusivity for the reference-listed drug has expired. The FDCA provides a period of five years of non-patent exclusivity for a new drug containing a new chemical entity, or NCE. Specifically, in cases where such exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification that a patent covering the reference-listed drug is either invalid or will not be infringed by the generic product, in which case the applicant may submit its application four years following approval of the reference-listed drug. When the composition of matter patents underlying our product candidates expire, it is possible that another applicant could obtain approval to produce generic versions of our product candidates. If any product we develop does not receive five years of NCE exclusivity, the FDA may approve generic versions of such product three years after its date of approval, subject to the requirement that the ANDA applicant certifies to any patents listed for our products in the Orange Book. Manufacturers may seek to launch these generic products following the expiration of the applicable marketing exclusivity period, even if we still have patent protection for our product.

Product liability lawsuits against us or any licensees could cause us or our licensees to incur substantial liabilities and could limit commercialization of any products that we or they may develop.

We face an inherent risk of product liability exposure related to the testing of eganelisib or any future product candidates in human clinical trials, and we and any licensees will face an even greater risk as we or they commercially sell any products that we or they may develop, such as duvelisib. If we or our licensees cannot successfully defend ourselves or themselves against claims that our product candidates or products caused injuries, we could incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in, among other consequences, decreased demand for any product candidates or medicines that we may develop, injury to our reputation and significant negative media attention, withdrawal of clinical trial participants, significant costs to defend the related litigation, substantial monetary awards to trial participants or patients, loss of revenue, reduced resources of our management to pursue our business strategy, and the inability to commercialize any medicines that we may develop. Although we maintain product liability insurance coverage, it may not be adequate to cover all liabilities that we may incur. We anticipate that we will need to increase our insurance coverage as we advance or expand our clinical trials and if we successfully commercialize any products. Insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise. In addition, if one of our licensees were to become subject to product liability claims or were unable to successfully defend themselves against such claims, any such licensee could be more likely to terminate such relationship with us and therefore substantially limit the commercial potential of our products.

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. The 2008 global financial crisis caused extreme volatility and disruptions in the capital and credit markets. More recently, the COVID-19 pandemic has also adversely impacted the global economy. A severe or prolonged economic downturn, such as that in 2008, could result in a variety of risks to our business, including weakened demand for eganelisib or any future product candidates we may develop and our ability to raise additional capital when needed on acceptable terms, if at all. A weak or declining economy could strain our suppliers, possibly resulting in supply disruption, or cause delays in payments for our services by third-party payors or our collaborators. 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 the COVID-19 Pandemic

Public health epidemics or outbreaks, including the COVID-19 pandemic, have had, and will continue to have, an adverse impact on our business.

In December 2019, a novel strain of coronavirus emerged in China causing the disease COVID-19. This disease has spread worldwide and was deemed a "pandemic" by the World Health Organization on March 11, 2020. The governor of Massachusetts, where our offices are located, issued a "stay-at-home order" effective March 24, 2020, requiring all "non-essential" businesses to close their physical workplaces and facilities and encouraging individuals to stay in their homes as much as possible. Similar restrictions were put in place by governments throughout the world. As of March 2022, case rates for COVID-19 have dropped considerably, and most government-mandated COVID-19 precautions have been lifted. However, given the volatile nature of COVID-19 to date, such restrictions could return in part or in whole during a future spike in case rates. We have highlighted the key risks associated with the COVID-19 pandemic on our operations throughout these risk factors, including without limitation the following:

- ***The COVID-19 pandemic may materially and adversely affect our clinical trial operations and our financial results.*** We are conducting our clinical trials at sites in geographies seriously impacted by the COVID-19 pandemic. We are continuing to evaluate enrollment trends in our studies as well as the impact of COVID-19 on our clinical programs. Patients currently enrolled on MARIO-275, MARIO-3 and MARIO-1 have continued treatment and study visits with limited disruption to date, and we are working closely with trial sites to support the continued treatment of patients in compliance with study protocols. At this time, there are no anticipated disruptions to drug supply.

- ***The COVID-19 pandemic could impact our future supply chain.*** We currently rely on third-party manufacturers to produce our preclinical and clinical drug supplies, and we may also rely upon third-party manufacturers to produce commercial supplies of eganelisib, also known as IPI-549. We believe we have already manufactured all drug product necessary to conduct our current clinical trials. Further, we believe that a sufficient supply of drug substance and drug product intermediates is available in the United States for additional drug product manufacturing if required to support our clinical development program and potential preclinical studies. However, the COVID-19 pandemic could impact our future supply chain. Refer to the risk factor entitled "We currently rely on third-party manufacturers to produce our preclinical and clinical drug supplies, and we may also rely upon third-party manufacturers to produce commercial supplies of eganelisib" for more information related to the risks related to our dependence on third-party manufacturers to produce preclinical, clinical, and commercial supplies of eganelisib.

- ***COVID safety protocols, quarantine requirements, and social distancing measures adopted by or imposed upon us and our vendors may impact our business operations.*** Governments and employers have combated the COVID-19 pandemic through implementation of safety protocols and quarantine requirements that may require prolonged absences from work and social distancing measures intended to keep individuals physically distant from one another. Such measures, which have only recently lifted in many parts of the United States and other nations, may be re-instated during periods of increased COVID case rates and have had or may have the following impact on our business operations:

    - Couriers worldwide, including those we rely upon to transfer biospecimens from study sites to laboratories and between laboratories, are experiencing shipping delays. According to publicly available statements by such vendors, social distancing measures, combined with increased demand for shipping and fewer flights, have contributed to such delays. For instance, in 2020 we experienced temporary biospecimen shipping delays in France, Italy, and Spain.

    - Multiple vendors, particularly our manufacturers and laboratories, have implemented social distancing measures, such as splitting work shifts to reduce the number of employees on site, that may cause delays to our study timelines. Two vendors temporarily closed operations to address COVID-19 concerns in mid-2020, but such closures did not materially affect our study timelines.

    - Two manufacturing vendors provided notice in January 2022 that the then-present increase in COVID-19 case rates caused significant staff shortages due to quarantine protocols and supply chain issues due to downstream vendors' staff shortages.

    - Our work-from-home policy enabled our employees to work remotely until February 2022, when we returned to work at the office on hybrid schedule. However, if necessary, we are able to quickly return to working fully remotely, at which time childcare and other household logistic complications due to COVID-19 social distancing and quarantine requirements may negatively impact the efficiency or effectiveness of our employees who are also caregivers and the hours that they can commit if required to work from home.

Risks Related to Our Dependence on Third Parties

If a collaborator terminates or fails to perform its obligations under agreements with us, the development and commercialization of eganelisib or any future product candidates we may develop could be delayed or terminated.

We currently have worldwide development and commercialization rights to eganelisib. We license certain patent and other intellectual property rights under the Takeda Agreement and the Secura Bio Agreement. We may in the future seek other third-party collaborators. The success of a strategic alliance with any partner is largely dependent on the resources, efforts, technology and skills brought to such alliance by such partner. The benefits of such alliances will be reduced or eliminated if any such partner:

- does not or cannot devote the necessary resources to the development, marketing and distribution of such product or products;
- decides not to pursue development and commercialization of the program or to continue or renew development or commercialization programs, based on clinical trial results, changes in the collaborators' strategic focus or available funding, the belief that other product candidates may have a higher likelihood of obtaining regulatory approval or potential to generate a greater return on investment, or external factors, such as an acquisition, that divert resources or create competing priorities;
- does not perform its obligations as expected;
- does not have sufficient resources necessary or is otherwise unable to carry the program through clinical development, regulatory approval and commercialization;
- cannot obtain the necessary regulatory approvals;
- delays clinical trials, provides insufficient funding for a clinical trial program, stops a clinical trial or abandons the program, repeats or conducts new clinical trials or requires a new formulation of the program for clinical testing;
- independently develops, or develops with third parties, products that compete directly or indirectly with the program;
- does not properly maintain or defend our intellectual property rights or uses 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;
- infringes the intellectual property rights of third parties, which may expose us to litigation and potential liability; or
- terminates the collaboration prior to its completion.

If such partner were to terminate its arrangements with us, or breach such arrangements, or fail to maintain the financial resources necessary to continue financing its portion of development, manufacturing, and commercialization costs, as applicable, we may not have the financial resources or capabilities necessary to continue development and commercialization of the product candidate on our own. Consequently, the development and commercialization of the affected product candidate could be delayed, curtailed or terminated, and we may find it difficult to attract a new collaborator for such product candidate.

Disputes and difficulties in these types of relationships are common, often due to priorities changing over time, conflicting priorities or conflicting interests. Merger and acquisition activity may exacerbate these conflicts. Much of the potential revenue from alliances consists of payments contingent upon the achievement of specified milestones and royalties payable on sales of any successfully developed drugs. Any such contingent revenue will depend upon our, and our collaborators', ability to successfully develop, launch, market and sell new drugs. In some cases, we will not be involved in some or all of these processes, and we will depend entirely on our collaborators.

If any future collaborator fails to develop or effectively commercialize a product candidate that is the subject of our strategic alliance with them, we may not be able to develop and commercialize such product candidate independently, and our financial condition and operations would be negatively impacted.

We might seek to establish collaborations in the future and, if we are not able to establish them on commercially reasonable terms, we may have to alter our development and commercialization plans.

In the future, we might seek out additional collaborators for the development and commercialization of eganelisib or any future product candidate we may develop. Likely collaborators may include large and mid-size pharmaceutical companies, regional and national pharmaceutical companies and biotechnology companies. In addition, if we are able to obtain marketing approval for eganelisib or any other product candidate from foreign regulatory authorities, we might enter into strategic relationships with international biotechnology or pharmaceutical companies for the commercialization of such product candidate outside of the United States.

We would face significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for an additional 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. Those factors may include the potential differentiation of our product candidate from competing product candidates, design or results of clinical trials, the likelihood of approval by the FDA or comparable foreign regulatory authorities and the regulatory pathway for any such approval, the potential market for our product candidate, the costs and complexities of manufacturing and delivering the product to patients and the potential of competing products. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available for collaboration and whether such a collaboration could be more attractive than the one with us for our product candidate.

We may not be able to negotiate new collaborations on a timely basis, on acceptable terms, or at all. In addition, any collaboration agreements that we enter into in the future may contain restrictions on our ability to enter into further potential collaborations or to otherwise develop eganelisib or any product candidate that we may develop in the future. If we are unable enter into new collaborations on acceptable terms, we may have to curtail the development of a given product candidate, reduce or delay its development, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense.

We rely on third parties to conduct our clinical trials, and those third parties may not perform satisfactorily.

We rely on third parties such as contract research organizations, medical institutions and external investigators to enroll qualified patients, conduct our clinical trials and provide services in connection with such clinical trials, and we intend to rely on these and other similar entities in the future. Our reliance on these third parties for clinical development activities reduces our control over these activities. Accordingly, these third-party contractors may not complete activities on schedule or conduct our clinical trials in accordance with regulatory requirements or the trial design. If these third parties do not successfully carry out their contractual obligations or meet expected deadlines, we may be required to replace them. Replacing a third-party contractor may result in a delay of the affected trial and unplanned costs. If this were to occur, our ability to obtain regulatory approval for and to commercialize eganelisib or any product candidate that we may develop in the future could be delayed.

In addition, we are responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocol for the trial. The FDA requires us to comply with certain standards, referred to as good clinical practices, for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. Our reliance on third parties that we do not control does not relieve us of these responsibilities and requirements. If any of our trial investigators or third-party contractors does not comply with good clinical practices, we may not be able to use the data and reported results from the trial. If this noncompliance were to occur, our ability to obtain regulatory approval for and to commercialize our product candidate could be delayed or put at risk.

We currently rely on third-party manufacturers to produce our preclinical and clinical drug supplies, and we may also rely upon third-party manufacturers to produce commercial supplies of eganelisib.

Eganelisib requires precise, high quality manufacturing under cGMP. The third-party manufacturers on which we rely may fail to comply with cGMPs and other applicable government regulations and corresponding foreign standards. These regulations govern manufacturing processes and procedures and the implementation and operation of systems to control and assure the quality of products. The FDA and foreign regulatory authorities may, at any time, audit or inspect a manufacturing facility to ensure compliance with cGMPs and other quality standards. Any failure by our contract manufacturers to achieve and maintain high manufacturing and quality control standards could result in the inability of eganelisib to be released for use in one or more countries. In addition, such a failure could result in, among other things, patient injury or death, product liability claims, penalties or other monetary sanctions, the failure of regulatory authorities to grant marketing approval of eganelisib, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of eganelisib, operating restrictions and/or criminal prosecution, any of which could significantly and adversely affect supply of eganelisib and seriously hurt our business.

Contract manufacturers may also encounter difficulties involving production yields or delays in performing their services. We do not have control over third-party manufacturers' performance and compliance with applicable regulations and standards. If, for any reason, including natural disaster, epidemic or pandemic, such as the ongoing COVID-19 pandemic, our manufacturers cannot perform as agreed, we may be unable to replace such third-party manufacturers in a timely manner, and the production of eganelisib or any future product candidates would be interrupted, resulting in delays in clinical trials and additional costs. Switching manufacturers may be difficult because the number of potential manufacturers is limited, the demand for such services is high and, depending on the type of material manufactured at the contract facility, the change in contract manufacturer must be submitted to and/or approved by the FDA and comparable regulatory authorities outside of the United States. In addition, a new manufacturer would have to be educated in, or develop substantially equivalent processes for, production of our product candidates after receipt of regulatory approval. It may be difficult or impossible for us to quickly find a replacement manufacturer on acceptable terms, or at all.

To date, eganelisib has been manufactured for preclinical testing and clinical trials primarily by third-party manufacturers. If the FDA or other regulatory agencies approve eganelisib for commercial sale, we expect that we would continue to rely, at least initially, on third-party manufacturers to produce commercial quantities of eganelisib. These manufacturers may not be able to successfully increase the manufacturing capacity for eganelisib in a timely or economical manner, or at all, particularly if impacted by COVID-19. Significant scale-up of manufacturing might entail changes in the manufacturing process that would have to be submitted to or approved by the FDA or other regulatory agencies. If contract manufacturers engaged by us are unable to successfully increase the manufacturing capacity for eganelisib, or we are unable to establish our own manufacturing capabilities, the commercial launch of any approved products may be delayed or there may be a shortage in supply.

Risks Related to Our Intellectual Property

If we fail to obtain or maintain necessary or useful intellectual property rights, we could encounter substantial delays in the research, development and commercialization of eganelisib and any product candidates that we may develop in the future.

We currently have rights to certain intellectual property through the Takeda Agreement to develop eganelisib and other product candidates that we may in the future develop under our PI3K inhibitor program. In addition, we have rights to certain intellectual property through the Takeda Agreement that we have exclusively licensed to Secura Bio pursuant to the Secura Bio Agreement. We may decide to license additional third-party technology that we deem necessary or useful for our business. However, we may be unable to acquire or in-license any compositions, methods of use, processes or other intellectual property rights from third parties that we identify as necessary for eganelisib at a reasonable cost, or at all. The licensing or acquisition of third-party intellectual property rights is a competitive area, and several more established companies may pursue strategies to license or acquire third-party intellectual property rights that we may consider attractive. These established companies may have a competitive advantage over us due to their size, capital resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us.

We sometimes collaborate with non-profit and academic institutions to accelerate our preclinical research or development under written agreements with these institutions. Typically, these institutions 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 or we may decide not to execute such option if we believe such license is not necessary to pursue our program. If we are unable or opt not to do so, the institution may offer the intellectual property rights to other parties, potentially blocking our ability to pursue our program.

If we do not obtain or maintain these intellectual property rights which we require, we could encounter substantial delays in developing and commercializing eganelisib or any other potential product candidate while we attempt to develop alternative technologies, methods and product candidates, which we may not be able to accomplish. If we are ultimately unable to do so, we may be unable to develop or commercialize our product candidate, which could harm our business significantly.

If we fail to comply with our obligations under our existing and any future intellectual property licenses with third parties, we could lose license rights that are important to our business.

We are party to several license agreements under which we license patent rights and other intellectual property related to our business including the Takeda Agreement, under which we obtained rights to discover, develop and commercialize pharmaceutical products targeting the delta and/or gamma isoforms of PI3K, including eganelisib and duvelisib. We may enter into additional license agreements in the future. For example, pursuant to the Takeda Agreement, we paid a $2.0 million success-based milestone payment to Takeda in October 2019 associated with MARIO-275. We are obligated to pay Takeda up to $3.0 million in remaining success-based development milestone payments and up to $165.0 million in remaining regulatory and commercialization success-based milestone payments for one product candidate other than duvelisib, which could be eganelisib. Our license agreements impose, and we expect that future license agreements will impose, various diligence, milestone payment, royalty, insurance and other obligations on us. If we fail to comply with our obligations under these licenses, our licensors may have the right to terminate these license agreements, in which event we might not be able to market eganelisib or any other product candidate that is covered by these agreements, or our licensors may convert the license to a non-exclusive license, which could adversely affect the value of eganelisib or any other product candidate being developed under the license agreement. Termination of these license agreements or reduction or elimination of our licensed rights may also result in our having to negotiate new or reinstated licenses with less favorable terms. For example, if we fail to use diligent efforts to develop and commercialize products licensed under the Takeda Agreement, or if Secura Bio materially breaches the Secura Bio Agreement, we could lose our license rights under the Takeda Agreement, including rights to eganelisib.

Our intellectual property licenses with third parties may be subject to disagreements over contract interpretations, which could narrow the scope of our rights to the relevant intellectual property or technology or increase our financial or other obligations to our licensors.

The agreements under which we currently license intellectual property or technology from third parties are complex, and certain provisions in such agreements may be susceptible to multiple interpretations. The resolution of any contract interpretation disagreement that may arise could narrow what we believe to be the scope of our rights to the relevant intellectual property or technology, or increase what we believe to be our financial or other obligations under the relevant agreement, either of which could harm our business, financial condition, results of operations and prospects.

Our success depends substantially upon our ability to obtain and maintain intellectual property protection for eganelisib.

We own or hold exclusive licenses to a number of U.S. and foreign patents and patent applications directed to eganelisib. Our success depends on our ability to obtain patent protection both in the United States and in other countries for eganelisib, our methods of manufacture and our methods of use. Our ability to protect eganelisib from unauthorized or infringing use by third parties depends substantially on our ability to obtain and enforce our patents.

Due to evolving legal standards relating to the patentability, validity and enforceability of patents covering pharmaceutical inventions and molecular diagnostics and the claim scope of these patents, our ability to obtain and enforce patents that may issue from any pending or future patent applications is uncertain and involves complex legal, scientific and factual questions. The standards that the United States Patent and Trademark Office, or USPTO, and its foreign counterparts use to grant patents are not always applied predictably or uniformly and are subject to change. To date, no consistent policy has emerged regarding the breadth of claims allowed in pharmaceutical or molecular diagnostics patents. Thus, we cannot guarantee that any patents will issue from any pending or future patent applications owned by or licensed to us. Even if patents do issue, we cannot guarantee that the claims of these patents will be held valid or enforceable by a court of law, will provide us with any significant protection against competitive products or will afford us a commercial advantage over competitive products.

The Leahy-Smith America Invents Act, or the America Invents Act, reforms United States patent law in part by changing the standard for patent approval for certain patents from a “first to invent” standard to a “first to file” standard and developing a post-grant review system. This new law changes United States patent law in a way that may severely weaken our ability to obtain patent protection in the United States. Additionally, recent judicial decisions establishing new case law and a reinterpretation of past case law, as well as regulatory initiatives, may make it more difficult for us to protect our intellectual property.

Issued patents that we have or may obtain or license may not provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Our competitors may be able to circumvent our patents by developing similar or alternative technologies or products in a non-infringing manner.

If we do not obtain adequate intellectual property protection for our products in the United States, competitors could duplicate them without repeating the extensive testing that we will have been required to undertake to obtain approval by the FDA. Regardless of any patent protection, under the current statutory framework, the FDA is prohibited by law from approving any generic version of any of our products for up to five years after it has approved our product. Upon the expiration of that period, or if that time period is altered, the FDA could approve a generic version of our product unless we have patent protection sufficient for us to block that generic version. Without sufficient patent protection, the applicant for a generic version of our product would only be required to conduct a relatively inexpensive study to show that its product is bioequivalent to our product and would not have to repeat the studies that we conducted to demonstrate that the product is safe and effective.

In the absence of adequate patent protection in other countries, competitors may similarly be able to obtain regulatory approval in those countries for products that duplicate eganelisib. The laws of some foreign jurisdictions do not protect intellectual property rights to the same extent as in the United States. Many companies have encountered significant difficulties in protecting and defending such rights in foreign jurisdictions. Some of our development efforts may be performed in China, India and other countries outside of the United States through third-party contractors. We may not be able to monitor and assess intellectual property developed by these contractors effectively; therefore, we may not be able to appropriately protect this intellectual property and could lose valuable intellectual property rights. In addition, the legal protection afforded to inventors and owners of intellectual property in countries outside of the United States may not be as protective of intellectual property rights as in the United States, and we may, therefore, be unable to acquire and protect intellectual property developed by these contractors to the same extent as if these development activities were being conducted in the United States. If we encounter difficulties in protecting our intellectual property rights in foreign jurisdictions, our business prospects could be substantially harmed.

In addition, we rely on intellectual property assignment agreements with our collaborators, vendors, employees, consultants, clinical investigators, scientific advisors and other collaborators to grant us ownership of new intellectual property that is developed by them. These agreements may not result in the effective assignment to us of that intellectual property.

Other agreements through which we license patent rights may not give us control over patent prosecution or maintenance, so that we may not be able to control which claims or arguments are presented and may not be able to secure, maintain, or successfully enforce necessary or desirable patent protection from those patent rights. If we are unable to obtain control over patent prosecution in these other agreements, we cannot be certain that patent prosecution and maintenance activities by our licensors have been or will be conducted in compliance with applicable laws and regulations or will result in valid and enforceable patents.

We, or any future partners, collaborators or licensees, may fail to identify patentable aspects of inventions made in the course of development and commercialization activities before it is too late to obtain patent protection for them. Therefore, we may miss potential opportunities to strengthen our patent position.

It is possible that defects of form in the preparation or filing of our patents or patent applications may exist, or may arise in the future, for example with respect to proper priority claims, inventorship, claim scope or patent term adjustments. If we or our partners, collaborators, licensees, or licensors, whether current or future, fail to establish, maintain or protect such patents and other intellectual property rights, such rights may be reduced or eliminated. If our partners, collaborators, licensees or licensors are not fully cooperative or disagree with us as to the prosecution, maintenance or enforcement of any patent rights, such patent rights could be compromised. If there are material defects in the form, preparation, prosecution, or enforcement of our patents or patent applications, such patents may be invalid and/or unenforceable, and such applications may never result in valid, enforceable patents. Any of these outcomes could impair our ability to prevent competition from third parties, which may have an adverse impact on our business. As a result, our ownership of key intellectual property could be compromised.

Confidentiality agreements may not adequately prevent disclosure of trade secrets and other proprietary information.

To protect our proprietary technology, we rely in part on confidentiality agreements with our vendors, collaborators, employees, consultants, scientific advisors, clinical investigators and other collaborators. We generally require each of these individuals and entities to execute a confidentiality agreement at the commencement of a relationship with us. These agreements may not effectively prevent disclosure of confidential information and may not provide an adequate remedy in the event of unauthorized disclosure or misuse of confidential information or other breaches of the agreements.

In addition, we may rely on trade secrets to protect our technology, especially where we do not believe patent protection is appropriate or obtainable. Trade secrets are, however, difficult to protect. Others may independently discover our trade secrets and proprietary information, and in such case we could not assert any trade secret rights against such party. Enforcing a claim that a party illegally obtained and is using our trade secrets is difficult, expensive and time consuming, and the outcome is unpredictable. In addition, courts outside of the United States may be less willing to protect trade secrets. Costly and time-consuming litigation could be necessary to seek to enforce and determine the scope of our proprietary rights and could result in a diversion of management's attention, and failure to obtain or maintain trade secret protection could adversely affect our competitive business position.

Patent interference, opposition or similar proceedings relating to our intellectual property portfolio are costly, and an unfavorable outcome could prevent us from commercializing eganelisib.

Patent applications in the United States are maintained in confidence for up to 18 months after their filing. In some cases, however, patent applications remain confidential in the USPTO for the entire time prior to issuance as a U.S. patent. Similarly, publication of discoveries in the scientific or patent literature often lags behind actual discoveries. Consequently, we cannot be certain that we were the first to invent, or the first to file patent applications on, eganelisib or its therapeutic use. In the event that a third party has also filed a U.S. patent application relating to eganelisib or a similar invention, we may have to participate in interference or derivation proceedings declared by the USPTO or the third party to determine priority of invention in the United States. An adverse decision in an interference or derivation proceeding may result in the loss of rights under a patent or patent application. In addition, the cost of interference proceedings could be substantial.

Claims by third parties of intellectual property infringement are costly and distracting, and could deprive us of valuable rights we need to develop or commercialize eganelisib and any product candidate that we might develop in the future or impact the commercialization of duvelisib and the royalties owed to us under the Secura Bio Agreement.

Our commercial success will depend on whether there are third-party patents or other intellectual property relevant to our potential products that may block or hinder our ability to develop and commercialize eganelisib. We may not have identified all U.S. and foreign patents or published applications that may adversely affect our business either by blocking our ability to manufacture or commercialize our drugs or by covering similar technologies that adversely affect the applicable market. In addition, we may undertake research and development with respect to eganelisib, even when we are aware of third-party patents that may be relevant to eganelisib, on the basis that we may challenge or license such patents. There are no assurances that such licenses will be available on commercially reasonable terms, or at all. If such licenses are not available, we may become subject to patent litigation and, while we cannot predict the outcome of any litigation, it may be expensive and time consuming. If we are unsuccessful in litigation concerning patents owned by third parties, we may be precluded from selling eganelisib.

While we are not currently aware of any litigation or third-party claims of intellectual property infringement related to eganelisib or duvelisib, the biopharmaceutical industry is characterized by extensive litigation regarding patents and other intellectual property rights. Other parties may obtain patents and claim that the use of our or Secura Bio's technologies infringes these patents or that we or Secura Bio are employing their proprietary technology without authorization. We or Secura Bio could incur substantial costs and diversion of management and technical personnel in defending against any claims that the manufacture and sale of our potential products or use of our or Secura Bio's technologies infringes any patents, or defending against any claim that we or Secura Bio are employing any proprietary technology without authorization. The outcome of patent litigation is subject to uncertainties that cannot be adequately quantified in advance, including the demeanor and credibility of witnesses and the identity of the adverse party, especially in pharmaceutical patent cases that may turn on the testimony of experts as to technical facts upon which experts may reasonably disagree. In the event of a successful claim of infringement against us, we or Secura Bio may be required to:

- pay substantial damages;
- stop developing, manufacturing and/or commercializing eganelisib or duvelisib (as applicable);
- develop non-infringing product candidates, technologies and methods; and
- obtain one or more licenses from other parties, which could result in our or Secura Bio paying substantial royalties or the granting of cross-licenses to our or Secura Bio's technologies.

If any of the foregoing were to occur, we may be unable to commercialize eganelisib, or we may elect to cease certain of our business operations, either of which could severely harm our business.

We may undertake infringement or other legal proceedings against third parties, causing us to spend substantial resources on litigation and exposing our own intellectual property portfolio to challenge.

Competitors may infringe our patents. To prevent infringement or unauthorized use, we may need to file infringement suits, which are expensive and time-consuming. In an infringement proceeding, a court may decide that one or more of our patents is invalid, unenforceable, or both. Even if the validity of our patents is upheld, a court may refuse to stop the other party from using the technology at issue on the ground that the other party's activities are not covered by our patents. In this case, third parties may be able to use our patented technology without paying licensing fees or royalties. Policing unauthorized use of our intellectual property is difficult, and we may not be able to prevent misappropriation of our proprietary rights, particularly in countries where the laws may not protect such rights as fully as in the United States. In addition, third parties may affirmatively challenge our rights to, or the scope or validity of, our patent rights.

Patent terms may be inadequate to protect our competitive position on our products for an adequate amount of time.

Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. We expect to seek extensions of patent terms in the United States and, if available, in other countries where we are prosecuting patents. In the United States, the Drug Price Competition and Patent Term Restoration Act of 1984 permits a patent term extension of up to five years beyond the normal expiration of the patent, which is limited to the approved indication (or any additional indications approved during the period of extension). However, the applicable authorities, including the FDA and the USPTO in the United States, and any equivalent regulatory authority in other countries, may not agree with our assessment of whether such extensions are available, and may refuse to grant extensions to our patents, or may grant more limited extensions than we request. If this occurs, our competitors may be able to take advantage of our investment in development and clinical trials by referencing our clinical and preclinical data and launch their product earlier than might otherwise be the case.

We may be subject to claims by third parties asserting that we or our employees have misappropriated their intellectual property, or claiming ownership of what we regard as our own intellectual property.

Many of our employees and our licensors' employees, including our senior management, were previously employed at universities or at other biotechnology or pharmaceutical companies, some of which may be competitors or potential competitors. Some of these employees, including each member of our senior management, executed proprietary rights, non-disclosure and non-competition agreements, or similar agreements, in connection with such previous employment. Although we try to ensure that our employees 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 these employees have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such third party. Litigation may be necessary to defend against such claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel or sustain damages. Such intellectual property rights could be awarded to a third party, and we could be required to obtain a license from such third party to commercialize our technology or products. Such a license may not be available on commercially reasonable terms or at all. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to our senior management and scientific personnel.

In addition, while we typically require our employees, consultants and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own, which may result in claims by or against us related to the ownership of such intellectual property. If we fail in prosecuting or defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to our senior management and scientific personnel.

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.

We have not yet registered trademarks in our potential markets. Any registered trademarks or trade names may be challenged, 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, which we need to build name recognition among potential partners or customers in our markets of interest. At times, competitors may adopt trade names or trademarks similar to ours, thereby impeding our ability to build brand identity and possibly leading to market confusion. In addition, there could be potential trade name or trademark infringement claims brought by owners of other registered trademarks or trademarks that incorporate variations of our registered or unregistered trademarks or trade names. Over the long term, if we are unable to establish name recognition based on our trademarks and trade names, then we may not be able to compete effectively and our business may be adversely

affected. Our efforts to enforce or protect our proprietary rights related to trademarks, trade secrets, domain names, copyrights or other intellectual property may be ineffective and could result in substantial costs and diversion of resources and could adversely impact our financial condition or results of operations.

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.

The USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other provisions during the patent process. There are situations in which non-compliance can result in abandonment or lapse of a patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. If we or our sublicensees fail to comply with these requirements, competitors might be able to enter the market earlier than would otherwise have been the case, which could decrease our revenue from that product.

Intellectual property rights do not necessarily address all potential threats.

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

- others may be able to make products that are similar to eganelisib or any future product candidates we may develop but that are not covered by the claims of the patents that we own or license or may own in the future;
- we, or any partners or collaborators, might not have been the first to make the inventions covered by the issued patent or pending patent application that we license or may own in the future;
- we, or any partners or collaborators, might not have been the first to file patent applications covering certain of our or their inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our owned or licensed intellectual property rights;
- it is possible that our pending licensed patent applications or those that we may own in the future will not lead to issued patents;
- issued patents that we hold rights to may be held invalid or unenforceable, including as a result of legal challenges by our competitors;
- our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we may not develop additional proprietary technologies that are patentable;
- the patents of others may have an adverse effect on our business; and
- we may choose not to file a patent for certain trade secrets or know-how, and a third party may subsequently file a patent covering such intellectual property.

Risks Related to Regulatory Approval and Marketing of Eganelisib and Other Legal Compliance Matters

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

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

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

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

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

Failure to obtain marketing approval in foreign jurisdictions would prevent eganelisib from being marketed in such jurisdictions.

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

Additionally, we could face heightened risks with respect to seeking marketing approval in the United Kingdom as a result of the withdrawal of the United Kingdom from the EU, commonly referred to as Brexit. The United Kingdom is no longer part of the European Single Market and European Union Customs Union. As of January 1, 2021, the Medicines and Healthcare products Regulatory Agency, or the MHRA, became responsible for supervising medicines and medical devices in Great Britain, comprising England, Scotland and Wales under domestic law, whereas Northern Ireland will continue to be subject to European Union rules under the Northern Ireland Protocol. The MHRA will rely on the Human Medicines Regulations 2012 (SI 2012/1916) (as amended), or the HMR, as the basis for regulating medicines. The HMR has incorporated into the domestic law of the body of European Union law instruments governing medicinal products that pre-existed prior to the United Kingdom's withdrawal from the European Union. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, may force us to restrict or delay efforts to seek regulatory approval in the United Kingdom for our product candidates, which could significantly and materially harm our business.

We may seek certain designations for our product candidates, including Breakthrough Therapy, Fast Track and Priority Review designations in the US, and PRIME Designation in the EU, but we might not receive such designations, and even if we do, such designations may not lead to a faster development or regulatory review or approval process.

We may seek certain designations for one or more of our product candidates that could expedite review and approval by the FDA. A Breakthrough Therapy product is defined as a product that is intended, alone or in combination with one or more other products, to treat a serious 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.

The FDA may also designate a product for Fast Track review if it is intended, whether alone or in combination with one or more other products, for the treatment of a serious or life threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition. For Fast Track products, sponsors may have greater interactions with the FDA and the FDA may initiate review of sections of a Fast Track product's application before the application is complete. This rolling review may be available if the FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a Fast Track product may be effective.

We may also seek a priority review designation for one or more of our product candidates. If the FDA determines that a product candidate offers major advances in treatment or provides a treatment where no adequate therapy exists, the FDA may designate the product candidate for priority review. A priority review designation means that the goal for the FDA to review an application is six months, rather than the standard review period of ten months.

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

In the EU, we may seek PRIME designation for our product candidates in the future. PRIME is a voluntary program aimed at enhancing the EMA's role to reinforce scientific and regulatory support in order to optimize development and enable accelerated assessment of new medicines that are of major public health interest with the potential to address unmet medical needs. The program focuses on medicines that target conditions for which there exists no satisfactory method of treatment in the EU or even if such a method exists, it may offer a major therapeutic advantage over existing treatments. PRIME is limited to medicines under development and not authorized in the EU and the applicant intends to apply for an initial marketing authorization application through the centralized procedure. To be accepted for PRIME, a product candidate must meet the eligibility criteria in respect of its major public health interest and therapeutic innovation based on information that is capable of substantiating the claims.

The benefits of a PRIME designation include the appointment of a CHMP rapporteur to provide continued support and help to build knowledge ahead of a marketing authorization application, early dialogue and scientific advice at key development milestones, and the potential to qualify products for accelerated review, meaning reduction in the review time for an opinion on approvability to be issued earlier in the application process. PRIME enables an applicant to request parallel EMA scientific advice and health technology assessment advice to facilitate timely market access. Even if we receive PRIME designation for any of our product candidates, the designation may not result in a materially faster development process, review or approval compared to conventional EMA procedures. Further, obtaining PRIME designation does not assure or increase the likelihood of EMA's grant of a marketing authorization.

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

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

In addition, manufacturers of approved products and those manufacturers' facilities are required to comply with extensive FDA requirements, including ensuring that quality control and manufacturing procedures conform to cGMPs applicable to drug manufacturers or quality assurance standards applicable to medical device manufacturers, which include requirements relating to quality control and quality assurance as well as the corresponding maintenance of records and documentation and reporting requirements. We, any contract manufacturers we may engage in the future, our current or future collaborators and their contract manufacturers will also be subject to other regulatory requirements, including submissions of safety and other post-marketing information and reports, registration and listing requirements, requirements regarding the distribution of samples to physicians, recordkeeping, and costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of the product such as the requirement to implement a risk evaluation and mitigation strategy.

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

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

Eganelisib could be subject to restrictions or withdrawal from the market, and we may be subject to substantial penalties, if we or our collaborators fail to comply with regulatory requirements or if we or they experience unanticipated problems with eganelisib, when and if it is approved.

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

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

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

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

Similar restrictions apply to the approval of our products in the EU. The holder of a marketing authorization is required to comply with a range of requirements applicable to the manufacturing, marketing, promotion and sale of medicinal products. These include: compliance with the EU's stringent pharmacovigilance or safety reporting rules, which can impose post-authorization studies and additional monitoring obligations; the manufacturing of authorized medicinal products, for which a separate manufacturer's license is mandatory; and the marketing and promotion of authorized drugs, which are strictly regulated in the EU and are also subject to EU Member State laws.

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

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

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

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

If our operations are found to be in violation of any of the laws described above or any governmental regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines and the curtailment or restructuring of our operations. Any penalties, damages, fines, curtailment or restructuring of our operations could adversely affect our financial results. As we move toward potential commercialization of eganelisib, any corporate compliance program we design would be intended to ensure that we will market and sell any future products that we successfully develop from eganelisib or other product candidates we may develop in compliance with all applicable laws and regulations. However, if implemented, we cannot guarantee that such program would protect us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions.

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

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

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

In March 2010, President Obama signed into law the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the ACA. In addition, other legislative changes have been proposed and adopted since the ACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. These changes included aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2031. These Medicare sequester reductions have been suspended through the end of March 2022. From April 2022 through June 2022 a 1% sequester cut will be in effect, with the full 2% cut resuming thereafter, and up to 3% in the last year of the sequester. The American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used.

Since enactment of the ACA, there have been, and continue to be, numerous legal challenges and Congressional actions to repeal and replace provisions of the law. For example, with enactment of the Tax Cuts and Jobs Act of 2017, or the TCJA, Congress repealed the "individual mandate." The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, became effective in 2019. On December 14, 2018, a U.S. District Court judge in the Northern District of Texas ruled that the individual mandate portion of the PPACA is an essential and inseverable feature of the PPACA, and therefore because the mandate was repealed as part of the Tax Act, the remaining provisions of the PPACA are invalid as well. The U.S. Supreme Court heard this case on November 10, 2020 and, on June 17, 2021, dismissed this action after finding that the plaintiffs do not have standing to challenge the constitutionality of the ACA. Litigation and legislation over the PPACA are likely to continue, with unpredictable and uncertain results.

The Trump Administration also took executive actions to undermine or delay implementation of the ACA, including directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. On January 28, 2021, however, President Biden issued a new Executive Order which directs federal agencies to reconsider rules and other policies that limit Americans' access to health care, and consider actions that will protect and strengthen that access. Under this Order, federal agencies are directed to re-examine: policies that undermine protections for people with pre-existing conditions, including complications related to COVID-19; demonstrations and waivers under Medicaid and the ACA that may reduce coverage or undermine the programs, including work requirements; policies that undermine the Health Insurance Marketplace or other markets for health insurance; policies that make it more difficult to enroll in Medicaid and the ACA; and policies that reduce affordability of coverage or financial assistance, including for dependents. This Executive Order also directs the U.S. Department of Health and Human Services to create a special enrollment period for the Health Insurance Marketplace in response to the COVID-19 pandemic.

We expect that these healthcare reforms, as well as other healthcare reform measures that may be adopted in the future, may result in additional reductions in Medicare and other healthcare funding, more rigorous coverage criteria, new payment methodologies and additional downward pressure on the price that we receive for any approved product and/or the level of reimbursement physicians receive for administering any approved product we might bring to market. Reductions in reimbursement levels may negatively impact the prices we receive or the frequency with which our products are prescribed or administered. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. Accordingly, such reforms, if enacted, could have an adverse effect on anticipated revenue from product candidates that we may successfully develop and for which we may obtain marketing approval and may affect our overall financial condition and ability to develop or commercialize product candidates.

The prices of prescription pharmaceuticals in the United States and foreign jurisdictions is subject to considerable legislative and executive actions and could impact the prices we obtain for our products, if and when licensed.

The prices of prescription pharmaceuticals have also been the subject of considerable discussion in the United States. There have been several recent U.S. congressional inquiries, as well as proposed and enacted state and federal legislation designed to, among other things, bring more transparency to pharmaceutical pricing, review the relationship between pricing and manufacturer patient programs, and reduce the costs of pharmaceuticals under Medicare and Medicaid. In 2020, President Trump issued several executive orders intended to lower the costs of prescription products and certain provisions in these orders have been incorporated into regulations. These regulations include an interim final rule implementing a most favored nation model for prices that would tie Medicare Part B payments for certain physician-administered pharmaceuticals to the lowest price paid in other economically advanced countries, effective January 1, 2021. That rule, however, has been subject to a nationwide preliminary injunction and, on December 29, 2021, CMS issued a final rule to rescind it. With issuance of this rule, CMS stated that it will explore all options to incorporate value into payments for Medicare Part B pharmaceuticals and improve beneficiaries' access to evidence-based care.

In addition, in October 2020, HHS and the FDA published a final rule allowing states and other entities to develop a Section 804 Importation Program, or SIP, to import certain prescription drugs from Canada into the United States. The final rule is currently the subject of ongoing litigation, but at least six states (Vermont, Colorado, Florida, Maine, New Mexico, and New Hampshire) have passed laws allowing for the importation of drugs from Canada with the intent of developing SIPs for review and approval by the FDA. Further, on November 20, 2020, HHS finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a new safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers. The implementation of this rule has been delayed by the Biden administration until January 1, 2026.

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

In the European Union, similar political, economic and regulatory developments may affect our ability to profitably commercialize our product candidates, if approved. In markets outside of the United States and the European Union, reimbursement and healthcare payment systems vary significantly by country, and many countries have instituted price ceilings on specific products and therapies. In some countries, particularly the countries of the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be harmed, possibly materially.

We are subject to U.S. and foreign anti-corruption and anti-money laundering laws with respect to our operations and non-compliance with such laws can subject us to criminal and/or civil liability and harm our business.

We are subject to the U.S. Foreign Corrupt Practices Act of 1977, as amended, or the FCPA, the U.S. domestic bribery statute contained in 18 U.S.C. § 201, the U.S. Travel Act, the USA PATRIOT Act, and possibly other state and national anti-bribery and anti-money laundering laws in countries in which we conduct activities. Anti-corruption laws are interpreted broadly and prohibit companies and their employees, agents, third-party intermediaries, joint venture partners and collaborators from authorizing, promising, offering, or providing, directly or indirectly, improper payments or benefits to recipients in the public or private sector. We may have direct or indirect interactions with officials and employees of government agencies or government-affiliated hospitals, universities, and other organizations. In addition, we may engage third-party intermediaries to promote our clinical research activities abroad and/or to obtain necessary permits, licenses, and other regulatory approvals. We can be held liable for the corrupt or other illegal activities of these third-party intermediaries, our employees, representatives, contractors, partners, and agents, even if we do not explicitly authorize or have actual knowledge of such activities.

Compliance with the FCPA is expensive and difficult, particularly in countries in which corruption is a recognized problem. 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.

We cannot ensure that our employees and third-party intermediaries will comply with such anti-corruption laws. Noncompliance with anti-corruption and anti-money laundering laws could subject us to whistleblower complaints, investigations, sanctions, settlements, prosecution, other enforcement actions, disgorgement of profits, significant fines, damages, other civil and criminal penalties or injunctions, suspension and/or debarment from contracting with certain persons, the loss of export privileges, reputational harm, adverse media coverage, and other collateral consequences. If any subpoenas, investigations, or other enforcement actions are launched, or governmental or other sanctions are imposed, or if we do not prevail in any possible civil or criminal litigation, our business, results of operations and financial condition could be materially harmed. In addition, responding to any action will likely result in a materially significant diversion of management's attention and resources and significant defense and compliance costs and other professional fees. In certain cases, enforcement authorities may even cause us to appoint an independent compliance monitor which can result in added costs and administrative burdens.

Further, 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 prohibited in the European Union. The provision of benefits or advantages to physicians is also governed by the national anti-bribery laws of European Union Member States, such as the UK Bribery Act 2010. Infringement of these laws could result in substantial fines and imprisonment. Payments made to physicians in certain European Union 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 European Union Member States. These requirements are provided in the national laws, industry codes, or professional codes of conduct applicable in the European Union Member States. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines, or imprisonment.

We are subject to governmental export and import controls that could impair our ability to compete in international markets due to licensing requirements and subject us to liability if we are not in compliance with applicable laws.

Our products and solutions are subject to export control and import laws and regulations, including the U.S. Export Administration Regulations, U.S. Customs regulations, and various economic and trade sanctions regulations administered by the U.S. Treasury Department's Office of Foreign Assets Controls. Exports of our products and solutions outside of the United States must be made in compliance with these laws and regulations. If we fail to comply with these laws and regulations, we and certain of our employees could be subject to substantial civil or criminal penalties, including the possible loss of export or import privileges; fines, which may be imposed on us and responsible employees or managers; and, in extreme cases, the incarceration of responsible employees or managers.

In addition, changes in our products or solutions or changes in applicable export or import laws and regulations may create delays in the introduction, provision, or sale of our products and solutions in international markets, prevent customers from using our products and solutions or, in some cases, prevent the export or import of our products and solutions to certain countries, governments or persons altogether. Any limitation on our ability to export, provide, or sell our products and solutions could adversely affect our business, financial condition and results of 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 laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. From time to time and in the future, our operations may involve the use of hazardous and flammable materials, including chemicals and biological materials, and may also produce hazardous waste products. Even if we contract with third parties for the disposal of these materials and waste products, we cannot completely eliminate the risk of contamination or injury resulting from these materials. In the event of contamination or injury resulting from the use or disposal of our hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties for failure to comply with such laws and regulations.

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

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

Our internal computer systems, or those of any collaborators or contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our product development programs.

Despite the implementation of security measures and certain data recovery measures, our internal computer systems and those of third parties with which we contract are vulnerable to damage from cyber-attacks, computer viruses, unauthorized access, sabotage, natural disasters, terrorism, war, and telecommunication and electrical failures. Any system failure, accident or security breach that causes interruptions in our operations, for us or those third parties with which we contract, could result in a material disruption of our product development programs and business operations, in addition to possibly requiring substantial expenditures of resources to remedy. For example, the loss of clinical trial data from completed clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach results in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we may incur liabilities and the further development of eganelisib, or any future product candidates we may develop, may be delayed. In addition, we may not have adequate insurance coverage to provide compensation for any losses associated with such events.

We could be subject to risks caused by misappropriation, misuse, leakage, falsification or intentional or accidental release or loss of information maintained in the information systems and networks of our company, including personal information of our employees. In addition, outside parties may attempt to penetrate our systems or those of our vendors or fraudulently induce our employees or employees of our vendors to disclose sensitive information to gain access to our data. Like other companies, we may experience threats to our data and systems, including malicious codes and viruses, and other cyber-attacks. The number and complexity of these threats continue to increase over time. If a material breach of our security or that of our vendors occurs, the market perception of the effectiveness of our security measures could be harmed, we could lose business and our reputation and credibility could be damaged. We could be required to expend significant amounts of money and other resources to repair or replace information systems or networks. Although we develop and maintain systems and controls designed to prevent these events from occurring, and we have a process to identify and mitigate threats, the development and maintenance of these systems, controls and processes is costly and requires ongoing monitoring and updating as technologies change and efforts to overcome security measures become more sophisticated. Moreover, despite our efforts, the possibility of these events occurring cannot be eliminated entirely.

Compliance with global privacy and data security requirements could result in additional costs and liabilities to us or inhibit our ability to collect and process data globally, and the failure to comply with such requirements could have a material adverse effect on our business, financial condition or results of operations.

The regulatory framework for the collection, use, safeguarding, sharing, transfer and other processing of information worldwide is rapidly evolving and is likely to remain uncertain for the foreseeable future. Globally, virtually every jurisdiction in which we operate has established its own data security and privacy frameworks with which we must comply. For example, the European Union's General Data Protection Regulation 2016/679, or GDPR, imposes strict obligations on the processing of personal data, including personal health data, and the free movement of such data. The GDPR applies to any company established in the European Union as well as any company outside the European Union that processes personal data in connection with the offering of goods or services to individuals in the European Union or the monitoring of their behavior. The GDPR enhances data protection obligations for processors and controllers of personal data, including, for example, obligations relating to: processing health and other sensitive data; obtaining consent of individuals; providing notice to individuals regarding data processing activities; responding to data subject requests; taking certain measures when engaging third-party processors; notifying data subjects and regulators of data breaches; implementing safeguards to protect the security and confidentiality of personal data; and transferring personal data to countries outside the European Union, including the United States. The GDPR imposes additional obligations and risks upon our business and substantially increases the penalties to which we could be subject in the event of any non-compliance, including fines of up to €20 million or 4% of total worldwide annual turnover, whichever is higher. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies and obtain compensation for damages. Given the breadth and depth of changes in data protection obligations, preparing for and complying with the GDPR's requirements has required and will continue to require significant time, resources and a review of our technologies, systems and practices, as well as those of any third-party collaborators, service providers, contractors or consultants that process or transfer personal data collected in the European Union. The GDPR and other changes in laws or regulations associated with the enhanced protection of certain types of sensitive data, such as health care data or other personal information from our clinical trials, could require us to change our business practices or lead to government enforcement actions, private litigation or significant fines and penalties against us, reputational harm and could have a material adverse effect on our business, financial condition or results of operations.

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

We are exposed to the risk of employee fraud or other misconduct, including intentional failures to comply with FDA regulations or similar regulations of comparable foreign regulatory authorities, provide accurate information to the FDA or comparable foreign regulatory authorities, comply with manufacturing standards we have established, comply with federal and state health care fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable foreign regulatory authorities, report financial information or data accurately or disclose unauthorized activities to us. Employee misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. It is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws, standards or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and results of operations, including the imposition of significant fines or other sanctions.

Risks Related to Employee Matters and Managing Potential Future Growth

If we are not able to retain key personnel and advisors, we may not be able to operate our business successfully.

We are highly dependent on our executive leadership team. All of these individuals are employees-at-will, which means that neither we nor the employee is obligated to a fixed term of service and that the employment relationship may be terminated by either us or the employee at any time, without notice and whether or not cause or good reason exists for such termination. The loss of the services of any of these individuals might impede the achievement of our research, development and commercialization objectives. We do not maintain "key person" insurance on any of our employees.

Retaining qualified scientific and business personnel is also critical to our success. Our industry has experienced a high rate of turnover of management personnel in recent years. If we lose one or more of our executive officers or other key employees, our ability to implement our business strategy successfully could be seriously harmed. This competition is particularly intense near our headquarters in Cambridge, Massachusetts. We may not be able to attract or retain these personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. In addition, we may face additional challenges in retaining our existing senior management and key employees for our company as our business needs change.

We also experience competition in the hiring of scientific personnel from universities and research institutions. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development strategy. Our consultants and advisors may be employed by other entities, have commitments under consulting or advisory contracts with third parties that limit their availability to us, or both.

We may undertake strategic acquisitions in the future, and any difficulties from integrating acquired businesses, products, product candidates and technologies could adversely affect our business and our stock price.

We may acquire additional businesses, products, product candidates, or technologies that complement or augment our existing business. We may not be able to integrate any acquired businesses, products, product candidates or technologies successfully or operate any acquired business profitably. Integrating any newly acquired business, product, product candidate, or technology could be expensive and time-consuming. Integration efforts often place a significant strain on managerial, operational and financial resources and could prove to be more difficult or expensive than we expect. The diversion of the attention of our management to, and any delay or difficulties encountered in connection with, any future acquisitions we may consummate could result in the disruption of our ongoing business or inconsistencies in standards, controls, procedures and policies that could adversely affect our ability to maintain relationships with customers, suppliers, collaborators, employees and others with whom we have business dealings. We may need to raise additional funds through public or private debt or equity financings to acquire any businesses, products, product candidates, or technologies which may result in, among other things, dilution for stockholders or the incurrence of indebtedness.

As part of our efforts to acquire businesses, products, product candidates and technologies or to enter into other significant transactions, we conduct business, legal and financial due diligence to identify and evaluate material risks involved in the transaction. We will also need to make certain assumptions regarding acquired product candidates, including, among other things, development costs, the likelihood of receiving regulatory approval and the market for such product candidates. If we are unsuccessful in identifying or evaluating all such risks or our assumptions prove to be incorrect, we might not realize some or all of the intended benefits of the transaction. If we fail to realize intended benefits from acquisitions we may consummate in the future, our business and financial results could be adversely affected.

In addition, we will likely incur significant expenses in connection with our efforts, if any, to consummate acquisitions. These expenses may include fees and expenses for investment bankers, attorneys, accountants and other advisers in connection with our efforts and could be incurred whether or not an acquisition is consummated. Even if we consummate a particular acquisition, we may incur as part of such acquisition substantial closure costs associated with, among other things, elimination of duplicate operations and facilities. In such case, the incurrence of these costs could adversely affect our financial results for particular quarterly or annual periods.

Risks Related to Our Common Stock

Our common stock may have a volatile trading price and low trading volume.

The market price of our common stock has been and we expect it to continue to be subject to significant fluctuations. Some of the factors that may cause the market price of our common stock to fluctuate include:

- the results of our current and any future clinical trials of eganelisib;
- future sales of, and the trading volume in, our common stock;
- the impact of the COVID-19 pandemic on the economy or our business;
- announcements regarding the timing of enrollment and data readouts from our trials, including any delays;
- announcements of strategic transactions relating to our programs or our company;
- our entry into key agreements, including those related to the acquisition or in-licensing of new programs, or the termination of key agreements, including the Takeda Agreement or the Secura Bio Agreement;
- the results and timing of regulatory reviews relating to the approval of eganelisib;
- the initiation of, material developments in, or conclusion of litigation, including but not limited to litigation to enforce or defend any of our intellectual property rights or to defend product liability claims;
- the failure of eganelisib, if approved, to achieve commercial success;
- the results of clinical trials conducted by others on drugs that would compete with eganelisib;
- the regulatory approval of drugs that would compete with eganelisib;
- issues in manufacturing eganelisib;
- the loss of executive officers or other key employees;

- changes in estimates or recommendations, or publication of inaccurate or unfavorable research about our business, by securities analysts who cover our common stock;
- future financings through the issuance of equity or debt securities or otherwise;
- health care reform measures, including changes in the structure of health care payment systems;
- our cash position and period-to-period fluctuations in our financial results; and
- general and industry-specific economic and/or capital market conditions.

Moreover, the stock markets in general have experienced substantial volatility that has often been unrelated to the operating performance of individual companies. These broad market fluctuations may also adversely affect the trading price of our common stock.

In the past, when the market price of a stock has been volatile, as our stock price may be, holders of that stock have occasionally brought securities class action litigation against the company that issued the stock. If any of our stockholders were to bring a lawsuit of this type against us, even if the lawsuit is without merit, negative publicity could be generated, and we could incur substantial costs defending the lawsuit. A stockholder lawsuit could also divert the time and attention of our management.

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

Our common stock is currently listed for quotation on the Nasdaq Global Select Market. We are required to meet specified requirements in order to maintain our listing on the Nasdaq Global Select Market, including, among other things, a minimum bid price of $1.00 per share, or the Minimum Bid Price. On July 1, 2020, we received a deficiency letter from the Listing Qualifications Department of the Nasdaq Stock Market, LLC, or Nasdaq, notifying us that, for the last 30 consecutive business days, the bid price for our common stock was below the Minimum Bid Price required to maintain continued listing on the Nasdaq Global Select Market under Nasdaq Listing Rule 5450(a)(1), or the Minimum Bid Requirement. We had 180 days to regain compliance by maintaining the Minimum Bid Price for a minimum of ten consecutive business days. On August 24, 2020, we received a letter from Nasdaq notifying us that we had regained compliance with the Minimum Bid Requirement and that the matter was closed.

Our bid price fell below $1 on March 25, 2022, and we will fall out of compliance with the Minimum Bid Requirement again if our stock does not exceed $1 before May 9, 2022. If we fail to satisfy the Nasdaq Global Select Market's continued listing requirements, including the Minimum Bid Requirement, we may transfer to the Nasdaq Capital Market, which generally has lower financial requirements for initial listing, to avoid delisting, or, if we fail to meet its listing requirements, the OTC Bulletin Board. A transfer of our listing to the Nasdaq Capital Market or having our common stock trade on the OTC Bulletin Board could adversely affect the liquidity of our common stock. Any such event could make it more difficult to dispose of, or obtain accurate quotations for the price of, our common stock, and there also would likely be a reduction in our coverage by securities analysts and the news media, which could cause the price of our common stock to decline further. We may also face other material adverse consequences in such event, such as negative publicity, a decreased ability to obtain additional financing, diminished investor and/or employee confidence, and the loss of business development opportunities, some or all of which may contribute to a further decline in our stock price.

The estimates and judgments we make, or the assumptions on which we rely, in preparing our consolidated financial statements could prove inaccurate.

Our consolidated financial statements 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 judgments that affect the reported amounts of our assets, liabilities, revenues and expenses. Such estimates and judgments include those related to revenue recognition, impairment of long-lived assets, accrued expenses, assumptions in the valuation of stock-based compensation and income taxes. We base our estimates and judgments on historical experience, facts and circumstances known to us and on various assumptions that we believe to be reasonable under the circumstances. These estimates and judgments, or the assumptions underlying them, may change over time or prove inaccurate. If this is the case, we may be required to restate our financial statements, which could in turn subject us to securities class action litigation. Defending against such potential litigation relating to a restatement of our financial statements would be expensive and would require significant attention and resources of our management. Moreover, our insurance to cover our obligations with respect to the ultimate resolution of any such litigation may be inadequate. As a result of these factors, any such potential litigation could have a material adverse effect on our financial results and cause our stock price to decline.

If we are not able to maintain effective internal control under Section 404 of the Sarbanes-Oxley Act, our business and stock price could be adversely affected.

Section 404 of the Sarbanes-Oxley Act of 2002 requires us, on an annual basis, to review and evaluate our internal control. Any failure by us to maintain the effectiveness of our internal control in accordance with the requirements of Section 404 of the Sarbanes-Oxley Act, which could be impacted by employee turnover, as such requirements exist today or may be modified, supplemented or amended in the future, could have a material adverse effect on our business, operating results and stock price.

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

We have incurred significant net losses since our inception and cannot guarantee when, if ever, we will become profitable. To the extent that we continue to generate federal and state taxable losses, unused net operating loss and tax credit carryforwards will carry forward to offset future taxable income, subject to applicable limitations on the use of those losses. Losses incurred in taxable years ending on or before December 31, 2017, are eligible to be carried forward for up to 20 years, and to be deducted in full against income for the years to which they may be carried. Losses incurred in taxable years ending after December 31, 2017, are eligible to be carried forward indefinitely, but may offset no more than 80% of the taxable income for the years to which they are carried (computed without regard to the deduction for carryovers of net operating losses). Net operating loss carryovers from periods ending on or before December 31, 2017, and tax credit carryovers from all periods, could expire unused and be unavailable to offset future income tax liabilities.

In addition, under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, or the Internal Revenue Code, and corresponding provisions of state law, if a corporation undergoes an "ownership change," which is generally defined as a greater than 50% change, by value, in its equity ownership over a three-year period, the corporation's ability to use its pre-change net operating loss and credit carryovers to reduce its tax liability for post-change periods may be limited. We have had ownership changes in the past and may experience future ownership changes as a result of subsequent shifts in our stock ownership, some of which may be outside of our control. In addition, we have not conducted a detailed study to document whether our historical activities qualify to support the research and development credits currently claimed as a carryover. A detailed study could result in adjustment to our research and development credit carryovers. Our ability to use our historical net operating loss and tax credit carryovers to offset future income tax liabilities is limited by prior ownership changes and may become limited by additional ownership changes in the future. In addition, if our research and development credit carryforwards are adjusted, our use of those attributes to offset future income tax liabilities would be adversely impacted.

Comprehensive changes to the U.S. tax code made by 2017's tax reform law and other recent laws could adversely affect our business and financial condition.

On December 22, 2017, then-President Trump signed into law the TCJA, which significantly revised the Internal Revenue Code. The TCJA, as amended by the CARES Act, among other things, contains significant changes to corporate taxation, including reduction of the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, limitation of the tax deduction for interest expense to 30% of adjusted earnings (except for certain small businesses), limitation of the deduction for net operating losses to 80% of current year taxable income and elimination of net operating loss carrybacks, in each case, for losses arising in taxable years beginning after December 31, 2017 (though any such net operating losses may be carried forward indefinitely and such net operating losses arising in taxable years beginning before January 1, 2021 are generally eligible to be carried back up to five years), one time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, elimination of U.S. tax on foreign earnings (subject to certain important exceptions), immediate deductions for certain new investments instead of deductions for depreciation expense over time, and modifying or repealing many business deductions and credits.

Notwithstanding the reduction in the corporate income tax rate, the overall impact of the TCJA remains uncertain and our business and financial condition could be adversely affected. In addition, as part of Congress' response to the COVID-19 pandemic, economic relief legislation has been enacted in 2020 and 2021. This legislation contains numerous tax provisions. Regulatory guidance under the TCJA and such additional legislation is and continues to be forthcoming, and such guidance could ultimately increase or lessen their impact on our business and financial condition. Also, as a result of the changes in the U.S. presidential administration and control of the U.S. Senate in 2021, additional tax legislation may also be enacted; any such additional legislation could have an impact on us. In addition, it is uncertain if and to what extent various states will conform to the TCJA and additional tax legislation.

Our effective tax rate may fluctuate, and we may incur obligations in tax jurisdictions in excess of accrued amounts.

Our effective tax rate may be different than experienced in the past due to numerous factors, including as a result of applying the provisions of the TCJA (as such provisions may be elaborated on or further developed in guidance, regulations and technical corrections pertaining to the TCJA), changes in the mix of our profitability apportioned to tax jurisdictions in which we may operate, the results of examinations and audits of our tax filings, our inability to secure or sustain acceptable agreements with tax authorities, changes in accounting for income taxes and changes in tax laws. Any of these factors could cause us to experience an effective tax rate significantly different from previous periods or our current expectations and may result in tax obligations in excess of amounts accrued in our financial statements.

Because we do not anticipate paying cash dividends, stock price appreciation, if any, will be our stockholders' sole return on investment.

We anticipate retaining any future earnings for reinvestment in the infrastructure and personnel necessary to support our development and potential commercialization efforts. Therefore, we do not anticipate paying cash dividends in the future. As a result, only appreciation of the price of our common stock will provide a return to stockholders. Investors seeking cash dividends should not invest in our common stock.

Inadequate funding for the FDA, the SEC and other government agencies could hinder their ability to hire and retain key leadership and other personnel, prevent new products and services from being developed or commercialized in a timely manner or otherwise prevent those agencies from performing normal business functions on which the operation of our business may rely, which could negatively impact our business.

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. 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, over the last several years, the U.S. government has shut down several times and certain regulatory agencies, such as the FDA and the SEC, have had to furlough critical employees and stop critical activities. If a prolonged government shutdown occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business. Further, future government shutdowns could impact our ability to access the public markets and obtain necessary capital in order to properly capitalize and continue our operations.

Anti-takeover provisions in our organizational documents and Delaware law may make an acquisition of us difficult.

We are incorporated in Delaware. Anti-takeover provisions of Delaware law and our organizational documents may make a change in control more difficult. Also, under Delaware law, our Board of Directors may adopt additional anti-takeover measures. For example, our charter authorizes our Board of Directors to issue up to 1,000,000 shares of undesignated preferred stock and to determine the terms of those shares of stock without any further action by our stockholders. If our Board of Directors exercises this power, it could be more difficult for a third party to acquire a majority of our outstanding voting stock. Our charter and bylaws also contain provisions limiting the ability of stockholders to call special meetings of stockholders.

Our stock incentive plan generally permits our Board of Directors to provide for acceleration of vesting of options granted under that plan in the event of certain transactions that result in a change of control. If our Board of Directors uses its authority to accelerate vesting of options, this action could make an acquisition more costly, and it could prevent an acquisition from going forward.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law statute, which generally prohibits a person who owns in excess of 15% of our outstanding voting stock from engaging in a transaction with us for a period of three years after the date on which such person acquired in excess of 15% of our outstanding voting common stock, unless the transaction is approved by our Board of Directors and holders of at least two-thirds of our outstanding voting stock, excluding shares held by such person. The prohibition against such transactions does not apply if, among other things, prior to the time that such person became an interested stockholder, our Board of Directors approved the transaction in which such person acquired 15% or more of our outstanding voting stock. The existence of the foregoing provisions could limit the price that investors might be willing to pay in the future for shares of our common stock.

Our investments are subject to risks that may cause losses and affect the liquidity of these investments.

As of December 31, 2021, we had $80.7 million in cash and cash equivalents. We historically have invested these amounts in money market funds, corporate obligations, U.S. government-sponsored enterprise obligations, and U.S. Treasury securities meeting the criteria of our investment policy, which prioritizes the preservation of our capital. Corporate obligations may include obligations issued by corporations in countries other than the United States, including some issues that have not been guaranteed by governments and government agencies. Our investments are subject to general credit, liquidity, market and interest rate risks and instability in the financial markets. We may realize losses in the fair value of these investments or a complete loss of these investments. In addition, should our investments cease paying or reduce the amount of interest paid to us, our interest income would suffer. These market risks associated with our investment portfolio may have a material adverse effect on our financial results and the availability of cash to fund our operations.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

On April 5, 2019, we entered into a lease, effective April 3, 2019, for 10,097 square feet of office space at 1100 Massachusetts Avenue, Cambridge, Massachusetts. The lease expires on August 1, 2024.

Item 3. Legal Proceedings

We are not a party to any material legal proceedings.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

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

Market Information and Holders

Our common stock is traded on the Nasdaq Global Select Market under the symbol "INFI." As of March 25, 2022, there were 45 holders of record of our common stock. This number does not include beneficial owners whose shares are held by nominees in street name.

Dividends

We have not declared or paid any cash dividends on our common stock since our inception. We intend to retain all available funds and any future earnings to finance the operation and expansion of our business and do not anticipate paying any cash dividends in the foreseeable future.

Securities Authorized for Issuance Under Equity Compensation Plans

The section entitled "Securities Authorized for Issuance Under Equity Compensation Plans" appearing in the definitive proxy statement we will file in connection with our 2022 Annual Meeting of Stockholders is incorporated herein by reference.

Sales of Unregistered Securities

None.

Repurchase of Equity Securities

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

Item 6. Reserved

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

The following discussion of our financial condition and results of operations should be read in conjunction with our consolidated financial statements and related notes included elsewhere in this report. Some of the information contained in this discussion and analysis and set forth elsewhere in this report, including information with respect to our plans and strategy for our business, includes forward-looking statements that involve risks and uncertainties. You should review the section titled "Risk Factors" in Part I, Item 1A of this Annual Report on Form 10-K for a discussion of important factors that could cause actual results to differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

Overview

We are a clinical-stage innovative biopharmaceutical company dedicated to developing novel medicines for people with cancer. We combine proven scientific expertise with a passion for developing novel small molecule drugs that target disease pathways for potential applications in oncology. We are focusing on advancing eganelisib, also known as IPI-549, an orally administered, clinical-stage, immuno-oncology product candidate that selectively inhibits the enzyme phosphoinositide-3-kinase-gamma, or PI3K-gamma. We believe eganelisib is the only selective inhibitor of PI3K-gamma being investigated in clinical trials. We have worldwide development and commercialization rights to eganelisib, subject to certain success-based milestone payment obligations to our licensor, Takeda Pharmaceutical Company Limited, or Takeda, as described in more detail under Part I, Item 1, "Business Overview – Alliances, Collaborations, and Other Arrangements – Takeda."

MARIO-3 (MAcrophage Reprogramming in Immuno-Oncology-3)

MARIO-3 is a multi-arm Phase 2 study designed to evaluate eganelisib in the front-line treatment for both metastatic triple negative breast cancer, or TNBC, and renal cell carcinoma, or RCC. The TNBC cohort is evaluating eganelisib in combination with atezolizumab, an anti-PD-L1 monoclonal antibody also known as Tecentriq®, and nab-paclitaxel, an albumin-

bound chemotherapy drug also known as Abraxane®, in approximately 60 patients with unresectable locally advanced or metastatic TNBC. The RCC cohort is evaluating eganelisib in combination with atezolizumab and bevacizumab, also known as Avastin®, in approximately 30 patients with RCC. We entered into clinical supply agreements with Roche under which Roche has agreed to supply atezolizumab and bevacizumab for our use in MARIO-3.

On December 10, 2021, we presented data at the 2021 San Antonio Breast Cancer Symposium, or SABCS, from the TNBC cohort of our ongoing MARIO-3 study, a multi-arm Phase 2 study designed to evaluate eganelisib in the front-line setting for TNBC and front-line renal cell carcinoma, or RCC. The TNBC cohort is evaluating eganelisib in combination with atezolizumab, also known as Tecentriq®, and nab-paclitaxel, also known as Abraxane®, in up to approximately 60 patients with front-line TNBC. As of the October 2, 2021 data cutoff date, we had enrolled 44 evaluable patients and 50 patients total, with a median duration of follow up of 9.9 months. Using the same cutoff standard used in the F. Hoffmann-La Roche Ltd., or Roche, benchmark IMpassion130 study for a protein called programmed-death ligand 1, or PD-L1, we refer to patients with tumors that test below 1% PD-L1 at baseline as "PD-L1(-) patients" and those with tumors that test equal to or greater than 1% as "PD-L1(+) patients." The MARIO-3 data presented at SABCS and an investor event following SABCS include the following findings:

- Of evaluable patients, tumor reduction was observed in 92.8% of patients with PD-L1(+) tumors and 85.2% of patients with PD-L1(-) tumors
- Disease control rate (DCR)
    - 92.8% (13/14) DCR in patients with PD-L1(+) tumors: complete response (CR) 14.3% (2/14), partial response (PR) 57.1% (8/14), stable disease (SD) 21.4% (3/14)
    - 81.4% (22/27) DCR in patients with PD-L1(-) tumors: CR 0% (0/27), PR 48.1% (13/27), SD 33.3% (9/27)
- Progression free survival (PFS)
    - In patients with PD-L1(+) tumors, median PFS in MARIO-3 was 11.0 months, a 47% improvement in median PFS compared to the 7.5 months reported for the atezolizumab and nab-paclitaxel doublet in IMpassion130
    - In patients with PD-L1(-) tumors, median PFS in MARIO-3 was 7.3 months, a 30% improvement compared to the 5.6 months reported for the atezolizumab and nab-paclitaxel doublet in IMpassion130
- 67% of the PD-L1(-) patients who reached the median PFS of 7.3 months remained on treatment

We expect to provide updated data from the MARIO-3 TNBC cohort in the second half of 2022. Enrollment has been completed in the RCC cohort and we expect to present data from the RCC cohort in the second half of 2022.

MARIO-275

MARIO-275 is our global, randomized, placebo-controlled Phase 2 study evaluating the effect of adding eganelisib to nivolumab, also known as Opdivo®, in checkpoint-naïve advanced urothelial cancer, or UC, patients whose cancer has progressed or recurred following treatment with platinum-based chemotherapy. Nivolumab is an immune checkpoint inhibitor therapy commercialized by Bristol Myers Squibb Company, or BMS. Further details regarding the study are provided under the section entitled Part I, Item 1, "Business Overview – Eganelisib Clinical Development Program – MARIO-275)." The following are the key developments related to MARIO-275:

We presented MARIO-275 data at the American Society of Clinical Oncology Genitourinary Cancers Symposium, or ASCO GU, in February 2021, and presented updates on overall survival data in July 2021 and January 2022. The data from the 49 patients enrolled in the trial include the following findings:

- Median overall survival (mOS) in the intent to treat population as of July 2021 was 15.4 months (6.2, NE) on the eganelisib plus nivolumab combination arm as compared to 7.9 months (2.3, NE) on the control arm of nivolumab alone with a hazard ratio (HR) 0.62 (0.28, 1.36), reflecting a 38% lower probability of death.
    - In a one-year landmark analysis of the ITT population, 59% of patients in the nivolumab combination were alive, compared to 32% in the nivolumab control arm.
- The mOS in PD-L1(-) patients, as updated in January 2022, was 15.3 months (4.7, NE) on the eganelisib plus nivolumab arm versus 7.9 months (1.9, NE) on the nivolumab control arm with an HR 0.58 (0.21, 1.66), reflecting a 42% lower probability of death.
    - In a one-year landmark analysis of patients with PD-L1(-) tumors, 54% on the eganelisib plus nivolumab combination remained alive, compared to 17% in the nivolumab control arm.

The most common TEAEs for the eganelisib plus nivolumab combination arm across all doses, all causality, were pyrexia (33.3%), decreased appetite (30.3%), pruritus (27.3%), asthenia (27.3%), rash (27.3%), and increased alanine aminotransferase (24.2%); and the most common ≥Grade 3 TEAEs across all doses, all causality, were anemia (12.1%), and hepatic AEs including hepatotoxicity (15.2%), increased ALT (12.1%), and increased AST (12.1%) with no Hy's Law. No Grade 5 AEs were reported.

2022 Eganelisib Development Strategy: Advancing and Expanding MARIO Clinical Development Program

Building on data from MARIO-275 and MARIO-3, we expect to initiate two new studies in 2022. We are planning a randomized, double-blind, registration study in front-line mTNBC, which we refer to as MARIO-4. For the PD-L1(-) patients in the future MARIO-4 study, eganelisib in combination with chemotherapy and a checkpoint inhibitor (the eganelisib triplet) will be evaluated against chemotherapy. In the PD-L1(+) patients, the eganelisib triplet will be evaluated against the combination of chemotherapy and a checkpoint inhibitor. We expect MARIO-4 to include endpoints of PFS and OS. Pending feedback from a MARIO-3 end-of-Phase 2 meeting with global regulatory authorities, we will finalize the MARIO-4 trial design. We also expect to initiate MARIO-P, a platform study to evaluate the clinical benefit of eganelisib to support the initiation of future registration focused studies across various solid tumor indications, on a rolling basis beginning in the third quarter of 2022.

Financial Overview

Revenue

To date, all of our revenue has been generated under collaboration agreements, including payments to us of upfront license fees, funding or reimbursement of research and development efforts, milestone payments if specified objectives are achieved, and royalties on product sales. In the future, we may generate revenue from a combination of product sales, research and development support services and milestone payments in connection with strategic relationships, as well as royalties resulting from the sales of products developed under licenses of our intellectual property. We expect that any potential future revenue we generate will fluctuate from year to year as a result of the timing and amount of license fees, research and development reimbursement, milestone, royalty and other payments earned under our collaborative or strategic relationships and the amount and timing of payments that we earn upon the sale of our products, to the extent any are successfully commercialized.

Research and Development Expense

We are a drug development company. Our research and development expense has historically consisted primarily of the following:

- compensation of personnel associated with research and development activities;
- clinical testing costs, including payments made to contract research organizations;
- costs of combination and comparator drugs used in clinical studies;
- costs of manufacturing product candidates for preclinical testing and clinical studies;
- costs associated with the licensing of research and development programs;
- preclinical testing costs, including costs of toxicology studies;
- fees paid to external consultants;
- fees paid to professional service providers for independent monitoring and analysis of our clinical trials;
- costs for collaboration partners to perform research and development activities, including development milestones for which a payment is due when achieved;
- depreciation of equipment; and
- allocated costs of facilities.

General and Administrative Expense

General and administrative expense primarily consists of compensation of personnel in executive, finance, accounting, legal and intellectual property, information technology, corporate communications, and human resources functions. Other costs include facilities costs not otherwise included in research and development expense and professional fees for legal and accounting services.

Royalty Expense

Royalty expense is recorded when incurred and represents the expense associated with amounts owed to third parties as a result of royalty revenue recognized and the amounts owed by us to Takeda in relation to sale of future royalties.

Other Income and Expense

Other income and expense typically consist of interest earned on cash, cash equivalents and available-for-sale securities, non-cash interest expense, and changes in fair value of warrant liability.

Critical Accounting Policies and Significant Judgments and Estimates

The following 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 financial statements requires us to make judgments, estimates and assumptions that affect the amounts reported in the financial statements and accompanying notes. On an ongoing basis, we evaluate our estimates, including those related to cumulative revenue related to variable consideration, accrued expenses, estimates of future net royalty payments used in the calculation of our liability related to the sale of future royalties, and assumptions in the valuation of stock-based compensation. We base our estimates on historical experience and on various other assumptions that we believe to be reasonable under the circumstances. Actual results could differ from those estimates. Differences between actual and estimated results have not been material and have been adjusted in the period they become known. We believe that the following accounting policies and estimates are most critical to understanding and evaluating our reported financial results. Please refer to Note 2 to our consolidated financial statements included in this report for a description of our significant accounting policies.

Revenue Recognition

To date, all our revenue has been generated under collaboration agreements, including payments to us of upfront license fees, funding or reimbursement of research and development efforts, milestone payments if specified objectives are achieved, and/or royalties on product sales.

We recognize revenue when we transfer goods or services to customers in an amount that reflects the consideration that we expect to receive for those goods or services. These principles are applied using a five-step model: 1) identify the customer contract; 2) identify the contract's performance obligations; 3) determine the transaction price; 4) allocate the transaction price to the performance obligations; and 5) recognize revenue when or as a performance obligation is satisfied. We evaluate all promised goods and services within a customer contract and determine which of those are separate performance obligations. This evaluation includes an assessment of whether the good or service is capable of being distinct and whether the good or service is separable from other promises in the contract. When a performance obligation is satisfied, we recognize as revenue the amount of the transaction price, excluding estimates of variable consideration that are constrained, that is allocated to that performance obligation. For contracts that contain variable consideration, such as milestone payments, we estimate the amount of variable consideration by using either the expected value method or the most likely amount method. In making this assessment, we evaluate factors such as the clinical, regulatory, commercial and other risks that must be overcome to achieve the milestone. Each reporting period we re-evaluate the probability of achievement of such milestones and any related constraints. We will include variable consideration, without constraint, in the transaction price to the extent it is probable that a significant reversal in the amount of cumulative revenue recognized will not occur when the uncertainty associated with the variable consideration is subsequently resolved.

We recognize sales-based milestones and royalty revenue based upon net sales by the licensee of licensed products in licensed territories, and in the period the sales occur under the sales- and usage-based royalty exception when the sole or predominate item to which the royalty relates is a license to intellectual property.

In the event of an early termination of a collaboration agreement, any contract liabilities would be recognized in the period in which all our obligations under the agreement have been fulfilled.

Accrued Expenses

As part of the process of preparing financial statements, we are required to estimate accrued expenses. This process involves identifying services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for such service as of each balance sheet date. Examples of services for which we must estimate accrued expenses include contract service fees paid to contract manufacturers in conjunction with pharmaceutical development work and to contract research organizations in connection with clinical trials and preclinical studies. In connection with these service fees, our estimates are most affected by our understanding of the status and timing of services provided. The majority of

our service providers invoice us in arrears for services performed. In the event that we do not identify certain costs that have been incurred by our service providers, or if we under- or over-estimate the level of services performed or the costs of such services in any given period, our reported expenses for such period would be too low or too high, respectively. We often rely on subjective judgments to determine the date on which certain services commence, the level of services performed on or before a given date and the cost of such services. We make these judgments based upon the facts and circumstances known to us. Our estimates of expenses in future periods may be under- or over-accrued.

Liabilities Related to Sale of Future Royalties

We treat the liabilities related to sale of future royalties as debt financings, amortized under the effective interest rate method over the estimated life of the related royalty streams. The liabilities related to sale of future royalties and the debt amortization are based on our current estimates of future royalties expected to be paid over the life of the arrangements. We will periodically assess the expected royalty payments using projections from external sources. To the extent our estimates of future royalty payments are greater or less than previous estimates or the estimated timing of such payments is materially different than previous estimates, we will adjust the effective interest rate and recognize related non-cash interest expense on a prospective basis. Non-cash royalty revenue is reflected as royalty revenue, and non-cash amortization of debt is reflected as interest expense in the Consolidated Statements of Operations and Comprehensive Loss included in Part II, Item 8, "Financial Statements and Supplementary Data," of this Annual Report on Form 10-K.

Results of Operations

The following table summarizes our results of operations for the years ended December 31, 2021 and 2020, in thousands, together with the change in each item as a percentage.

	2021	2020	% Change
Royalty revenue	$ 1,858	$ 1,719	8 %
Research and development expense	(31,647)	(26,761)	18 %
General and administrative expense	(14,174)	(12,418)	14 %
Royalty expense	(1,120)	(1,037)	8 %
Investment and other income	1	450	(100)%
Non-cash interest expense	(180)	(153)	18 %
Non-cash related party interest expense	—	(2,292)	(100)%
Net loss	(45,262)	(40,492)	12 %

Revenue

For the year ended December 31, 2021, we recognized $1.9 million in royalty revenue, an increase of 8% as compared to $1.7 million in royalty revenue for the year ended December 31, 2020. Royalty revenue for both periods is related to royalties on net sales of duvelisib from Verastem and Secura Bio. A portion of the royalties received is owed to Mundipharma and Purdue. We refer to such portion as the Trailing Mundipharma Royalties (see Note 11 of the notes to our consolidated financial statements included in Part II, Item 8, "Financial Statements and Supplementary Data," of this Annual Report on Form 10-K). We and HCR entered into a purchase and sale agreement in March 2019, or the HCR Agreement, pursuant to which HCR acquired our interest in royalties received from Verastem and Secura Bio on net sales of duvelisib, less the Trailing Mundipharma Royalties (see Note 9 of the notes to our consolidated financial statements included in Part II, Item 8, "Financial Statements and Supplementary Data," of this Annual Report on Form 10-K).

Research and Development Expense

Research and development expenses represented approximately 67% our total operating expenses for each of the years ended December 31, 2021 and 2020. For the year ended December 31, 2021, we recognized $31.6 million in research and development expense, an increase of approximately 18% as compared to $26.8 million in research and development expense for the year ended December 31, 2020. The increase is primarily attributable to an increase in clinical and development expenses for eganelisib of $2.4 million, an increase in compensation expense of $1.3 million due primarily to new hires during the year and an increase in consulting expense of $0.7 million to support continued development of eganelisib.

We began to track and accumulate costs by major program starting on January 1, 2006. These expenses primarily relate to payroll and related expenses for personnel working on the programs, process development and manufacturing, preclinical toxicology studies, clinical trial costs and allocated costs of facilities. During the years ended December 31, 2021 and 2020 and from January 1, 2006 through December 31, 2021, we estimate that we incurred $31.6 million, $26.8 million and $715.0 million of costs, respectively, on our PI3K inhibitor program, including eganelisib and duvelisib.

We expect our research and development expense to vary as a result of our continued clinical development of eganelisib. We do not believe that the historical costs associated with our lead drug development programs are indicative of the future costs associated with these programs, nor represent what any other future drug development programs we initiate may cost. Due to the variability in the length of time and scope of activities necessary to develop a product candidate and uncertainties related to our cost estimates and our ability to obtain marketing approval for eganelisib or any future product candidates we may develop, accurate and meaningful estimates of the total costs required to bring product candidates to market are not available.

Because of the risks inherent in drug development, we cannot reasonably estimate or know:

- the nature, timing and estimated costs of the efforts necessary to complete the development of our programs;
- the completion dates of these programs; or
- the period in which material net cash inflows are expected to commence, if at all, from the programs described above and any potential future product candidates.

There is significant uncertainty regarding our ability to successfully develop any product candidates. These risks include the uncertainty of:

- the scope, rate of progress and cost of our clinical trials that we are currently conducting or may commence in the future;
- clinical trial results;
- the cost of establishing clinical supplies of any product candidates;
- the cost and availability of combination and comparator drugs;
- the cost of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights relating to our programs under development;
- the terms and timing of any collaborations, licensing and other arrangements that we have or may establish in the future relating to our programs under development;
- the cost and timing of regulatory approvals;
- the effect of competing technological and market developments; and
- the impact of the COVID-19 pandemic.

General and Administrative Expense

For the year ended December 31, 2021, we recognized $14.2 million in general and administrative expense, an increase of 14% as compared to approximately $12.4 million in general and administrative expense for the year ended December 31, 2020. The increase was primarily attributable to an increase of $0.8 million in stock-based compensation, an increase of $0.5 million in professional services expense, and an increase of $0.5 million in consulting expense.

Royalty Expense

For the year ended December 31, 2021, we recognized $1.1 million in royalty expense, an increase of 8% as compared to approximately $1.0 million in royalty expense for the year ended December 31, 2020. Royalty expense for both periods is related to royalties paid to Mundipharma, Purdue and Takeda on net sales of duvelisib by Secura Bio and Verastem (see Note 11 of the notes to our consolidated financial statements included in Part II, Item 8, “Financial Statements and Supplementary Data,” of this Annual Report on Form 10-K).

Investment and Other Income

Investment and other income decreased by $0.4 million for the year ended December 31, 2021 as compared to the year ended December 31, 2020 primarily attributable to lower yields on our cash equivalents and available-for-sale securities and changes in the fair value of the warrant liability.

Non-cash Interest Expense

Non-cash interest expense for the year ended December 31, 2021 was the result of the sale of future royalties in relation to the HCR Agreement and BVF Funding Agreement, which we recognized as liabilities that are being amortized using the effective interest method over the life of the arrangement (see Note 9 of the notes to our consolidated financial statements included in Part II, Item 8, "Financial Statements and Supplementary Data," of this Annual Report on Form 10-K). Non-cash interest expense for the year ended December 31, 2020 was the result of the sale of future royalties in relation to the HCR Agreement. Over the course of the arrangements, the non-cash interest expense will be affected by the amount and timing of estimated royalty revenue, if any. We reassess the effective interest rate on a quarterly basis and adjust the rate prospectively as needed.

Non-cash Related Party Interest Expense

Non-cash related party interest expense for the year ended December 31, 2020 was the result of the sale of future royalties in relation to the BVF Funding Agreement. Effective February 17, 2021, Biotechnology Value Fund, L.P. is no longer considered our related party. As a result, we have reclassed the related interest expense for the year ended December 31, 2021 as non-cash interest expense.

Liquidity and Capital Resources

We have primarily incurred operating losses since inception. Our net loss was $45.3 million and $40.5 million for the years ended December 31, 2021 and 2020, respectively. As of December 31, 2021, we had an accumulated deficit of $811.6 million. As we have no approved products, we have not generated any revenue from product sales to date, and we do not expect to generate any such revenue for the foreseeable future, if at all. We have instead relied on the proceeds from sales of equity securities, sales of future royalties, issuances of debt, interest on investments, up-front license fees, expense reimbursements, milestones, royalties and cost sharing under our collaborations to fund our operations. Because eganelisib is in clinical development and the outcome of our effort is uncertain, we cannot estimate the actual amounts necessary to successfully complete the development and commercialization of eganelisib or whether, or when, we may achieve profitability.

We expect to continue to spend significant resources to fund the development and potential commercialization of eganelisib. We expect to incur substantial operating losses over the next several years as our clinical trial and drug manufacturing activities increase. In addition, in connection with seeking and possibly obtaining regulatory approval of eganelisib or any future product candidates we may develop, we expect to incur significant commercialization expenses for product sales, marketing, manufacturing and distribution. As a result, we expect that our accumulated deficit will also increase significantly.

The following table summarizes the components of our financial condition:

	December 31, 2021	December 31, 2020
	(in thousands)	
Cash, cash equivalents and available-for-sale securities	$ 80,726	$ 34,108
Working capital	68,968	24,973

	Year Ended December 31,	
	2021	2020
	(in thousands)	
Cash (used in) provided by:		
Operating activities	$ (40,618)	$ (35,739)
Investing activities	5,489	14,631
Financing activities	87,105	27,441

Cash Flows

The principal use of cash in operating activities in all periods presented was related to our research and development programs. Our cash used in operating activities for the year ended December 31, 2021 increased compared to the year ended December 31, 2020 primarily due to increased operating expenses as we continue clinical development of eganelisib.

Our cash used in operating activities in future periods may vary significantly due to various factors, including potential cash inflows from future collaboration agreements and potential cash outflows for licensing new programs from third parties. We cannot be certain whether and when we may enter into any such collaboration agreements or license agreements.

Our cash provided by investing activities for the years ended December 31, 2021 and 2020 included purchases and proceeds from maturities of available-for-sale securities and purchases of property and equipment. Net cash provided by investing activities decreased for the year ended December 31, 2021 as compared to the year ended December 31, 2020 primarily due to net proceeds from maturities of available-for-sale securities of $5.5 million as compared to net proceeds from maturities and purchases of available-for-sale securities of $14.7 million for the year ended December 31, 2020.

Net cash provided by financing activities for the year ended December 31, 2021 included $85.8 million in net proceeds from our public offering in February 2021. Net cash provided by financing activities for the year ended December 31, 2020 included $19.6 million in net proceeds from the sale of future royalties in relation to the BVF Funding Agreement and net proceeds from our common stock sales facility of $7.7 million.

We will need substantial additional funds to support our planned operations. We believe that our existing cash and cash equivalents at December 31, 2021 will be adequate to satisfy our current operating plans for at least the next twelve months from the issuance of these financial statements. We do not expect to generate significant revenue from product sales unless and until we obtain regulatory approval of and commercialize one of our current or future product candidates. Until we can generate sufficient levels of cash from operations, and because sufficient funds may not be available to us when needed from collaborations, we expect that we will be required to continue to fund our operations in part through the sale of debt or equity securities or through licensing select programs or partial economic rights that include up-front, royalty and/or milestone payments. Our need to raise additional funds may be accelerated if our research and development expenses exceed our current expectations, if we acquire a third party, or if we acquire or license rights to additional product candidates or new technologies from one or more third parties. Our future funding requirements, both short-term and long-term, will depend on many factors, including, but not limited to:

- the scope, progress, results and costs of developing eganelisib, currently in clinical development;
- the impact of delays in patient enrollment and site activation, such as those related to the COVID-19 pandemic;
- the timing of, and the costs involved in, obtaining regulatory approvals for eganelisib;
- subject to receipt of marketing approval, revenue, if any, received from commercial sales of eganelisib;
- the timing and amount of additional revenues, if any, received from strategic agreements and funding arrangements
- the timing and amount of additional royalty and milestone payments owed to Takeda;
- the costs involved in preparing, filing, prosecuting, maintaining, defending and enforcing patent claims, including litigation costs and the outcome of such litigation;
- any breach, acceleration event or event of default under any agreements with third parties;
- the outcome of any lawsuits that could be brought against us;
- the cost of acquiring raw materials for, and of manufacturing, eganelisib is higher than anticipated;
- the cost or quantity required of comparator or combination drugs used in clinical studies increases;
- the effect of competing technological and market developments;
- any federal government shutdown that prevents or delays the U.S. Securities and Exchange Commission, or SEC, from processing any future registration statements we may file to register shares for capital raising purposes; and
- a loss in our investments due to general market conditions or other reasons.

Historically, we have relied on our collaborations for a significant portion of our research and development funding needs through upfront payments, milestones, royalties, and cost reimbursements.

As of December 31, 2021, we have received $348.0 million of net proceeds from our public stock offerings, including our common stock sales facility. This includes net proceeds of $85.8 million we received from our public stock offering in February 2021.

We may continue to seek additional funding through public or private financings of equity and/or debt securities, but such financings may not be available on acceptable terms, if at all. In addition, the terms of our financings may be dilutive to, or otherwise adversely affect, holders of our common stock, and such terms may impact our ability to make capital expenditures or incur additional debt.

We may also seek additional funds through arrangements with collaborators or other third parties, or through project financing. These arrangements would generally require us to relinquish or encumber rights to some of our technologies or product candidates, and we may not be able to enter into such agreements on acceptable terms, if at all. If we are unable to obtain additional funding on a timely basis, we may be required to curtail or terminate some or all of our development programs or to scale back, suspend or terminate our business operations.

Equity Offerings

On June 28, 2019, we entered into a Capital on Demand Sales Agreement with JonesTrading Institutional Services LLC, or JonesTrading, and on July 29, 2019 we amended and restated the sales agreement to add B. Riley FBR, Inc., or B. Riley FBR, as a party to the agreement. On July 27, 2021, we entered into an amendment to the agreement to increase the maximum aggregate offering price of the shares of common stock that we may issue and sell from time to time under the agreement by $75.0 million to an aggregate of $95.0 million. We refer to the amended and restated sales agreement, as amended, as the ATM Sales Agreement. As of December 31, 2021, we had an aggregate of $86.8 million available for future sales under the ATM Sales Agreement. Pursuant to the ATM Sales Agreement we may offer and sell shares of our common stock from time to time through JonesTrading or B. Riley FBR, each acting as our sales agent. We have agreed to pay commissions to the sales agents for their services in acting as agents in the sale of our common stock in the amount of up to 3.0% of the gross proceeds from sales of our common stock pursuant to the ATM Sales Agreement. Sales of shares of our common stock under the ATM Sales Agreement may be made in sales deemed to be "at the market offerings" as defined in Rule 415(a)(4) promulgated under the Securities Act of 1933, as amended. With our prior written approval, JonesTrading or B. Riley FBR may also sell the shares by any other method permitted by law, including in negotiated transactions. We and JonesTrading or B. Riley FBR may suspend or terminate the offering of shares upon notice to the other party and subject to other conditions. During the year ended December 31, 2021, we issued and sold 89,520 shares of common stock at a weighted average price per share of $3.83 at-the-market pursuant to the ATM Sales Agreement for $0.3 million in net proceeds. During the year ended December 31, 2020, we issued and sold 6,725,691 shares of common stock at a weighted average price per share of $1.17 at-the-market pursuant to the ATM Sales Agreement for $7.7 million in net proceeds.

On February 11, 2021, we entered into a purchase agreement with Piper Sandler & Co., as representative of the underwriters named therein, pursuant to which we issued and sold to the underwriters in an underwritten public offering an aggregate of 24,150,000 shares of our common stock, including 3,150,000 shares of common stock sold in connection with the exercise in full of a 15% over-allotment option by the underwriters. The public offering price was $3.80 per share. The gross proceeds to us from this offering were approximately $91.8 million. After underwriting discounts and commissions and offering expenses, we received net proceeds from the offering of approximately $85.8 million.

Inflation

We do not believe that inflation has had a significant impact on our revenues or results of operations since inception.

Item 7A. Quantitative and Qualitative Disclosures about Market Risk

Not applicable.

Item 8. Financial Statements and Supplementary Data

Report of Independent Registered Public Accounting Firm

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

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Infinity Pharmaceuticals, Inc. (the Company) as of December 31, 2021 and 2020, the related consolidated statements of operations and comprehensive loss, stockholders' equity and cash flows for each of the two years in the period ended December 31, 2021, 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, 2021 and 2020, and the results of its operations and its cash flows for each of the two years in the period ended December 31, 2021, in conformity with U.S. generally accepted accounting principles.

Basis for Opinion

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

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

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 account or disclosures to which it relates.

Accrued Clinical Expenses

Description of the Matter

The Company's accrual for clinical expenses totaled $5.0 million as of December 31, 2021. As discussed in Note 2 to the consolidated financial statements, the Company is required to estimate accruals for clinical expenses using judgment based on certain information, including actual costs incurred or level of effort expended, as provided by its vendors. Payments for such activities are based on the terms of the individual arrangements, which may differ from the pattern of costs incurred.

Auditing the Company's accrual for clinical expenses was complex and judgmental, as the amounts are based on various estimates from third-party vendors, including patient enrollment. Furthermore, due to the duration of the Company's ongoing clinical activities and the timing of invoicing received from third parties, the actual amounts incurred are not typically known by the date the financial statements are issued.

How We Addressed the Matter in Our Audit

To evaluate the accruals for clinical expenses, our audit procedures included, among others, testing the accuracy and completeness of the underlying data used in the estimates and evaluating the significant judgments and estimates noted above that are used by management to estimate the amounts recorded. We corroborated the progress of clinical activities through discussion with the Company's research and development personnel that oversee the clinical projects. We also inspected the Company's contracts with third parties and any pending change orders to assess the impact on amounts recorded. Additionally, we reviewed information received by the Company directly from certain sites and other third parties, which included third parties' estimates of costs incurred to date. We also performed analytical procedures over fluctuations in accruals by vendor, study, or other significant work orders throughout the period subject to audit and inspected subsequent invoices received from third parties to assess the impact to the accrual.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2001.
Boston, Massachusetts
March 29, 2022

INFINITY PHARMACEUTICALS, INC.

Consolidated Balance Sheets

(in thousands, except share and per share amounts)

	December 31,	
	2021	2020
Assets		
Current assets:		
Cash and cash equivalents	$ 80,726	$ 28,593
Available-for-sale securities	—	5,515
Prepaid expenses and other current assets	1,542	1,912
Total current assets	82,268	36,020
Property and equipment, net	1,241	1,710
Restricted cash, less current portion	158	165
Operating lease right-of-use assets	1,064	1,419
Other assets	54	5
Total assets	$ 84,785	$ 39,319
Liabilities and stockholders' equity (deficit)		
Current liabilities:		
Accounts payable	$ 2,320	$ 2,982
Accrued expenses and other current liabilities	10,980	8,065
Total current liabilities	13,300	11,047
Liabilities related to sale of future royalties, net, less current portion (Note 9)	48,727	28,021
Liability related to sale of future royalties to a related party, net (Note 9)	—	21,559
Operating lease liability, less current portion	917	1,436
Other liabilities	270	245
Total liabilities	63,214	62,308
Commitments and contingencies		
Stockholders' equity (deficit):		
Preferred Stock, $0.001 par value; 1,000,000 shares authorized, no shares issued and outstanding at December 31, 2021 and 2020	—	—
Common Stock, $0.001 par value; 200,000,000 shares authorized; 89,155,311 and 64,320,244 shares issued and outstanding at December 31, 2021 and 2020, respectively	89	64
Additional paid-in capital	833,065	743,269
Accumulated deficit	(811,583)	(766,321)
Accumulated other comprehensive income (loss)	—	(1)
Total stockholders' equity (deficit)	21,571	(22,989)
Total liabilities and stockholders' equity	$ 84,785	$ 39,319

The accompanying notes are an integral part of these consolidated financial statements.

INFINITY PHARMACEUTICALS, INC.

Consolidated Statements of Operations and Comprehensive Loss

(in thousands, except share and per share amounts)

	Years Ended December 31,	
	2021	2020
Royalty revenue	$ 1,858	$ 1,719
Operating expenses:		
Research and development	31,647	26,761
General and administrative	14,174	12,418
Royalty expense (Note 11)	1,120	1,037
Total operating expenses	46,941	40,216
Loss from operations	(45,083)	(38,497)
Other income (expense):		
Investment and other income	1	450
Non-cash interest expense (Note 9)	(180)	(153)
Non-cash related party interest expense (Note 9)	—	(2,292)
Total other expense	(179)	(1,995)
Net loss	$ (45,262)	$ (40,492)
Basic and diluted loss per common share	$ (0.53)	$ (0.68)
Basic and diluted weighted average number of common shares outstanding	85,597,264	59,857,860
Other comprehensive loss:		
Net unrealized holding gains (losses) on available-for-sale securities arising during the period	$ 1	$ (13)
Comprehensive loss	$ (45,261)	$ (40,505)

The accompanying notes are an integral part of these consolidated financial statements.

INFINITY PHARMACEUTICALS, INC.

Consolidated Statements of Cash Flows

(in thousands)

	Years Ended December 31,	
	2021	**2020**
Operating activities		
Net loss	$ (45,262)	$ (40,492)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation	480	483
Stock-based compensation	2,695	1,456
Non-cash royalty revenue	(984)	(910)
Non-cash interest expense	180	153
Non-cash related party interest expense	—	2,292
Other, net	59	(106)
Changes in operating assets and liabilities:		
Prepaid expenses and other assets	171	585
Operating lease right-of-use asset	355	298
Accounts payable, accrued expenses and other liabilities	2,177	882
Operating lease liability	(489)	(380)
Net cash used in operating activities	(40,618)	(35,739)
Investing activities		
Purchases of property and equipment	(11)	(43)
Purchases of available-for-sale securities	—	(43,006)
Proceeds from maturities of available-for-sale securities	5,500	57,680
Net cash provided by investing activities	5,489	14,631
Financing activities		
Proceeds from public offering, net	85,838	—
Proceeds from sale of future royalties to a related party, net	—	19,572
Proceeds from common stock sales facility, net of issuance costs	336	7,711
Proceeds from issuances of common stock, net	931	158
Net cash provided by financing activities	87,105	27,441
Net increase in cash, cash equivalents and restricted cash	51,976	6,333
Cash, cash equivalents and restricted cash at beginning of period	28,908	22,575
Cash, cash equivalents and restricted cash at end of period	$ 80,884	$ 28,908
Reconciliation of cash, cash equivalents, and restricted cash to the consolidated balance sheets		
Cash and cash equivalents	80,726	28,593
Prepaid expenses and other current assets	—	150
Restricted cash, less current portion	158	165
Total cash, cash equivalents and restricted cash	$ 80,884	$ 28,908
Supplemental schedule of noncash activities		
Issuance of common stock for compensation	$ —	$ 444

The accompanying notes are an integral part of these consolidated financial statements.

INFINITY PHARMACEUTICALS, INC.

Consolidated Statements of Stockholders' Equity

(in thousands, except share amounts)

	Common Stock		Additional Paid-in Capital	Accumulated Deficit	Accumulated Other Comprehensive Income (Loss)	Total Stockholders' Equity
	Shares	Amount				
Balance at December 31, 2019	57,077,550	$ 57	$ 733,486	$ (725,829)	$ 12	$ 7,726
Exercise of stock options	46,433		85			85
Stock-based compensation expense			1,456			1,456
Issuance of common stock related to sales facility, net of issuance costs	6,725,691	7	7,704			7,711
Issuance of common stock, net	470,570		538			538
Unrealized loss on marketable securities					(13)	(13)
Net loss				(40,492)		(40,492)
Balance at December 31, 2020	64,320,244	$ 64	$ 743,269	$ (766,321)	$ (1)	$ (22,989)
Exercise of stock options	531,864	1	859			860
Stock-based compensation expense			2,695			2,695
Issuance of common stock related to public offering, net of issuance costs	24,150,000	24	85,814			85,838
Issuance of common stock related to sales facility, net of issuance costs	89,520		336			336
Issuance of common stock, net	63,683		92			92
Unrealized gain on marketable securities					1	1
Net loss				(45,262)		(45,262)
Balance at December 31, 2021	89,155,311	$ 89	$ 833,065	$ (811,583)	$ —	$ 21,571

The accompanying notes are an integral part of these consolidated financial statements.

1. Organization

Infinity Pharmaceuticals, Inc., is a clinical-stage innovative biopharmaceutical company dedicated to developing novel medicines for people with cancer. As used throughout these audited, consolidated financial statements, the terms "Infinity," "we," "us," and "our" refer to the business of Infinity Pharmaceuticals, Inc., and its wholly owned subsidiaries.

2. Summary of Significant Accounting Policies

Basis of Presentation

These consolidated financial statements include the accounts of Infinity and its wholly owned subsidiaries. We have eliminated all significant intercompany accounts and transactions in consolidation.

The preparation of consolidated financial statements in accordance with generally accepted accounting principles requires our management to make estimates and judgments that may affect the reported amounts of assets, liabilities, revenues and expenses, and related disclosure of contingent assets and liabilities. On an ongoing basis, we evaluate our estimates and judgments. We base our estimates on historical experience and on various other assumptions that are believed to be reasonable, the results of which form the basis for making judgments about the carrying values of assets and liabilities. Actual results may differ from these estimates under different assumptions or conditions.

Segment Information

We operate in one business segment, which focuses on drug development. We make operating decisions based upon the performance of the enterprise as a whole and utilize our consolidated financial statements for decision making.

Cash Equivalents and Available-For-Sale Securities

Cash equivalents and available-for-sale securities primarily consist of money market funds and U.S. Treasury securities. We consider all highly liquid investments with maturities of three months or less at the time of purchase to be cash equivalents. Cash equivalents, which consist of money market funds and U.S. Treasury securities, are stated at fair value. They are also readily convertible to known amounts of cash and have such short-term maturities that each presents insignificant risk of change in value due to changes in interest rates. Our classification of cash equivalents is consistent with prior periods.

We determine the appropriate classification of marketable securities at the time of purchase and reevaluate such designation at each balance sheet date. We have classified all of our marketable securities at December 31, 2021 and 2020 as "available-for-sale." We carry available-for-sale securities at fair value. Unrealized gains and losses on available-for-sale debt securities are reported in accumulated other comprehensive income (loss), which is a separate component of stockholders' equity.

We adjust the cost of available-for-sale debt securities for amortization of premiums and accretion of discounts to maturity. We include such amortization and accretion in investment and other income. The cost of securities sold is based on the specific identification method. We include in investment income interest and dividends on securities classified as available-for-sale.

We conduct periodic reviews to identify and evaluate each available-for-sale debt security that is in an unrealized loss position in order to determine whether an other-than-temporary impairment exists. An unrealized loss exists when the current fair value of an individual security is less than its amortized cost basis. For available-for-sale debt securities in an unrealized loss position, we perform an analysis to assess whether we intend to sell or whether we would more likely than not be required to sell the security before the expected recovery of the amortized cost basis. Where we intend to sell a security, or may be required to do so, the security's decline in fair value is deemed to be other-than-temporary, and the full amount of the unrealized loss is recorded within earnings as an impairment loss. Unrealized losses on available-for-sale debt securities that are determined to be temporary, and not related to credit loss, are recorded, net of tax, in accumulated other comprehensive loss.

Regardless of our intent to sell a security, we perform additional analysis on all securities in an unrealized loss position to evaluate losses associated with the creditworthiness of the security. Credit losses are identified where we do not expect to receive cash flows sufficient to recover the amortized cost basis of a security and are recorded within earnings as an impairment loss.

Liquidity

As of December 31, 2021, our cash and cash equivalents balance was $80.7 million. We have primarily incurred operating losses since inception and have relied on our ability to fund our operations through collaboration and license arrangements, or other strategic arrangements, and through the sale of stock.

We expect to continue to spend significant resources to fund the development and potential commercialization of eganelisib, also known as IPI-549, an orally administered immuno-oncology product candidate that selectively inhibits the enzyme phosphoinositide-3 kinase gamma, or PI3K gamma, and to incur significant operating losses for the foreseeable future.

We believe that our existing cash and cash equivalents at December 31, 2021 will be adequate to satisfy our current operating plans for at least the next twelve months from the issuance date of these financial statements.

Concentration of Credit Risk

Cash and cash equivalents are primarily maintained with two major financial institutions in the United States. Deposits at banks may exceed the insurance provided on such deposits. Generally, these deposits may be redeemed upon demand and, therefore, bear minimal risk. Financial instruments that potentially subject us to concentration of credit risk primarily consist of available-for-sale securities. Available-for-sale securities consist of U.S. Treasury securities. Our investment policy, which has been approved by our Board of Directors, limits the amount that we may invest in any one issuer of investments, thereby reducing credit risk concentrations.

Property and Equipment

Property and equipment are stated at cost. Depreciation is recorded using the straight-line method over the estimated useful lives of the applicable assets. Application development costs incurred for computer software developed or obtained for internal use are capitalized. Upon sale or retirement, the cost and related accumulated depreciation are eliminated from the respective account, and the resulting gain or loss, if any, is included in current operations. Amortization of leasehold improvements, building improvements and finance leases is recorded as depreciation expense and included in research and development and general and administrative expense, as applicable. Repairs and maintenance charges that do not increase the useful life of the assets are charged to operations as incurred. Property and equipment are depreciated over the following periods:

Computer equipment and software	3 to 5 years
Leasehold improvements	Shorter of lease term or useful life of asset
Furniture and fixtures	7 to 10 years

Impairment of Long-Lived Assets

We evaluate our long-lived assets for potential impairment. Potential impairment is assessed when there is evidence that events or changes in circumstances have occurred that indicate that the carrying amount of a long-lived asset may not be recovered. Recoverability of these assets is assessed based on undiscounted expected future cash flows from the assets, considering a number of factors, including past operating results, budgets and economic projections, market trends and product development cycles. An impairment in the carrying value of each asset is assessed when the undiscounted expected future cash flows, including its eventual residual value, derived from the asset are less than its carrying value. Impairments, if any, are recognized in earnings. An impairment loss would be recognized in an amount equal to the excess of the carrying amount over the undiscounted expected future cash flows.

Fair Value Measurements

We define fair value as the price that we would receive to sell an asset or paid to transfer a liability in an orderly transaction between market participants at the measurement date. We determine fair value based on the assumptions market participants use when pricing the asset or liability. We use a valuation hierarchy for disclosure of the inputs used to measure fair value. This hierarchy prioritizes the inputs into three broad levels. Level 1 inputs, which we consider the highest level inputs, are quoted prices (unadjusted) in active markets for identical assets or liabilities. Level 2 inputs are quoted prices for similar assets and liabilities in active markets or inputs that are observable for the asset or liability, either directly or indirectly through market corroboration, for substantially the full term of the financial instrument. Level 3 inputs are unobservable inputs based on our own assumptions used to measure assets and liabilities at fair value. The classification of a financial asset or liability within the hierarchy is determined based on the lowest level input that is significant to the fair value measurement.

We value our available-for-sale securities utilizing third-party pricing services. The pricing services use many observable market inputs to determine value, including benchmark yields, reportable trades, broker/dealer quotes, issuer spreads, two-sided markets, benchmark securities, bids, offers, reference data, new issue data, monthly payment information and collateral performance. We validate the prices provided by our third-party pricing services by understanding the models used, obtaining market values from other pricing sources and confirming that those securities trade in active markets.

Liabilities Related to Sale of Future Royalties

We treat the liabilities related to sale of future royalties (see Note 9) as debt financings, amortized under the effective interest rate method over the estimated life of the related expected royalty stream. The liabilities related to sale of future royalties and the debt amortization are based on our current estimates of future royalties expected to be paid over the life of the arrangement. We will periodically assess the expected royalty payments using projections from external sources. To the extent our estimates of future royalty payments are greater or less than previous estimates or the estimated timing of such payments is materially different than previous estimates, we will adjust the effective interest rate and recognize related non-cash interest expense on a prospective basis. Non-cash royalty revenue is reflected as royalty revenue, and non-cash amortization of debt is reflected as interest expense in the Consolidated Statements of Operations and Comprehensive Loss.

Leases

We have entered into leases for office space and a data center. As of January 1, 2019, we adopted the provisions of Accounting Standards Codification, or ASC, Topic 842, Leases, or ASC 842. Accordingly, we recorded a right-of-use asset and a corresponding lease liability related to our leases. Rights and obligations related to our leases are included within operating lease right-of-use assets, accrued expenses and other current liabilities, and operating lease liability, less current portion in the Consolidated Balance Sheets.

We recognize a right-of-use asset and a lease liability upon the commencement of a lease that has a term of more than twelve months. We combine lease and nonlease components for our leases. Lease payments included in determining the right-of-use asset and lease liability recognized include fixed payments to be paid over the term of the lease, less any lease incentives to be paid or payable to us by the lessor. Variable lease payments are included if they are based on an index or rate. Variable lease payments that are not based on an index or rate are recognized as expense in the period incurred. The lease term is determined at lease commencement, and includes the noncancellable period during which we have the right to use the underlying asset. Any period covered by an option to extend or terminate a lease is also included in the lease term if we are reasonably certain that the option to extend will be exercised or the option to terminate will not be exercised.

Our leases do not provide an implicit rate; therefore, we use an estimate of our incremental borrowing rate based on the information available at the adoption date or lease commencement date in determining the present value of lease payments.

Revenue Recognition

To date, all our revenue has been generated under collaboration agreements, including payments to us of upfront license fees, funding or reimbursement of research and development efforts, milestone payments, if specified objectives are achieved, and royalties on product sales.

We recognize revenue when we transfer goods or services to customers in an amount that reflects the consideration that we expect to receive for those goods or services. These principles are applied using a five-step model: 1) identify the customer contract; 2) identify the contract's performance obligations; 3) determine the transaction price; 4) allocate the transaction price to the performance obligations; and 5) recognize revenue when or as a performance obligation is satisfied. We evaluate all promised goods and services within a customer contract and determine which of those are separate performance obligations. This evaluation includes an assessment of whether the good or service is capable of being distinct and whether the good or service is separable from other promises in the contract. When a performance obligation is satisfied, we recognize as revenue the amount of the transaction price, excluding estimates of variable consideration that are constrained, that is allocated to that performance obligation. For contracts that contain variable consideration, such as milestone payments, we estimate the amount of variable consideration by using either the expected value method or the most likely amount method. In making this assessment, we evaluate factors such as the clinical, regulatory, commercial and other risks that must be overcome to achieve the milestone. Each reporting period we re-evaluate the probability of achievement of such milestones and any related constraints. We will include variable consideration, without constraint, in the transaction price to the extent it is probable that a significant reversal in the amount of cumulative revenue recognized will not occur when the uncertainty associated with the variable consideration is subsequently resolved.

We recognize sales-based milestones and royalty revenue based upon net sales by the licensee of licensed products in licensed territories, and in the period the sales occur under the sales- and usage-based royalty exception when the sole or predominate item to which the royalty relates is a license to intellectual property.

In the event of an early termination of a collaboration agreement, any contract liabilities would be recognized in the period in which all our obligations under the agreement have been fulfilled.

Research and Development Expense

Research and development expense consists of expenses incurred in performing research and development activities, including salaries and benefits, overhead expenses including facilities expenses, materials and supplies, preclinical expenses, clinical trial and related clinical manufacturing expenses, comparator and combination drug expenses, stock-based compensation expense, depreciation of property and equipment, contract services, and other outside expenses. We also include as research and development expense upfront license payments related to acquired technologies which have not yet reached technological feasibility and have no alternative use. We expense research and development costs as they are incurred. Prepaid comparator and combination drug expenses are capitalized and then recognized as expense when title transfers to us. We have been a party to collaboration agreements in which we were reimbursed for work performed on behalf of the collaborator, as well as one in which we reimbursed the collaborator for work it had performed. We record all appropriate expenses under our collaborations as research and development expense. If the arrangement provides for reimbursement of research and development expenses incurred by us, we evaluate the terms of the arrangement to determine whether the reimbursement should be recorded as revenue or as an offset to research and development expense. If the arrangement provides for us to reimburse the collaborator for research and development expenses or for the achievement of a development milestone for which a payment is due, we record the reimbursement or the achievement of the development milestone as research and development expense.

Stock-based Compensation Expense

For awards granted to employees, directors, non-employees, and awards granted under our 2013 Employee Stock Purchase Plan, or ESPP, we measure stock-based compensation cost at the grant date based on the estimated fair value of the award and recognize it as expense over the requisite service period on a straight-line basis. Stock-based compensation costs for non-employees are recognized as expense over the vesting period on a ratable basis. We use the Black-Scholes valuation model in determining the fair value of all equity awards. For awards with performance conditions, we estimate the likelihood of satisfaction of the performance conditions, which affects the period over which the expense is recognized. When the performance conditions related to these awards are determined to be probable, we recognize the expense over the requisite service period. We have no awards with market conditions.

Royalty Expense

Royalty expense is recorded when incurred and represents the expense associated with amounts owed to third parties as a result of royalty revenue recognized and the amounts owed by us to Takeda Pharmaceutical Company Limited, or Takeda, in relation to sale of future royalties (see Note 11).

Income Taxes

We use the liability method to account for income taxes. Deferred tax assets and liabilities are determined based on differences between financial reporting and income tax basis of assets and liabilities, as well as net operating loss and tax credit carryforwards, and are measured using the enacted tax rates and laws that will be in effect when the differences reverse. Deferred tax assets are reduced by a valuation allowance to reflect the uncertainty associated with their ultimate realization. The effect of a change in tax rate on deferred taxes is recognized in income or loss in the period that includes the enactment date.

We use our judgment for the financial statement recognition and measurement of a tax position taken or expected to be taken in a tax return. We recognize any material interest and penalties related to unrecognized tax benefits in income tax expense.

Due to the uncertainty surrounding the realization of the net deferred tax assets in future periods, we have recorded a full valuation allowance against our otherwise recognizable net deferred tax assets as of December 31, 2021 and 2020.

Basic and Diluted Net Loss per Common Share

Basic net loss per share is based upon the weighted average number of common shares outstanding during the period, excluding restricted stock that has been issued but has not yet vested. Diluted net loss per share is based upon the weighted average number of common shares outstanding during the period plus the effect of additional weighted average common equivalent shares outstanding during the period when the effect of adding such shares is dilutive. Common equivalent shares result from the assumed exercise of outstanding stock options and the exercise of outstanding warrants (the proceeds of which are then assumed to have been used to repurchase outstanding stock using the treasury stock method) and the vesting of restricted shares of common stock. In addition, the assumed proceeds under the treasury stock method include the average unrecognized compensation expense of stock options that are in-the-money. This results in the "assumed" buyback of additional shares, thereby reducing the dilutive impact of stock options. The two-class method is used for outstanding warrants as such warrants are considered to be participating securities, and this method is more dilutive than the treasury stock method. The following outstanding shares of common stock equivalents were excluded from the computation of net loss per share attributable to common stockholders for the periods presented because including them would have been antidilutive:

	At December 31,	
	2021	2020
Stock options	12,689,439	12,664,664
Unvested restricted stock	50,000	—
Warrants (excluded from treasury stock method)	—	1,000,000

Comprehensive Loss

Comprehensive loss is comprised of net loss and other comprehensive loss. Other comprehensive loss is comprised of unrealized holding gains and losses arising during the period on available-for-sale securities that are not other-than-temporarily impaired. During the year ended December 31, 2021, there were no material reclassifications out of accumulated other comprehensive loss.

New Accounting Pronouncements

In June 2016, the Financial Accounting Standards Board, or FASB, issued Accounting Standard Update, or ASU, No. 2016-13, *Financial Instruments – Credit Losses (Topic 326): Measurement of Credit Losses on Financial Statements*, or ASU No. 2016-13, which requires that credit losses be reported using an expected losses model rather than the incurred losses model that is currently used, and it establishes additional disclosure requirements related to credit risks. For available-for-sale debt securities with expected credit losses, this standard now requires allowances to be recorded instead of reducing the amortized cost of the investment. In November 2019, the FASB subsequently issued ASU 2019-10, *Financial Instruments—Credit Losses (Topic 326), Derivatives and Hedging (Topic 815), and Leases (Topic 842): Effective Dates*, whereby the effective date of this standard for smaller reporting companies was deferred to annual reporting periods beginning after December 15, 2022, including interim periods within those annual reporting periods, and early adoption is still permitted. We are currently evaluating the impact of ASU No. 2016-13 on our consolidated financial statements and related disclosures.

In August 2020, the FASB issued ASU No. 2020-06, *Debt—Debt with Conversion and Other Options (Subtopic 470-20) and Derivatives and Hedging—Contracts in Entity's Own Equity (Subtopic 815-40): Accounting for Convertible Instruments and Contracts in an Entity's Own Equity*, or ASU No. 2020-06, which simplifies the guidance on an issuer's accounting for convertible instruments and contracts in its own equity. The provisions of ASU No. 2020-06 are applicable for fiscal years beginning after December 15, 2023, with early adoption permitted no earlier than fiscal years beginning after December 15, 2020. We are currently evaluating the impact of ASU No. 2020-06 on our consolidated financial statements.

In November 2021, the FASB issued ASU No. 2021-10, *Government Assistance (Topic 832): Disclosures by Business Entities about Government Assistance*, or ASU No. 2021-10, which requires additional annual disclosures about transactions with a government that are accounted for by applying a grant or contribution accounting model by analogy. The additional disclosures required by this standard include 1) information about the nature of the transactions and the related accounting policy used to account for the transactions, 2) the financial statement line items that are impacted by the transactions and the amounts applicable to each financial statement line item and 3) significant terms and conditions of the transactions, including commitments and contingencies. ASU No. 2021-10 is effective for annual periods beginning after December 15, 2021, with early adoption permitted. We are currently evaluating the impact of ASU No. 2021-10 on our consolidated financial statements and related disclosures.

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 No. 2018-15, which aligns the requirements for capitalizing implementation costs incurred in a hosting arrangement that is a service contract with the requirements for capitalizing implementation costs incurred to develop or obtain internal-use software. We adopted this standard effective January 1, 2020 on a prospective basis. The adoption of the standard has not had a material impact on our consolidated financial statements.

3. Stock-Based Compensation

Under each of the stock incentive plans described below, stock option awards made to new employees upon commencement of employment typically provide for vesting of 25% of the shares underlying the award at the end of the first year of service with the remaining 75% of the shares underlying the award vesting ratably on a monthly basis over the following three-year period subject to continued service. Annual grants to existing employees typically provide for ratable vesting over specified periods determined by the Board of Directors. In addition, under each plan, all options granted expire no later than ten years after the date of grant.

2019 Equity Incentive Plan

Our 2019 Equity Incentive Plan, or the 2019 Plan, was approved by our stockholders in June 2019. The 2019 Plan provides for the grant of incentive stock options intended to qualify under Section 422 of the Internal Revenue Code of 1986, as amended, or IRC, as well as nonstatutory stock options, stock appreciation rights, restricted stock, restricted stock units and other stock-based and cash-based awards. Up to 6,031,009 shares of our common stock may be issued pursuant to awards granted under the 2019 Plan, plus an additional amount of our common stock underlying awards issued under the 2010 Stock Incentive Plan, or the 2010 Plan, that expire or are canceled without the holders receiving any shares under those awards. As of December 31, 2021, an aggregate of 5,226,973 shares of our common stock were reserved for issuance upon the exercise of outstanding awards, and up to 2,069,146 shares of common stock may be issued pursuant to awards granted under the 2019 Plan.

2010 Stock Incentive Plan

The 2010 Plan provided for the grant of incentive stock options under the IRC, as well as nonstatutory stock options, stock appreciation rights, restricted stock, restricted stock units and other stock-based and cash-based awards. As of December 31, 2021, an aggregate of 6,912,466 shares of our common stock were reserved for issuance upon the exercise of outstanding awards granted under the 2010 Plan. The 2010 Plan was terminated upon approval of the 2019 Plan; therefore, no further grants may be made under the 2010 Plan.

2013 Employee Stock Purchase Plan

Our ESPP permits eligible employees to purchase shares of our common stock at a discount and consists of consecutive, overlapping 24-month offering periods, each consisting of four six-month purchase periods. On the first day of each offering period, each employee who is enrolled in the ESPP will automatically receive an option to purchase up to a whole number of shares of our common stock. The purchase price of each of the shares purchased, in a given purchase period, will be 85% of the closing price of a share of our common stock, on the first day of the offering period or the last day of the purchase period, whichever is lower. During the year ended December 31, 2021, 57,561 shares of common stock were purchased for total proceeds of approximately $0.1 million. During the year ended December 31, 2020, 91,696 shares of common stock were purchased for total proceeds of approximately $0.1 million.

Compensation Expense

Total stock-based compensation expense, related to all equity awards, comprised the following:

	Year Ended December 31,	
	2021	2020
	(in thousands)	
Research and development	$ 830	$ 383
General and administrative	1,865	1,073
Total stock-based compensation expense	$ 2,695	$ 1,456

As of December 31, 2021, we had approximately $5.6 million of total unrecognized compensation cost related to unvested common stock options and awards under our ESPP, which are expected to be recognized over a weighted-average period of 2.7 years.

Stock Options

Valuation Assumptions

We estimate the fair value of stock options at the date of grant using the Black-Scholes valuation model with the following weighted-average assumptions:

	December 31,	
	2021	2020
Risk-free interest rate	0.9 %	1.0 %
Expected annual dividend yield	—	—
Expected stock price volatility	106.3 %	98.3 %
Expected term of options	5.9 years	5.7 years

The valuation assumptions were determined as follows:

- *Risk-free interest rate:* The yield on zero-coupon U.S. Treasury securities for a period that was commensurate with the expected term of the awards.
- *Expected annual dividend yield:* The estimate for annual dividends was zero because we have not historically paid a dividend and do not intend to do so in the foreseeable future.
- *Expected stock price volatility:* We determined the expected volatility by using our available implied and historical price information.
- *Expected term of options:* The expected term of the awards represents the period of time that the awards were expected to be outstanding. We use the simplified method to estimate expected term, whereby, the expected life equals the average of the vesting term and the original contractual term of the option.

We recognize forfeitures related to employee share-based payments as they occur.

A summary of our stock option activity for the year ended December 31, 2021 is as follows:

	Stock Options	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Life (years)	Aggregate Intrinsic Value (in millions)
Outstanding at January 1, 2021	12,664,664	$ 3.51		
Granted	999,040	3.32		
Exercised	(531,864)	1.62		
Forfeited	(221,708)	1.87		
Expired	(220,693)	7.50		
Outstanding at December 31, 2021	12,689,439	$ 3.53	6.4	$ 7.0
Exercisable at December 31, 2021	9,076,912	$ 4.15	5.6	$ 5.2

The weighted-average fair value per share of options granted during the years ended December 31, 2021 and 2020 was $2.69 and $1.15, respectively.

The aggregate intrinsic value of options outstanding at December 31, 2021 was calculated based on the positive difference, if any, between the closing fair market value of our common stock on December 31, 2021 and the exercise price of the underlying options.

The aggregate intrinsic value of options exercised during the year ended December 31, 2021 was $0.8 million.

No related income tax benefits were recorded during the years ended December 31, 2021 or 2020.

We settle employee stock option exercises with newly issued shares of our common stock.

4. Cash, Cash Equivalents and Available-for-Sale Securities

The following is a summary of cash, cash equivalents and available-for-sale securities:

	December 31, 2021			
	Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
	(in thousands)			
Cash and cash equivalents	$ 80,726	$ —	$ —	$ 80,726
Total cash and cash equivalents	$ 80,726	$ —	$ —	$ 80,726

	December 31, 2020			
	Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
	(in thousands)			
Cash and cash equivalents	$ 28,593	$ —	$ —	$ 28,593
Available-for-sale securities:				
U.S. Treasury securities due in one year or less	5,516	—	(1)	5,515
Total available-for-sale securities	5,516	—	(1)	5,515
Total cash, cash equivalents and available-for-sale securities	$ 34,109	$ —	$ (1)	$ 34,108

We evaluated our securities for other-than-temporary impairments based on quantitative and qualitative factors as of December 31, 2020. As of December 31, 2021, we did not hold any securities in an unrealized loss position.

We had no material realized gains or losses on our available-for-sale securities for the years ended December 31, 2021 and 2020. There were no other-than-temporary impairments recognized for the years ended December 31, 2021 and 2020.

5. Fair Value

The following table provides the assets and liabilities carried at fair value measured on a recurring basis as of December 31, 2021 and 2020:

	December 31, 2021		
	Level 1	Level 2	Level 3
		(in thousands)	
Assets:			
Cash and cash equivalents	$ 80,726	$ —	$ —
Total assets	$ 80,726	$ —	$ —
Liabilities:			
Warrant liability	$ —	$ —	$ 220
Total liabilities	$ —	$ —	$ 220

	December 31, 2020		
	Level 1	Level 2	Level 3
		(in thousands)	
Assets:			
Cash and cash equivalents	$ 28,593	$ —	$ —
U.S. Treasury securities	—	5,515	—
Total assets	$ 28,593	$ 5,515	$ —
Liabilities:			
Warrant liability	$ —	$ —	$ 198
Total liabilities	$ —	$ —	$ 198

The fair value of the available-for-sale securities and cash and cash equivalents is based on the following inputs for U.S. Treasury securities: benchmark yields, reported trades, broker/dealer quotes, issuer spreads, two-sided markets, benchmark securities, bids, offers and reference data including TRACE® reported trades.

There have been no changes to our valuation methods during the year ended December 31, 2021. We had no available-for-sale securities that were classified as Level 3 at any point during the year ended December 31, 2021.

Warrant liability relates to potential future warrants that may be issued. The fair value of the warrant liability on the date of the commitment and on each re-measurement date for those warrants classified as liabilities was estimated using the Monte Carlo simulation model, which involves a series of simulated future stock price paths over the remaining life of the commitment. The fair value is estimated by taking the average of the fair values under each of many Monte Carlo simulations. The fair value estimate is affected by our stock price, as well as estimated future financing needs, including timing and sources of the financing and subjective variables including expected stock price volatility over the remaining life of the commitment and risk-free interest rate. Due to the nature of these inputs, the valuation of the warrants is considered a Level 3 measurement. The fair value of the warrant liability as of December 31, 2021 and December 31, 2020 has been included in other liabilities on our consolidated balance sheet. See Note 9 for further discussions of the accounting for the warrants.

The carrying amounts reflected in the consolidated balance sheets for prepaid expenses and other current assets, other assets, accounts payable and accrued expenses and other current liabilities approximate their fair value due to their short-term maturities.

6. Prepaid Expenses and Other Current Assets

Prepaid expenses and other current assets consist of the following:

	December 31,	
	2021	2020
	(in thousands)	
Prepaid expenses	$ 1,143	$ 1,528
Other current assets	399	234
Restricted cash, current portion	—	150
Total prepaid expenses and other current assets	$ 1,542	$ 1,912

7. Property and Equipment

Property and equipment consist of the following:

	December 31,	
	2021	2020
	(in thousands)	
Computer equipment and software	$ 1,904	$ 1,893
Furniture and fixtures	446	446
Leasehold improvements	1,743	1,743
	4,093	4,082
Less accumulated depreciation	(2,852)	(2,372)
	$ 1,241	$ 1,710

8. Accrued Expenses and Other Current Liabilities

Accrued expenses and other current liabilities consisted of the following:

	December 31,	
	2021	2020
	(in thousands)	
Accrued clinical	$ 4,998	$ 3,168
Accrued compensation and benefits	2,835	2,385
Accrued development	755	343
Liability related to sale of future royalties, net, current portion	897	848
Operating lease liability, current portion	519	489
Other	976	832
Total accrued expenses	$ 10,980	$ 8,065

9. Liabilities Related to Sale of Future Royalties

HCR Agreement

In 2016, we and Verastem Inc., or Verastem, entered into an amended and restated license agreement, or the Verastem Agreement, under which we granted to Verastem an exclusive worldwide license in oncology indications for the research, development, commercialization, and manufacture of duvelisib, or Copiktra®, an oral, dual inhibitor of PI3K delta and gamma, and products containing duvelisib, which we refer to as Licensed Products. In September 2020, Verastem completed a disposition of its rights, title, and interest in and to duvelisib to Secura Bio, Inc., or Secura Bio, whereby Secura Bio assumed all liabilities and obligations under the Verastem Agreement. We now refer to the Verastem Agreement as the Secura Bio Agreement.

Secura Bio is obligated to pay us royalties on worldwide net sales of Licensed Products ranging from the mid-single digits to the high-single digits, a portion of which we are obligated to share with Takeda Pharmaceuticals Company Limited, or Takeda, as described in Note 11.

In March 2019, we entered into a royalty purchase agreement, or the HCR Agreement, with HealthCare Royalty Partners III, L.P., or HCR, providing for the acquisition by HCR of our interest in certain royalty payments based on worldwide annual net sales of Licensed Products under the Secura Bio Agreement for gross proceeds of $30.0 million, which is non-refundable. After sharing with Takeda in accordance with the Takeda Amendment, as defined in Note 11, we retained $22.5 million in gross proceeds, or approximately $20.9 million in net proceeds. Under the HCR Agreement, HCR obtained the right to receive the royalty payments up to agreed upon thresholds of royalties, the amount of which depends on when the aggregate royalties received by HCR reach specified thresholds. If the specified threshold has been met through royalty payments from Secura Bio or if we elect to make a payment to meet the threshold amount, the HCR Agreement will automatically terminate and all rights to the royalty stream under the HCR Agreement will revert back to us. If the specified threshold has not been achieved by June 30, 2025, the HCR Agreement will continue through the term of the Secura Bio Agreement.

We recognized the receipt of the $30.0 million payment from HCR as a liability, net of debt discount and issuance costs of approximately $2.4 million. As the basis for our determination, we considered, in accordance with the relevant accounting guidance, the potential for the royalty stream to revert back to us if specified royalty thresholds have been met and our right to terminate the HCR Agreement by making a payment to achieve the threshold. We are not obligated to repay any of the proceeds received under the HCR Agreement. In order to determine the amortization of the liability, we are required to estimate the total amount of future net royalty payments to be made to HCR over the term of the HCR Agreement. The total threshold of net royalties to be paid, less the net proceeds received, will be recorded as interest expense over the life of the liability. We impute interest on the unamortized portion of the liability using the effective interest method. Interest and debt discount amortization expense is reflected as non-cash interest expense in the Consolidated Statements of Operations and Comprehensive Loss. Over the course of the HCR Agreement, the actual interest rate will be affected by the amount and timing of royalty revenue recognized and changes in forecasted royalty revenue. On a quarterly basis, we reassess the effective interest rate and adjust the rate prospectively as needed.

The following table shows the activity within the liability account for the years ended December 31, 2021 and 2020:

	December 31,	
	2021	2020
	(in thousands)	
Liability related to sale of future royalties - beginning balance	$ 28,869	$ 29,626
Non-cash royalty revenue	(984)	(910)
Non-cash interest expense recognized	153	153
Liability related to sale of future royalties, net - ending balance	$ 28,038	$ 28,869
Less: current portion	(897)	(848)
Liability related to sale of future royalties, net, less current portion	$ 27,141	$ 28,021

As royalties are due to HCR by Secura Bio, the balance of the recognized liability will be effectively repaid over the life of the HCR Agreement. There are a number of factors that could materially affect the amount and timing of royalty payments from Secura Bio, none of which are within our control.

BVF Agreement

On January 8, 2020, or the BVF Closing Date, we entered into a funding agreement, or the BVF Funding Agreement, with BVF Partners, L.P., or BVF, and Royalty Security, LLC, a wholly owned subsidiary of BVF, or the Buyer. BVF was subsequently replaced as a party to the BVF Funding Agreement with Royalty Security Holdings, LLC. The BVF Funding Agreement provides for the acquisition by the Buyer of our interest in all royalty payments based on worldwide annual net sales of a clinical-stage product candidate IPI-926, or patidegib, part of the hedgehog inhibitor program we licensed to PellePharm Inc., or PellePharm, in 2013, or the BVF Licensed Product, excluding relevant Trailing Mundipharma Royalties, as defined in Note 11, which is related to patidegib. We refer to all BVF Licensed Product royalties owed to us less Trailing Mundipharma Royalties as the Royalty or Royalties. Such Royalties are owed to us pursuant to the PellePharm Agreement, as defined in Note 11, entered into by and between us and PellePharm. The Buyer and BVF are affiliates of Biotechnology Value Fund, L.P., which beneficially owned approximately 30% of our common stock at the time of the transaction. Effective February 17, 2021, Biotechnology Value Fund, L.P. is no longer considered our related party.

Pursuant to the BVF Funding Agreement, we received a non-refundable payment of $20.0 million, or the Upfront Purchase Price, less certain transaction expenses. We transferred to the Buyer (i) the Royalty, (ii) the PellePharm Agreement (subject to our rights to milestone payments and rights to equity in PellePharm under the PellePharm Agreement), and (iii) certain patent rights established in the BVF Funding Agreement, with (i), (ii), and (iii) together referred to as Transferred Assets. We preserved our rights under the PellePharm Agreement to receive potential regulatory, commercial, and success-based milestone payments. We have the option to terminate the BVF Funding Agreement by purchasing 100% of the outstanding equity interests of the Buyer under specified terms for a specified amount under the BVF Funding Agreement through January 8, 2023. In addition, the BVF Funding Agreement may be terminated by mutual written agreement between us and the Buyer.

We recognized the proceeds received under the BVF Funding Agreement as a related party liability that will be amortized using the effective interest method over the life of the arrangement. We recorded the receipt of the $20.0 million Upfront Purchase Price as a liability, net of debt issuance costs of approximately $0.4 million and warrant liability of $0.3 million. The related party liability has been reclassified to liabilities related to sale of future royalties since Biotechnology Value Fund, L.P. is no longer considered our related party. We are not obligated to repay any of the proceeds received under the BVF Funding Agreement. In order to determine the amortization of the liability, we are required to estimate the total amount of potential future net royalty payments to be made by PellePharm to the Buyer over the term of the BVF Funding Agreement. The total estimated net royalties to be paid, less the net proceeds received, will be recorded as interest expense over the life of the liability. Interest and debt discount amortization expense is reflected as non-cash related party interest expense as of December 31, 2020 and non-cash interest expense as of December 31, 2021 in our Consolidated Statements of Operations and Comprehensive Loss. Over the course of the BVF Funding Agreement, the actual interest rate will be affected by the amount and timing of royalty revenue recognized, if any, and changes in forecasted royalty revenue. There are a number of factors that could materially affect the amount and timing of royalty payments from PellePharm, none of which are within our control. On a quarterly basis, we will reassess the effective interest rate and adjust the rate prospectively as needed.

The following table shows the activity within the liability account for the years ended December 31, 2021 and 2020:

	December 31,	
	2021	2020
	(in thousands)	
Liability related to sale of future royalties - beginning balance	$ 21,559	$ —
Proceeds from sale of future royalties	—	20,000
Debt discount and issuance costs	—	(428)
Warrant liability	—	(305)
Non-cash interest expense recognized	27	2,292
Liability related to sale of future royalties, net - ending balance	$ 21,586	$ 21,559

For so long as we have not exercised an option to repurchase the Buyer's equity interest under the BVF Funding Agreement, (a) if, during the 36-month period following the BVF Closing Date, we issue a specified number of shares of our common stock, which we refer to as the Warrant Threshold, and (b) any shares in excess of the Warrant Threshold are issued for consideration to us of less than $3.75 per share (as adjusted for any stock splits, reverse stock splits or other similar recapitalization events), or the Threshold Price, then we are obligated to issue to BVF warrants to purchase a number of shares of our common stock. Such warrants would equal 50% of the number of qualifying shares at an exercise price equal to 1.5 times the price per share of such qualifying shares issued. The requirement to issue warrants to BVF does not apply to certain issuances of our common stock. As of December 31, 2021, the Warrant Threshold has been met and any future qualifying shares of our common stock issued below the Price Threshold will result in warrants to purchase our common stock to be issued to BVF. No warrants have been issued to BVF as of December 31, 2021.

We determined that the commitment to issue warrants represents a freestanding financial instrument and accounted for it as a liability as of the BVF Closing Date. The fair value of the warrant liability was estimated using the Monte Carlo simulation model. The fair value of the warrant liability as of December 31, 2021 has been included in other liabilities on our consolidated balance sheet. We will re-measure the warrant liability at each reporting date. Changes in fair value of the warrant liability are included in investment and other income (expense) in our consolidated statements of operations and comprehensive loss. See Note 5 for further discussions of the fair value of the warrants.

10. Commitments and Contingencies

On April 5, 2019, we entered into a lease agreement, or the Lease, with Sun Life Assurance Company of Canada, or the Landlord, effective April 3, 2019, or the Commencement Date, for the lease of approximately 10,097 square feet of office space at 1100 Massachusetts Avenue, Cambridge, Massachusetts, or the Leased Premises. The term of the Lease commenced on the Commencement Date and expires on August 1, 2024, or the Expiration Date, approximately five years after the Rent Commencement Date as defined below.

Beginning August 1, 2019, or the Rent Commencement Date, the total base rent of the Lease was $47,961 per month and increases by approximately 3% on each anniversary of the Rent Commencement Date until the Expiration Date. In addition to the base rent, we are also responsible for our share of the operating expenses, insurance, real estate taxes and certain capital costs, and we are responsible for utility expenses in the Leased Premises, all in accordance with the terms of the Lease. Pursuant to the terms of the Lease, we provided a security deposit in the form of a letter of credit in the initial amount of $300,000, which was reduced to $150,000 during the year ended December 31, 2021 in accordance with the terms of the Lease. The initial security deposit plus the associated bank fee of $15,000 is included in our consolidated balance sheet as prepaid expenses and other current assets and restricted cash, less current portion as of December 31, 2020. The remaining portion of the security deposit plus the associated bank fee of $7,500 is included in our consolidated balance sheet as restricted cash as of December 31, 2021. The Landlord provided a lease incentive allowance of $0.6 million to fund certain improvements to be made by us to the Leased Premises.

Subject to certain conditions specified in the Lease, we have the right to extend the term of the Lease for two years, if we provide notice to the Landlord not earlier than twelve months, nor later than nine months, prior to expiration of the Lease. The base rent for the extension term shall be equal to the greater of the base rent in effect for the last year of the initial lease term or a fair market base rent determined according to the terms of the Lease.

The Lease contains customary provisions allowing the Landlord to, among other things, accelerate payments under the Lease or terminate the Lease in its entirety if we fail to remedy a default of any of our obligations under the Lease within specified time periods or upon our bankruptcy or insolvency.

We have recorded a right-of-use asset and lease liability related to our data center lease and the Lease. The lease of our data center expired during the year ended December 31, 2021. The following is a summary of our current lease included in the respective balance sheet classifications:

	December 31,	
	2021	2020
Assets	(in thousands)	
Operating lease right-of-use assets	$ 1,064	$ 1,419
Liabilities		
Accrued expenses and other current liabilities	$ 519	$ 489
Operating lease liability	917	1,436
Total lease liabilities	$ 1,436	$ 1,925

As of December 31, 2021, the weighted average term remaining on our lease is 2.6 years, and the weighted average discount rate is 10%. As of December 31, 2020, the weighted average term remaining on our leases was 3.5 years, and the weighted average discount rate was 10%.

Operating lease costs, including variable costs, of $0.7 million were incurred during both the years ended December 31, 2021 and 2020. Cash paid for amounts included in the measurement of lease liabilities were $0.7 million during both the years ended December 31, 2021 and 2020.

As of December 31, 2021, future minimum lease payments of our operating lease liabilities are as follows:

	Operating Leases (in thousands)
2022	$ 640
2023	658
2024	334
Total future minimum lease payments	1,632
Less: imputed interest	(196)
Total lease liability	$ 1,436

11. Strategic Agreements

We have worldwide development and commercialization rights to eganelisib, subject to certain obligations to our licensor, Takeda Pharmaceutical Company Limited, or Takeda, as described in more detail below. Additionally, we are obligated to pay Mundipharma International Corporation Limited, or Mundipharma, and Purdue Pharmaceutical Products L.P., or Purdue, a 4% royalty in the aggregate on worldwide net sales of products that were previously subject to our strategic alliance with Mundipharma and Purdue that was terminated in 2012. Such products include eganelisib; duvelisib, the PI3K delta and gamma inhibitor that we licensed to Verastem in 2016, the rights to which Verastem sold to Secura Bio in 2020; and IPI-926, or patidegib, part of the hedgehog inhibitor program we licensed to PellePharm in 2013. We refer to such royalties as Trailing Mundipharma Royalties. After Mundipharma and Purdue have recovered approximately $260.0 million in royalty payments from all products that were previously subject to the strategic alliance, which represents the funding paid to us for research and development services performed by us under this strategic alliance, the Trailing Mundipharma Royalties will be reduced to a 1% royalty on net sales in the United States of such products. As of December 31, 2021, Mundipharma and Purdue have recovered $2.2 million.

PellePharm

In June 2013, we entered into a license agreement with PellePharm, under which we granted PellePharm exclusive global development and commercialization rights to our hedgehog inhibitor program, including patidegib. We refer to our license agreement with PellePharm as the PellePharm Agreement and products covered by the PellePharm Agreement as Hedgehog Products. We assessed this arrangement in accordance with ASC 606 and concluded that at the date of contract inception there was only one performance obligation, consisting of the license, which was satisfied at contract inception.

Under the PellePharm Agreement, PellePharm is obligated to pay us up to $9.0 million in remaining regulatory and commercial-based milestone payments through the first commercial sale of a Hedgehog Product. PellePharm is also obligated to pay us up to $37.5 million in success-based milestone payments upon the achievement of certain annual net sales thresholds, as well as a share of certain revenue received by PellePharm in the event that PellePharm sublicenses its rights under the PellePharm Agreement and tiered royalties on annual net sales of Hedgehog Products subject to specified conditions. The remaining milestones have not been recognized as they represent variable consideration that is constrained. In making this assessment, we considered numerous factors, including the fact that achievement of the milestones is outside of our control and contingent upon the future success of clinical trials, PellePharm's actions, and the receipt of regulatory approval. As the single performance obligation was previously satisfied, all regulatory and commercial-based milestones will be recognized as revenue in full in the period in which the constraint is removed. Any consideration related to sales-based milestone payments, including royalties, will be recognized when the related sales occur as these amounts have been determined to relate predominantly to the license granted to PellePharm and therefore are recognized at the later of when the performance obligation is satisfied, or the related sales occur.

PellePharm is also obligated to pay us tiered royalties on annual net sales of Hedgehog Products, which are subject to reduction after a certain aggregate funding threshold has been achieved. On January 8, 2020, we entered into the BVF Funding Agreement, as further described in Note 9, pursuant to which we sold our interest in all royalty payments based on worldwide annual net sales of the BVF Licensed Product, excluding Trailing Mundipharma Royalties related to patidegib.

Takeda

In July 2010, we entered into a development and license agreement with Intellikine, Inc., or Intellikine, under which we obtained rights to discover, develop and commercialize pharmaceutical products targeting the gamma and/or delta isoforms of PI3K, including eganelisib and duvelisib. In January 2012, Intellikine was acquired by Takeda. In December 2012, we amended and restated our development and license agreement with Takeda and further amended the agreement in July 2014, September 2016, July 2017, and March 2019. We refer to the amended and restated development and license agreement, as amended, as the Takeda Agreement.

Duvelisib

Pursuant to the Takeda Agreement, prior to March 4, 2019, we were obligated to share equally with Takeda all revenue arising from certain qualifying transactions for duvelisib, including the Secura Bio Agreement, subject to certain exceptions including revenue we receive as reimbursement for duvelisib research and development expenses. On March 4, 2019, we entered into the fourth amendment to the Takeda Agreement, or the Takeda Amendment. Pursuant to the Takeda Amendment, Takeda agreed (i) to the sale of certain royalty payments based on worldwide annual net sales of Licensed Products under the Secura Bio Agreement to HCR, (ii) to forego its rights to an equal share of the royalties due from Secura Bio during the term of the HCR Agreement, and (iii) not to seek any payment from HCR with respect to the royalties owed to Takeda. As consideration for the Takeda Amendment, we paid Takeda $6.7 million representing 25% of the $30.0 million in gross proceeds we received from the closing of the HCR Agreement, net of 25% of the expenses incurred by us in connection with the HCR Agreement. In addition, we agreed to pay Takeda 25% of the royalties that would have been payable to us by Secura Bio but for the consummation of the HCR Agreement, which we refer to as the Interim Obligation. During each of the years ended December 31, 2021 and 2020, we recognized $0.2 million of Interim Obligation amounts owed to Takeda as royalty expense.

We have the right to extinguish the Interim Obligation by payment to Takeda of an amount equal to (i) the $6.7 million payment multiplied by the multiple set forth in the table below corresponding to the time period in which such extinguishing payment is made, minus (ii) any payments made to Takeda pursuant to the Interim Obligation:

Time Period	Multiple
From the Takeda Amendment Effective Date until June 30, 2022	145 %
From July 1, 2022 through June 30, 2023	155 %
From July 1, 2023 through June 30, 2024	165 %
From July 1, 2024 through June 30, 2025	175 %

The Interim Obligation shall expire upon the termination of the HCR Agreement and the reversion of related royalties to us, at which time our obligations to share the royalties payable under the Secura Bio Agreement equally with Takeda shall be reinstated.

Eganelisib

Pursuant to the Takeda Agreement, we are obligated to pay Takeda $3.0 million in a remaining success-based development milestone payment and up to $165.0 million in remaining regulatory and commercial-based milestone payments for one product candidate other than duvelisib, which could be eganelisib.

12. Income Taxes

We did not have any income tax expense for the years ended December 31, 2021 or 2020.

Our income tax expense for the years ended December 31, 2021 and 2020 differed from the expected U.S. federal statutory income tax expense as set forth below:

	Years Ended December 31,	
	2021	2020
	(in thousands)	
Expected federal tax benefit	$ (9,505)	$ (8,503)
Permanent differences	191	211
State taxes, net of the deferred federal benefit	(3,024)	(2,563)
Tax credit carryforwards	(1,416)	(837)
Adjustments to deferred tax assets and deferred tax liabilities	226	852
Other	(93)	69
Change in valuation allowance	13,621	10,771
Income tax expense (benefit)	$ —	$ —

The significant components of our deferred tax assets and liabilities are as follows:

	Years Ended December 31,	
	2021	2020
	(in thousands)	
Deferred tax assets (liabilities):		
Net operating loss carryforwards	$ 164,969	$ 151,752
Tax credit carryforwards	44,302	42,645
Intangible assets	15,151	17,028
Accrued expenses	1,255	645
Stock-based compensation	5,109	4,976
Sale of future royalties	13,557	13,742
Other	22	(44)
Valuation allowance	(244,365)	(230,744)
Net deferred tax assets	$ —	$ —

We have recorded a valuation allowance against our deferred tax assets in each of the years ended December 31, 2021, and 2020 because we believe that it is more likely than not that these assets will not be realized. The valuation allowance increased by approximately $13.6 million during the year ended December 31, 2021 primarily as a result of the increase in our unbenefited net operating loss for the current period. The valuation allowance increased by approximately $10.8 million during the year ended December 31, 2020 primarily as a result of the increase in our unbenefited net operating loss for the period and the BVF Agreement which created a deferred tax asset in the year due to the inclusion of the royalty sale proceeds in taxable income for 2020.

Subject to the limitations described below, at December 31, 2021, we have cumulative net operating loss carryforwards of approximately $631.3 million and $512.6 million available to reduce federal and state taxable income, respectively. For federal purposes, the net operating loss carryforwards have begun to expire and will continue to expire through 2037 for losses incurred before January 1, 2018. Federal losses generated after December 31, 2017 do not expire. As of December 31, 2021, we have approximately $106.6 million of federal losses that do not expire. The state net operating loss carryforwards begin to expire in 2031 and continue to expire through 2041. In addition, we have cumulative federal and state tax credit carryforwards of $36.3 million and $10.2 million, respectively, available to reduce federal and state income taxes which expire through 2041 and 2036, respectively. Our net operating loss carryforwards and tax credit carryforwards are limited as a result of certain ownership changes, as defined under Sections 382 and 383 of the Internal Revenue Code. This limits the annual amount of these tax attributes that can be utilized to offset future taxable income or tax liabilities. The amount of the annual limitation is determined based on our value immediately prior to an ownership change. Subsequent ownership changes may affect the limitation in future years. The net operating losses and tax credit carryforwards that have and will expire unused in the future as a result of Section 382 and 383 limitations have been excluded from the amounts disclosed above. The latest Section 382 study was performed through December 31, 2018. Ownership changes after that date could further reduce the Company's ability to utilize the net operating loss and other attribute carryforwards.

At December 31, 2021 and 2020, we had no unrecognized tax benefits. As of December 31, 2021 and 2020, we had no accrued interest or penalties related to uncertain tax positions and no amounts have been recognized in our Consolidated

Statements of Operations and Comprehensive Loss. We will recognize interest and penalties related to uncertain tax positions in income tax expense. For all years through December 31, 2021, we generated research credits but have not conducted a study to document the qualified activities. This study may result in an adjustment to our research and development credit carryforwards; however, until a study is completed and any adjustment is known, no amounts are being presented as an uncertain tax position. A full valuation allowance has been provided against our research and development credits and, if an adjustment is required, this adjustment would be offset by an adjustment to the deferred tax asset established for the research and development credit carryforwards and the valuation allowance.

We file U.S. federal and Massachusetts state income tax returns. The statute of limitations for assessment by the Internal Revenue Service, or IRS, and state tax authorities is closed for tax years prior to 2018, although carryforward attributes that were generated prior to tax year 2018 may still be adjusted upon examination by the IRS or state tax authorities if they either have been or will be used in a future period.

13. Stockholders' Equity

Common Stock Sales Facility

On June 28, 2019, we entered into a Capital on Demand Sales Agreement with JonesTrading Institutional Services LLC, or JonesTrading, and on July 29, 2019 we amended and restated the sales agreement to add B. Riley Securities (f/k/a B. Riley FBR, Inc.), or B. Riley Securities, as a party to the agreement. On July 27, 2021, we entered into an amendment to the agreement to increase the maximum aggregate offering price of the shares of common stock that we may issue and sell from time to time under the agreement by $75.0 million to an aggregate of $95.0 million. We refer to the amended and restated sales agreement, as amended, as the ATM Sales Agreement. As of December 31, 2021, we had an aggregate of $86.8 million available for future sales. Pursuant to the ATM Sales Agreement we may offer and sell shares of our common stock from time to time through JonesTrading or B. Riley Securities, each acting as our sales agent. We have agreed to pay commissions to the sales agents for their services in acting as agents in the sale of our common stock in the amount of up to 3.0% of the gross proceeds from sales of our common stock pursuant to the ATM Sales Agreement. Sales of shares of our common stock under the ATM Sales Agreement may be made by any method that is deemed to be an "at-the-market-offering" as defined in Rule 415(a)(4) promulgated under the Securities Act of 1933, as amended. With our prior written approval, JonesTrading or B. Riley Securities may also sell the shares by any other method permitted by law, including in negotiated transactions. We and JonesTrading or B. Riley Securities may suspend or terminate the offering of shares upon notice to the other parties and subject to other conditions. During the year ended December 31, 2021, we issued and sold 89,520 shares of common stock at a weighted average price per share of $3.83 at-the-market pursuant to the ATM Sales Agreement for $0.3 million in net proceeds. During the year ended December 31, 2020, we issued and sold 6,725,691 shares of common stock at a weighted average price per share of $1.17 at-the-market pursuant to the ATM Sales Agreement for $7.7 million in net proceeds.

Public Offering

On February 11, 2021, we entered into a purchase agreement with Piper Sandler & Co., as representative of the underwriters named therein, pursuant to which we issued and sold to the underwriters in an underwritten public offering an aggregate of 24,150,000 shares of our common stock, including 3,150,000 shares of common stock sold in connection with the exercise in full of a 15% over-allotment option by the underwriters. The public offering price was $3.80 per share. The gross proceeds to us from this offering were approximately $91.8 million. After underwriting discounts and commissions and offering expenses, we received net proceeds from the offering of approximately $85.8 million.

Warrants

On February 24, 2014, we entered into a facility agreement with affiliates of Deerfield Management Company, L.P., or Deerfield. In connection with the execution of the original facility agreement, we issued to Deerfield warrants to purchase an aggregate of 1,000,000 shares of common stock at an exercise price of $13.83 per share. The warrants have dividend rights to the same extent as if the warrants were exercised into shares of common stock. The warrants expire on the seventh anniversary of their issuance and contain certain limitations that prevent the holder from acquiring shares upon exercise of a warrant that would result in the number of shares beneficially owned by the holder exceeding 9.985% of the total number of shares of common stock then issued and outstanding. During the year ended December 31, 2021, the warrants expired without being exercised.

14. Defined Contribution Benefit Plan

We sponsor a 401(k) retirement plan in which substantially all of our full-time employees are eligible to participate. Participants may contribute a percentage of their annual compensation to this plan, subject to statutory limitations. During the years ended December 31, 2021 and 2020, we matched participants' contributions up to 6% of the participant's pre-tax salary. Our matching contributions for the years ended December 31, 2021 and 2020 was $0.2 million in both years.

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

There have been no disagreements with our independent accountants on accounting and financial disclosure matters.

Item 9A. Controls and Procedures

Disclosure Controls and Procedures

Our management, with the participation of our principal executive officer and principal financial officer, evaluated the effectiveness of our disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, or the Exchange Act) as of December 31, 2021. In designing and evaluating our disclosure controls and procedures, management recognized that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives, and our management necessarily applied its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on this evaluation, our principal executive officer and principal financial officer concluded that as of December 31, 2021, our disclosure controls and procedures were (1) designed to ensure that material information relating to us is made known to our management including our principal executive officer and principal financial officer by others, particularly during the period in which this report was prepared and (2) effective, in that they provide reasonable assurance that information required to be disclosed by us in the reports we file or submit under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the U.S. Securities and Exchange Commission's rules and forms.

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

Internal Control Over Financial Reporting

Management's Report on Internal Control Over Financial Reporting

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

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

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

Our management assessed the effectiveness of our internal control over financial reporting as of December 31, 2021. In making this assessment, management used the criteria set forth by the Committee of Sponsoring Organizations of the

Treadway Commission, or COSO, in Internal Control—Integrated Framework (2013). Based on its assessment, management believes that, as of December 31, 2021, our internal control over financial reporting is effective based on those criteria.

Changes in Internal Control Over Financial Reporting

No change in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) occurred during the fiscal quarter ended December 31, 2021 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information

None.

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections

Not applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance

The sections titled "Proposal 1—Election of Directors," "Board and Committee Meetings," "Delinquent Section 16(a) Reports," if applicable, and "Corporate Governance Guidelines; Code of Conduct and Ethics" appearing in the definitive proxy statement we will file in connection with our 2022 Annual Meeting of Stockholders are incorporated herein by reference. The information required by this item relating to executive officers may be found in Part I, Item 1 of this report under the heading "Business – Information about our Executive Officers."

Item 11. Executive Compensation

The section titled "Compensation of Executive Officers" appearing in the definitive proxy statement we will file in connection with our 2022 Annual Meeting of Stockholders is incorporated herein by reference.

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

The sections titled "Stock Ownership of Certain Beneficial Owners and Management" and "Securities Authorized for Issuance under Equity Compensation Plans" appearing in the definitive proxy statement we will file in connection with our 2022 Annual Meeting of Stockholders are incorporated herein by reference.

Item 13. Certain Relationships and Related Transactions, and Director Independence

The sections titled "Transactions with Related Persons," "Policies and Procedures for Related Persons Transactions," and "Determination of Independence" appearing in the definitive proxy statement we will file in connection with our 2022 Annual Meeting of Stockholders are incorporated herein by reference.

Item 14. Principal Accounting Fees and Services

The section titled "Audit Fees" appearing in the definitive proxy statement we will file in connection with our 2022 Annual Meeting of Stockholders is incorporated herein by reference.

PART IV

Item 15. Exhibits, Financial Statement Schedules

(a)(1) Financial Statements

The financial statements listed below are filed as a part of this Annual Report on Form 10-K.

(a)(2) Financial Statement Schedules

Financial statement schedules have been omitted because of the absence of conditions under which they are required or because the required information, where material, is shown in the financial statements or notes thereto.

(a)(3) Exhibits

Exhibit No.	Description	Incorporated by Reference			Filed with this 10-K
		Form	SEC Filing Date	Exhibit Number	
3.1	Restated Certificate of Incorporation of the Registrant, as amended.	10-Q	7/30/2020	3.1	
3.2	Amended and Restated Bylaws of the Registrant.	8-K	3/17/2009	3.1	
4.1	Form of Common Stock Certificate.	10-K	3/14/2008	4.1	
4.2	Description of Securities Registered Under Section 12 of the Exchange Act	10-K	3/16/2021	4.2	
Collaboration Agreements					
10.1†	Amended and Restated Development and License Agreement, dated as of December 24, 2012, by and between the Registrant and Intellikine, LLC.	10-K	3/5/2013	10.4	
10.2	Amendment to Amended and Restated Development and License Agreement, dated as of July 29, 2014, by and between Registrant and Intellikine LLC.	10-Q	11/10/2014	10.1	
10.3	Amendment No. 2 to Amended and Restated Development and License Agreement, dated as of September 27, 2016, by and between Registrant and Intellikine LLC.	10-Q	11/9/2016	10.1	
10.4	Amendment No. 3 to Amended and Restated Development and License Agreement, dated as of July 26, 2017, by and between the Registrant and Intellikine LLC.	10-Q	11/7/2017	10.1	
10.5	Amendment No. 4 to Amended and Restated Development and License Agreement, dated as of March 4, 2019, by and between the Registrant and Intellikine LLC.	10-Q	5/7/2019	10.1	
10.6	Convertible Promissory Note, dated as of July 26, 2017, by and between Registrant and Intellikine LLC.	10-Q	11/7/2017	10.2	
10.7†	Amended and Restated License Agreement, dated as of November 1, 2016, by and between the Registrant and Verastem, Inc.	10-K	3/14/2017	10.4	
10.8	Termination and Revised Relationship Agreement, dated as of July 17, 2012, between the Registrant and Mundipharma International Corporation Limited.	8-K	7/19/2012	10.2	
10.9	Termination and Revised Relationship Agreement, dated as of July 17, 2012, between the Registrant and Purdue Pharmaceutical Products L.P.	8-K	7/19/2012	10.3	
Financing Agreements					
10.11	Purchase and Sale Agreement, dated as of March 5, 2019, between the Registrant and HealthCare Royalty Partners III, L.P.	10-Q	5/7/2019	10.2	
10.12	Protective Rights Agreement, dated as of March 11, 2019, between the Registrant and HCR Collateral Managements, LLC.	10-Q	5/7/2019	10.3	
10.13	Capital on Demand™ Sales Agreement, dated June 28, 2019, by and between Infinity Pharmaceuticals, Inc. and JonesTrading Institutional Services LLC.	8-K	6/28/2019	1.1	
10.14	Amended and Restated Capital on Demand™ Sales Agreement, dated July 29, 2019, by and among Infinity Pharmaceuticals, Inc. and JonesTrading Institutional Services LLC and B. Riley FBR, Inc.	8-K	7/30/2019	1.1	
10.15	Amendment 1 to Amended and Restated Capital on Demand™ Sales Agreement, dated July 29, 2019, by and among Infinity Pharmaceuticals, Inc. and JonesTrading Institutional Services LLC and B. Riley Securities, Inc. (f/k/a B. Riley FBR, Inc.), dated July 27, 2021	10-Q	7/27/2021	10.2	
10.15	Purchase Agreement, dated as of February 11, 2021, between the Registrant and Piper Sandler & Co., as representative of the underwriters named therein.	8-K	2/12/2021	1.1	
10.16	Funding Agreement, dated January 8, 2020, by and among Infinity Pharmaceuticals, Inc., BVF Partners, L.P., and Royalty Security, LLC.	10-K	3/3/2020	10.15	
10.17	Novation and Amendment Agreement, dated January 27, 2020, by and among Infinity Pharmaceuticals, Inc., BVF Partners, L.P., Royalty Security, LLC, and Royalty Security Holdings, LLC	10-K	3/3/2020	10.16	

Exhibit No.	Description	Incorporated by Reference			Filed with this 10-K
		Form	SEC Filing date	Exhibit Number	
Leases					
10.18	Lease Agreement, dated April 3, 2019, between Registrant and Sun Life Assurance Company of Canada.	10-Q	5/7/2019	10.4	
Equity Plans					
10.19*	2010 Stock Incentive Plan.	8-K	5/28/2010	10.1	
10.20*	Form of Incentive Stock Option Agreement under 2010 Stock Incentive Plan.	8-K	5/28/2010	10.2	
10.21*	Form of Nonstatutory Stock Option Agreement under 2010 Stock Incentive Plan.	8-K	5/28/2010	10.3	
10.22*	Form of Restricted Stock Agreement under 2010 Stock Incentive Plan	10-K	3/14/2017	10.23	
10.23*	Form of Nonstatutory Stock Option Agreement for Inducement Grant Pursuant to Nasdaq Stock Market Rule 5635(c)(4)	10-K	3/14/2017	10.24	
10.24*	Form of Stock Option Award Agreement for Inducement Grant Pursuant to Nasdaq Stock Market Rule 5635(c)(4)	S-8	8/2/2021	99.1	
10.25*	Form of Restricted Stock Unit Agreement for Inducement Grant Pursuant to Nasdaq Stock Market Rule 5635(c)(4)	S-8	8/2/2021	99.2	
10.26*	Amendment No. 1 to 2010 Stock Incentive Plan.	8-K	12/14/2010	99.2	
10.27*	Amendment No. 2 to 2010 Stock Incentive Plan.	8-K	5/18/2012	99.1	
10.28*	Amendment No. 3 to 2010 Stock Incentive Plan.	8-K	6/13/2013	10.1	
10.29*	Amendment No. 4 to 2010 Stock Incentive Plan.	8-K	6/13/2013	10.1	
10.31*	Amendment No. 5 to 2010 Stock Incentive Plan.	8-K	6/16/2015	10.1	
10.32*	Amendment No. 6 to 2010 Stock Incentive Plan.	10-Q	5/4/2016	10.1	
10.33*‡	2013 Employee Stock Purchase Plan, as amended.	DEF14A	4/26/2021	A	
10.34*	2019 Equity Incentive Plan.	DEF14A	4/24/2019	A	
10.35*	Form of Stock Option Agreement under 2019 Equity Incentive Plan.	10-Q	7/30/2019	10.3	
Agreements With Executive Officers					
10.36*	Offer Letter between the Registrant and Lawrence E. Bloch, M.D., J.D. dated May 15, 2012.	8-K	7/25/2012	10.1	
10.37*	Offer Letter between IDI and Adelene Perkins dated as of February 6, 2002.	8-K	9/18/2006	10.11	
10.38*	Amendment to Offer Letter between IDI and Adelene Perkins dated as of October 25, 2007.	8-K	10/30/2007	99.5	
10.39*	Offer Letter between the Registrant and Seth A. Tasker, J.D. dated February 22, 2008	10-K	3/14/2017	10.34	
10.40*	Employment Retention Incentive Package Letter Agreement between the Registrant and Seth Tasker, J.D. dated July 1, 2016	10-K	3/14/2017	10.35	
10.41*	Offer Letter between the Registrant and Stephane Peluso, Ph.D., dated July 12, 2021.	10-Q	11/2/2021	10.1	
10.42*	Offer Letter between the Registrant and Robert Ilaria, Jr., M.D., dated August 11, 2021.	10-Q	11/2/2021	10.2	
10.43*	Infinity Pharmaceuticals, Inc. Executive Severance Benefits Plan effective February 6, 2013.	8-K	2/12/2013	10.1	
10.44*	Amendment No. 1, dated August 3, 2018, to Infinity Pharmaceuticals, Inc. Executive Severance Benefits Plan.	10-Q	11/5/2018	10.2	
Subsidiaries					
21.1	Subsidiaries of the Registrant.	10-K	3/3/2020	21.1	

Exhibit No.	Description	Incorporated by Reference			Filed with this 10-K
		Form	SEC Filing date	Exhibit Number	
Consent					
23.1	Consent of Ernst & Young LLP, Independent Registered Public Accounting Firm. Filed herewith.				X
Certifications					
31.1	Certification of principal executive officer pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934, as amended. Filed herewith.				X
31.2	Certification of principal financial officer pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934, as amended. Filed herewith.				X
32.1	Statement of principal executive officer pursuant to 18 U.S.C. §1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002. Filed herewith.				X
32.2	Statement of principal financial officer pursuant to 18 U.S.C. §1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002. Filed herewith.				X
101.INS	Inline XBRL Instance Document (the instance document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document)				X
101.SCH	Inline XBRL Taxonomy Extension Schema Document.				X
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document.				X
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document.				X
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document.				X
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document.				X
104	Cover Page Interactive Data File (formatted as Inline XBRL and contained in Exhibit 101).				X

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

‡ Complete exhibit filed on March 3, 2020 on our Form 10-K for the fiscal year ended December 31, 2019 replaces the incomplete exhibit previously filed on July 30, 2019 in our Form 10-Q for the quarter ended June 30, 2019.

* Indicates management contract or compensatory plan

Item 16. Form 10-K Summary

None.

SIGNATURES

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

INFINITY PHARMACEUTICALS, INC.

Date: March 29, 2022

By: /s/ ADELENE Q. PERKINS
Adelene Q. Perkins
Chief Executive Officer
(Principal Executive Officer)

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

Signature	Title	Date
/s/ ADELENE Q. PERKINS **Adelene Q. Perkins**	Chief Executive Officer; Chair of the Board of Directors *(Principal Executive Officer)*	March 29, 2022
/s/ LAWRENCE E. BLOCH, M.D., J.D. **Lawrence E. Bloch, M.D., J.D.**	President *(Principal Financial Officer, Principal Accounting Officer)*	March 29, 2022
/s/ SAMUEL AGRESTA, M.D., M.P.H. **Samuel Agresta, M.D., M.P.H**	Director	March 29, 2022
/s/ DAVID BEIER, J.D. **David Beier, J.D.**	Director	March 29, 2022
/s/ ANTHONY B. EVNIN, PH.D. **Anthony B. Evnin, Ph.D.**	Director	March 29, 2022
/s/ RICHARD GAYNOR, M.D. **Richard Gaynor, M.D.**	Director	March 29, 2022
/s/ BRIAN SCHWARTZ, M.D. **Brian Schwartz, M.D.**	Director	March 29, 2022
/s/ NORMAN C. SELBY **Norman C. Selby**	Director	March 29, 2022