Developing a Unique Approach to Treating Cancer

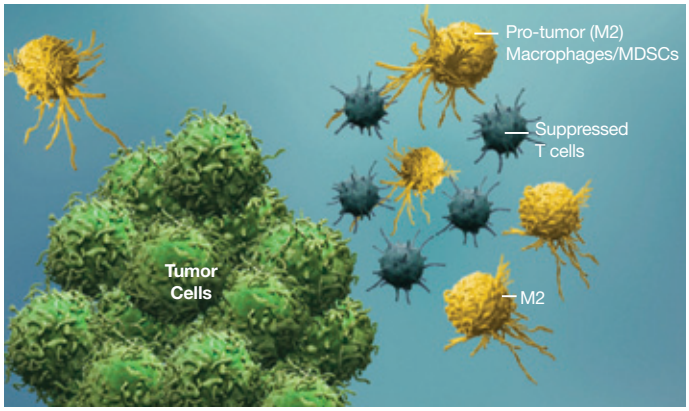
Annual Report 2018

Infinity™ PHARMACEUTICALS

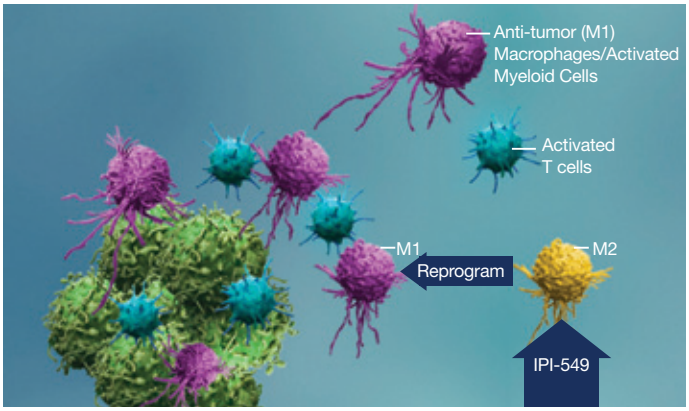
JEFFERY KUTOK, M.D., Ph.D.
Chief Scientific Officer

IPI-549: First-In-Class Approach to Target the Tumor Microenvironment by Selectively Inhibiting PI3K-Gamma

We are developing IPI-549, an oral, once-daily product candidate that selectively inhibits PI3K-gamma. Selective PI3K-gamma inhibition represents a unique and potentially transformative approach within immuno-oncology (I/O), and IPI-549 has the potential to be a first-in-class therapy. Preclinical research conducted by Infinity and academic collaborators demonstrates that IPI-549 works by reprogramming key immune suppressive cells (called M2 macrophages or myeloid derived suppressor cells (MDSCs)) within the tumor microenvironment from a pro-tumor function to an anti-tumor function, decreasing immune suppression and increasing immune activation, ultimately leading to the activation and proliferation of T cells that can attack cancer cells[1,2].

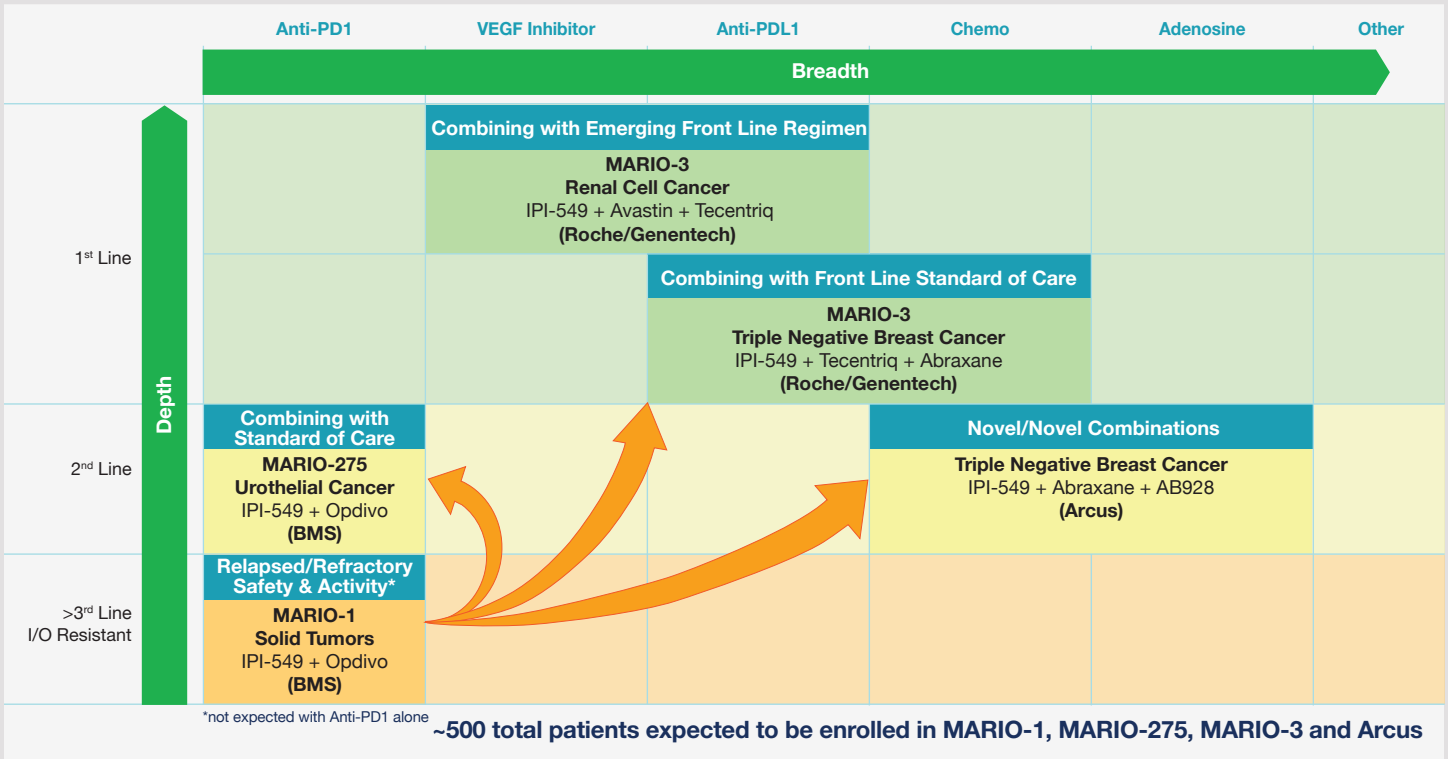


PI3K-gamma signaling in macrophages or MDSCs within the tumor microenvironment maintains the pro-tumor function, suppressing anti-tumor T cell activity and enabling tumor growth.



PI3K-gamma inhibition by IPI-549 activates an anti-tumor immune response by reducing immune suppression and increasing immune activation.

Expanding Breadth and Depth of IPI-549 Development



SAMUEL AGRESTA, M.D., M.P.H.
Chief Medical Officer

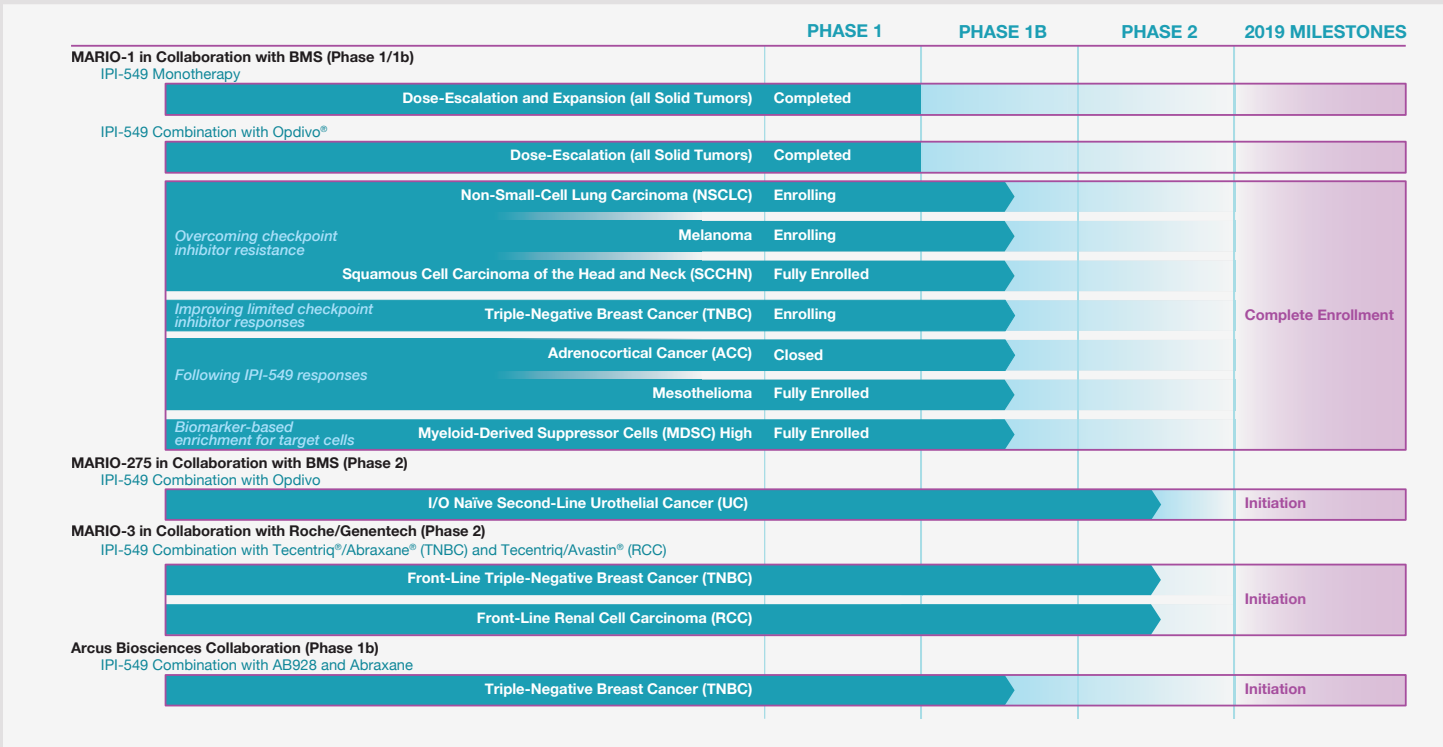
IPI-549 Clinical Activity, Tolerability and Translational Data Support Expanded Clinical Development

MARIO-1 clinical data demonstrated the safety and activity of IPI-549 as a monotherapy and in combination with Opdivo®[3]. Data presented at ASCO and SITC[4,5] in June and November of 2018 showed that IPI-549 is clinically active with objective responses as a monotherapy and in combination with Opdivo, in settings where activity with Opdivo monotherapy would not be expected, providing a compelling rationale to expand and accelerate the development of IPI-549.

Leveraging the data and insights from MARIO-1, IPI-549 is now being advanced in a broad and deep Phase 2 development program, adding IPI-549 to emerging standards of care to improve patient outcomes. Within the last 12 months, we announced collaborations with top tier partners to evaluate IPI-549 in earlier lines of therapy and in novel combinations.

- MARIO-275, in clinical collaboration with BMS: A randomized study of IPI-549 and Opdivo vs. Opdivo monotherapy in patients with I/O naïve urothelial cancer. MARIO-275 leverages our findings from MARIO-1 in which the majority of patients had a decrease in levels of MDSCs following treatment with IPI-549. High levels of MDSCs were associated with poorer outcomes in urothelial cancer patients treated with Opdivo monotherapy in BMS's approval study, Checkmate 275.
- MARIO-3, in clinical collaboration with Roche/Genentech: A novel triplet therapy in front line patients including IPI-549 + Tecentriq®[6] + Abraxane®[7] in 1L triple negative breast cancer patients and IPI-549 + Tecentriq + Avastin®[6] in 1L renal cell carcinoma patients.
- In clinical collaboration with Arcus: A novel triplet therapy combining IPI-549 + AB928 + Abraxane in patients with previously treated advanced triple negative breast cancer.

IPI-549 Development Pipeline



Dear Fellow Shareholders,

2018 was a milestone year in laying the foundation for Infinity value creation. Value will be driven by compelling clinical data with IPI-549, Infinity's first-in-class immuno-oncology therapy, resourced with a keen sensitivity to equity and product rights dilution, evidenced by recently accessed non-dilutive capital and collaborations. Our studies are generating potentially transformative Phase 2 data with top tier collaborators in novel combinations and earlier lines of therapy, leveraging insights from our Phase 1b study.

Advancing IPI-549 to generate compelling clinical data:

- IPI-549 is differentiated as the only potent, oral and selective PI3K-gamma inhibitor in clinical development, and data presented during 2018 underscore the importance of this unique and complementary mechanism in reducing the immuno-suppressive effects of macrophages/MDSCs and overcoming the limitations of other immuno-oncology approaches.
- Clinical data presented at ASCO and SITC in 2018 demonstrated the safety, on-mechanism effects and activity of IPI-549 both as a monotherapy and in combination with Opdivo, where activity with Opdivo monotherapy would not be expected, providing a convincing rationale to expand IPI-549 development.
- A robust Phase 2 development program is underway, adding IPI-549 to emerging standards of care in areas of great unmet need to improve patient outcomes.

Infinity clinical and scientific leadership in I/O development:

- We continue to attract exceptional talent and are thrilled that Dr. Sam Agresta joined us as Infinity's Chief Medical Officer during 2018. Dr. Agresta recently led the development and approval of Idhifa and Tibsovo in August 2017 and 2018 respectively, while at Agios.

Accessing dilution-sensitive resources:

- We have recently accessed over $60M of non-dilutive capital through the $22M FDA approval milestone of COPIKTRA, $20M in net proceeds for the monetization of COPIKTRA royalties, commitments from top-tier collaborators (BMS, Roche/Genentech and Arcus) and a $2M Phase 3 milestone from Pellepharm which has enabled us to significantly expand the development of IPI-549 while extending our cash runway into 2H 2020 and retaining worldwide product rights to IPI-549.

Our 2019 focus is on execution to expand IPI-549 development with important clinical milestones:

1H2019

- ❑ Initiate MARIO-275, a randomized study in I/O naïve urothelial cancer patients with BMS

2H2019

- ❑ Initiate MARIO-3, a novel triple therapy in front-line TNBC and RCC patients with Roche/Genentech
- ❑ Complete MARIO-1 enrollment in melanoma and TNBC expansion cohorts with BMS
- ❑ Initiate triple therapy in previously treated advanced TNBC patients with Arcus Biosciences

The breadth and depth of our clinical development program is designed to generate compelling clinical data with IPI-549 and to generate significant value for Infinity's shareholders. We continue to proceed with a great sense of urgency to bring the promise of this potentially transformative I/O therapy to patients and look forward to updating you on our progress.

Sincerely,

Adelene Q. Perkins

ADELENE Q. PERKINS
Chair and Chief Executive Officer

LAWRENCE E. BLOCH, M.D., J.D.
President

***IPI-549 is an investigational compound and its safety and efficacy has not been evaluated by the U.S. Food and Drug Administration or any other health authority.**

FOLLOWING IS THE COMPANY'S ANNUAL REPORT ON FORM 10-K
FOR THE FISCAL YEAR ENDED DECEMBER 31, 2018.

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

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

For the fiscal year ended: December 31, 2018

☐ **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.)**

784 Memorial Drive, Cambridge, Massachusetts 02139

(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:

Common Stock, $0.001 par value	**Nasdaq Global Select Market**
(Title of each class)	**(Name of each exchange on which listed)**

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

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

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

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

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☒

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See definitions of "large accelerated filer," "accelerated filer," and "smaller reporting company" and "emerging growth company" in Rule 12b-2 of the Exchange Act.

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

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

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

The aggregate market value of voting Common Stock held by non-affiliates of the registrant as of June 29, 2018 was $105,426,361 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 8, 2019: 56,925,528

Documents incorporated by reference:

Portions of our definitive proxy statement to be filed with the Securities and Exchange Commission no later than April 30, 2019 in connection with our 2019 annual meeting of stockholders are incorporated by reference into Part III of this Annual Report on Form 10-K.

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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 2019 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 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.

PART I

Item 1. Business

Overview

We are an 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 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 IPI-549 is the only clinical-stage selective inhibitor of PI3K-gamma currently being investigated.

Selective inhibition of PI3K-gamma by IPI-549 targets tumor-associated myeloid cells, thereby reducing pro-tumor macrophage function and increasing anti-tumor macrophage function. In preclinical studies, detailed further below, IPI-549 demonstrated the ability 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 IPI-549 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 IPI-549 significantly inhibits the regrowth of tumors that can occur following treatment with chemotherapy.

We have worldwide development and commercialization rights to IPI-549, subject to certain success-based milestone payment obligations to our licensor, Takeda Pharmaceutical Company Limited, or Takeda, as described in more detail under the heading *Collaborations —Takeda*. Additionally, we are obligated to pay our former strategic collaborators 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, including IPI-549, that were previously subject to the strategic alliance with Mundipharma and Purdue that was terminated in 2012. We refer to such royalties as Trailing Mundipharma Royalties. After Mundipharma and Purdue have recovered approximately $260 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 products that were previously subject to the strategic alliance, including IPI-549.

Preclinical Rationale for Development of IPI-549: 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 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 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 immune response and provide signals to cancer cells that facilitate tumor growth. The presence of the supportive TME is thought to be one reason why some cancer therapies, including checkpoint inhibitors, have shown limited durability and efficacy to date. Research has demonstrated that PI3K-gamma plays an important role in maintaining the immunosuppressive nature of tumor-associated macrophages and myeloid-derived suppressor cells, or MDSCs. Targeting these cells that suppress the immune system represents an emerging approach within the field of cancer immunotherapy, and inhibition of PI3K-gamma by IPI-549 represents a novel approach to targeting this immunosuppressive microenvironment.

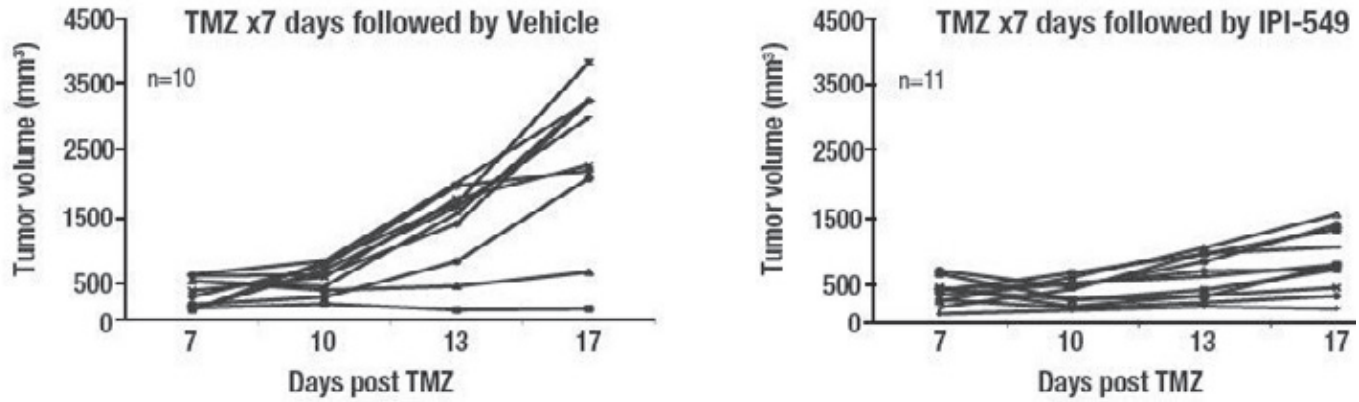
Anti-Tumor Activity of IPI-549 in Preclinical Models

Our preclinical research has shown that macrophage PI3K-gamma signaling results in a type of macrophage that suppresses anti-tumor T cells. Preclinical data demonstrated that blockade of PI3K-gamma by treatment with IPI-549 leads to a shift in the type of macrophages present in the TME from macrophages associated with suppression of the immune response, known as the M2 phenotype, to macrophages that are supportive of a pro-inflammatory, anti-tumor immune response, known as the M1 phenotype. In preclinical studies, treatment with IPI-549 in tumor models was shown to increase the M1/M2 macrophage ratio, the number of T cells that attack the tumor, and the production of pro-inflammatory, anti-tumor cytokines.

Preclinical studies to investigate the anti-tumor activity of IPI-549 have demonstrated dose-dependent, single-agent, anti-tumor activity in multiple solid tumor models, including models of lung cancer, colon cancer and breast cancer. Additionally, in preclinical models, treatment with IPI-549 in combination with a checkpoint inhibitor showed greater tumor growth inhibition and survival, including a greater number of complete tumor regressions, compared to treatment with either IPI-549 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 with the same tumor cells in the absence of any treatment.

Further, as illustrated below, a preclinical study in a murine glioblastoma model indicated that administration of IPI-549 following tumor regression with temozolomide, or TMZ, led to greater inhibition of tumor growth compared to no treatment.

IPI-549 Inhibits Tumor Regrowth Post Temozolomide (TMZ) in GL261 Gliobastoma Model



Two GL261 tumor bearing C57/BL6 Albino mice groups were treated with temozolomide 1mg/kg intraperitoneally, once daily for 7 days to regress tumors and then subsequently treated with either vehicle (left) or IPI-549 15 mg/kg orally, once daily (right).

Fig. source: McGovern et al. AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics Meeting, November 6, 2015, Boston, MA, USA

These findings support the hypothesis that inhibition of PI3K-gamma by IPI-549 reprograms macrophages from a pro-tumor immunosuppressive function to an anti-tumor immune-activating function and can augment the activity of checkpoint inhibitor therapies in models that are sensitive to checkpoint inhibitors. Additionally, IPI-549 can significantly inhibit tumor regrowth in a tumor model previously treated with chemotherapy.

Overcoming Resistance to Checkpoint Inhibition

In recent years, checkpoint inhibitors 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 and is directly mediated by the immunosuppressive activity of these macrophages on T cells. Furthermore, the data demonstrated that inhibition of PI3K-gamma by IPI-549 switched the function of the macrophages from a pro-tumor, immunosuppressive state to an anti-tumor, immune-activating state, leading to enhanced anti-tumor cytotoxic T cell activity, particularly when combined with checkpoint inhibitors. These data demonstrated that IPI-549 treatment was able to reverse the lack of response to checkpoint inhibitors in models that were initially insensitive to checkpoint inhibition as a single therapy.

IPI-549 Clinical Development Program

2019 Clinical Development Goals

Our ongoing Phase 1/1b study MARIO-1: MAcrophage Reprogramming in Immuno-Oncology, or MARIO-1, is designed to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and activity for IPI-549 both as a monotherapy and in combination with nivolumab, also known as Opdivo®, in approximately 220 patients with advanced solid tumors. Nivolumab is an immune checkpoint inhibitor therapy commercialized by Bristol-Myers Squibb Company, or BMS, that targets PD-1. We announced interim data from MARIO-1 in 2018 that showed that IPI-549 was well tolerated and associated with a favorable safety profile, both as a monotherapy and in combination with nivolumab, and demonstrated clinical activity both as a monotherapy and in combination with nivolumab. We further expanded our clinical trial pipeline in November 2018 with the announcement that we and BMS had entered into a clinical supply agreement, which we refer to as the BMS Agreement, under which we would operationalize MARIO-275, a global, randomized Phase 2 study designed to evaluate the effect of adding IPI-549 to nivolumab in checkpoint-naïve advanced urothelial cancer patients who have progressed or recurred following treatment with platinum-based chemotherapy.

Our clinical development goals for IPI-549 include the initiation in the first half of 2019 of MARIO-275, a global Phase 2 study in immuno-oncology naïve patients with urothelial cancer. In the second half of 2019 we intend to complete enrollment in the MARIO-1 combination expansion cohorts, initiate a study with Arcus Biosciences, Inc., or Arcus, investigating IPI-549 in a triple therapy combination in previously treated patients with advanced triple-negative breast cancer, or TNBC, and to initiate MARIO-3, a Phase 2 combination study of IPI-549 in front-line patients with advanced TNBC and renal cell carcinoma, or RCC. The following table summarizes our ongoing and planned clinical trials and the associated milestones we expect to achieve in 2019:

Study/Cohort	Status
MARIO-1 (Phase 1/1b)	
IPI-549 Monotherapy	
Dose-Escalation and Expansion (all Solid Tumors)	Completed
IPI-549 Combo with Nivolumab	
Dose-Escalation (all Solid Tumors)	Completed
Expansion	Enrollment Completion Expected Second Half 2019
Non-Small-Cell Lung Carcinoma (NSCLC)	*Enrollment Ongoing*
Expansion - Melanoma	*Enrollment Ongoing*
Squamous Cell Carcinoma of the Head and Neck (SCCHN)	*Fully Enrolled*
Triple-Negative Breast Cancer (TNBC)	*Enrollment Ongoing*
Mesothelioma	*Fully Enrolled*
Myeloid-Derived Suppressor Cells (MDSC)-High	*Fully Enrolled*
MARIO-275 (Phase 2)	
IPI-549 Combo with Nivolumab	
Immuno-Oncology Naïve Urothelial Cancer	Initiation Expected First Half 2019
Arcus Biosciences Collaboration (Phase 1b)	
IPI-549 Combo with AB928 and Chemo	
TNBC	Initiation Expected Second Half 2019
MARIO-3 in Collaboration with Roche/Genentech (Phase 2)	
IPI-549 Combo with Atezolizumab/Chemo (TNBC) and Atezolizumab/Bevacizumab (RCC)	
Front-Line TNBC	Initiation Expected Second Half 2019
Front-Line Renal Cell Carcinoma (RCC)	Initiation Expected Second Half 2019

MARIO-1: Phase 1/1b Dose-Escalation and Combination Expansion Study in Solid Tumors

MARIO-1 is our Phase 1/1b clinical study designed to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and activity for IPI-549 — both as a monotherapy and in combination with nivolumab — in approximately 220 patients with advanced solid tumors. The dose-escalation portions of MARIO-1 are complete, and enrollment is ongoing in the combination therapy expansion cohorts designed to evaluate patients dosed at 40 mg once daily, or QD, of IPI-549 in combination with the standard regimen of nivolumab. Three cohorts are designed to evaluate IPI-549 in combination in patients with non-small cell lung cancer, melanoma, or head and neck cancer whose tumors show initial resistance or initially respond to but subsequently develop resistance to immune checkpoint blockade therapy. Another combination cohort is evaluating patients with TNBC who have not been previously treated with immune checkpoint blockade therapy. The remaining combination cohorts are designed to evaluate combination treatment in patients with mesothelioma; and patients with high baseline blood levels of MDSCs. We have closed the cohort designed to evaluate combination treatment in patients with adrenocortical carcinomas. The cohorts investigating mesothelioma, MDSC-high, and head and neck cancers are all fully enrolled.

We reported data from the combination expansion cohorts of the MARIO-1 study in a late-breaking poster presentation at the 33rd Annual Meeting of the Society for Immunotherapy of Cancer on November 10, 2018. Among the 44 patients evaluable for activity as of the October 14, 2018 data-cutoff date, 15 patients showed a best response of stable disease or better, including one partial response in an advanced melanoma patient who progressed on immediate prior nivolumab therapy. In addition, a patient with chemotherapy-resistant TNBC showed a 26% reduction in tumor target lesions at the first assessment. Reductions in elevated baseline levels of MDSCs were seen in these patients, as well as corresponding increases in the proliferative fraction of previously exhausted memory cytotoxic T cells. Twenty-five patients remained on study and were not evaluable for activity as of the data-cutoff date. The data included long-term follow up on additional partial responses in

two patients from the combination dose escalation component of the study. One patient with microsatellite stable gallbladder cancer and another with adrenocortical carcinoma each achieved a partial response and had been on study over 12 months and 17 months, respectively. These patients also demonstrated sustained inhibition of MDSCs during the period in which the partial response was maintained.

Among the 82 patients evaluable for safety as of October 14, 2018, the majority of side effects reported were Grade 1 or Grade 2, with three (4%) patients discontinuing the study due to treatment-related toxicities. The most common Grade 3+ adverse events were rash (n=6, 7%) and increased liver enzymes AST (n=7, 9%) and ALT (n=5, 6%). There were no treatment-related deaths. The majority of the study population is in fourth-line therapy and resistant to anti-PD1/PDL1 therapy. This safety profile is consistent with the safety data from the dose-escalation portion of MARIO-1 that we presented on June 4, 2018, during a poster session and poster discussion session at the American Society of Clinical Oncology Annual Meeting, or ASCO. The data demonstrated that IPI-549 combined with nivolumab was well tolerated at all doses tested, up to the recommended combination therapy expansion dose of IPI-549 at 40 mg QD plus nivolumab at 240 mg once every two weeks. No maximum tolerated dose was determined, and there were no treatment-related deaths. Of the 31 patients evaluable for safety as of the April 25, 2018 data-cutoff date for ASCO, the majority of adverse events were Grade 1 or 2, and the only treatment-related Grade 3 adverse events were uncomplicated rash (19%), increased liver enzymes AST or ALT (10%), and abdominal pain (3%). The pharmacokinetic/pharmacodynamic profile of IPI-549 (up to the recommended combination expansion dose of 40 mg QD) was unaffected by nivolumab co-administration, and IPI-549 in combination with nivolumab reduced immune suppression and increased immune activation, as indicated by analyses of peripheral blood.

At ASCO, we also presented updated clinical and translational data from the fully enrolled monotherapy expansion portion of MARIO-1 that demonstrated that IPI-549 as a monotherapy continued to be well tolerated at all doses studied up to the recommended dose for monotherapy expansion of 60 mg QD. IPI-549 demonstrated evidence of monotherapy clinical activity, with one durable partial response in peritoneal mesothelioma, where a patient remained on study after 20 months as of the ASCO 2018 data-cutoff date of April 25, 2018. Further, IPI-549 monotherapy reduced immune suppression and increased immune activation, as indicated by analyses of peripheral blood and paired tumor biopsies.

MARIO-275: Investigating IPI-549 in Urothelial Cancer in Patients Naïve to Immuno-Oncology Treatment

On November 2, 2018, we and BMS entered into a clinical supply agreement under which we will operationalize MARIO-275, a global, randomized study designed to evaluate the effect of adding IPI-549 to nivolumab in checkpoint-naïve advanced urothelial cancer patients who have progressed or recurred following treatment with platinum-based chemotherapy. BMS has agreed to supply nivolumab for the study. Approximately 160 patients will be randomized between combination therapy and nivolumab monotherapy plus placebo. The primary endpoint of the trial will be the overall response rate, which will be assessed in the overall population as well as in subsets of patients with different baseline levels of MDSCs. The design of MARIO-275 is supported by data from MARIO-1 presented at ASCO 2018, which showed that MDSCs were reduced in the majority of patients treated with IPI-549 monotherapy, as well as an exploratory analyses of data from a BMS clinical study evaluating nivolumab monotherapy in patients with urothelial cancer, referred to as CheckMate-275, that showed that high levels of MDSCs were associated with shorter overall survival in patients treated with nivolumab.

Instances of urothelial cancer in the United States, Japan, France, Germany, Italy, Spain and the United Kingdom are expected to increase from 402,726 to 482,037 from 2016 to 2025. Bladder cancer, of which urothelial cancer makes up approximately 96% of all instances, is the fourth most prevalent cancer in men. In 2019 alone, the American Cancer Society estimates that there will be approximately 80,470 new cases and 17,670 deaths from bladder cancer.

Phase 1b Study of Novel Triple Combination Therapy in Advanced TNBC with Arcus

We will also be seeking to advance novel triple combination therapies with Arcus, initially evaluating IPI-549 in combination with AB928, Arcus's dual adenosine receptor antagonist, and chemotherapy in patients with previously treated, advanced TNBC. As both macrophages and high adenosine levels are believed to play critical roles in creating a highly immunosuppressive tumor microenvironment in cancer after chemotherapy, the novel immuno-oncology combination being evaluated in this setting represents a potentially promising approach to treating TNBC.

MARIO-3: IPI-549 Combinations as Front-Line Treatment

On March 7, 2019, we entered into a master clinical supply agreement and F. Hoffmann-La Roche Ltd., or Roche, which we refer to as the Roche Agreement. Under the Roche Agreement, Roche will supply atezolizumab to us for our use in MARIO-3, a Phase 2 multi-arm study evaluating IPI-549 in combination with atezolizumab and nab-paclitaxel in front-line TNBC and in combination with atezolizumab and bevacizumab in front-line RCC. We intend to initiate MARIO-3 in the second half of 2019.

Collaborations

Since our inception, corporate alliances and license agreements have been integral to our strategy. Many of these alliances have provided access to breakthrough science, significant research and development support and funding, and innovative drug development programs, all intended to help us realize the full potential of our product pipeline.

Verastem

On October 29, 2016, we and Verastem Inc., or Verastem, entered into a license agreement, which we and Verastem amended and restated on November 1, 2016, effective as of October 29, 2016. We refer to the amended and restated license agreement as the Verastem Agreement. Under the Verastem Agreement, we granted to Verastem an exclusive worldwide license for the research, development, commercialization, and manufacture of duvelisib, a selective PI3K-delta,gamma inhibitor, and products containing duvelisib, which we refer to as the Licensed Products, in each case in oncology indications. Upon entry into the Verastem Agreement, Verastem assumed financial responsibility for activities that were part of our ongoing duvelisib program, including a randomized, Phase 3 monotherapy clinical study in patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma, which we refer to as the DUO Study. Verastem is obligated to use diligent efforts, as defined in the Verastem Agreement, to develop and commercialize one Licensed Product. During the term of the Verastem Agreement, we have agreed not to research, develop, manufacture or commercialize duvelisib in any indication in humans or animals. Following a short transition period, which terminated December 31, 2016, Verastem assumed all financial and operational responsibility for the duvelisib program except for the clinical shutdown costs and certain clinical close-out activities that we agreed to retain.

On September 6, 2017, Verastem notified us that the DUO Study met certain pre-specified criteria at completion triggering a $6.0 million payment under the Verastem Agreement, which we received in cash on October 13, 2017. On November 2, 2018, we received a $22.0 million cash payment earned upon the approval by the U.S. Food and Drug Administration, or FDA, on September 24, 2018 of duvelisib for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma after at least two prior therapies, as well as adult patients with relapsed or refractory follicular lymphoma after at least two prior systemic therapies.

Verastem is also obligated to pay us royalties on worldwide net sales of Licensed Products ranging from the mid-single digits to the high-single digits. The royalty obligation will continue on a product-by-product and country-by-country basis until the latest to occur of (i) the last-to-expire patent right covering the applicable Licensed Product in the applicable country, (ii) the last-to-expire patent right covering the manufacture of the applicable Licensed Product in the country of manufacture of such Licensed Product, (iii) the expiration of non-patent regulatory exclusivity for such Licensed Product in the applicable country and (iv) ten years following the first commercial sale of a Licensed Product in the applicable country, provided that upon the expiration of the last-to-expire patent right covering the Licensed Product in the United States, the applicable royalty on net sales for such Licensed Product in the United States will be reduced by 50%. The royalties are also subject to reduction by 50% of certain third-party royalty payments or patent litigation damages or settlements which might be required to be paid by Verastem if litigation were to arise, with any such reductions capped at 50% of the amounts otherwise payable during the applicable royalty payment period. On March 5, 2019, we entered into a purchase and sale agreement, or the HCR Agreement, with HealthCare Royalty Partners III, L.P., or HCR, providing for the acquisition by HCR of our interest in the royalty payments from Verastem described above. See Part II, Notes to Consolidated Financial Statements, Note 14 for details of the transaction with HCR.

In addition to the foregoing, Verastem is obligated to pay us a royalty of 4% on worldwide net sales of Licensed Products to cover the Trailing Mundipharma Royalties owed by us to Mundipharma and Purdue. Once we have fully reimbursed Mundipharma and Purdue, the Trailing Mundipharma Royalties will be reduced to 1% of net sales in the United States. The Trailing Mundipharma Royalties are payable on a product-by-product basis until the latest to occur of (i) the last-to-expire patent right covering the applicable Licensed Product in the United States, (ii) the last-to-expire patent right covering the manufacture of the applicable Licensed Product in the country of manufacture of such Licensed Product, (iii) the expiration of non-patent regulatory exclusivity for such Licensed Product in the United States and (iv) ten years following the first commercial sale of such Licensed Product in the United States, provided that, upon the expiration of the last-to-expire patent right covering a Licensed Product in the United States, the applicable royalty on net sales for such Licensed Product in the United States will be reduced by 50%. In addition, the Trailing Mundipharma Royalties are subject to reduction by 50% of certain third-party royalty payments or patent litigation damages or settlements which might be required to be paid by Verastem if litigation were to arise, with any such reductions capped at 50% of the amounts otherwise payable during the applicable royalty payment period.

The Verastem Agreement expires when each party no longer has any obligations to the other party under the Verastem Agreement. Verastem has the right to terminate the Verastem Agreement upon at least 180 days' prior written notice to us at any time. Either party may terminate the Verastem Agreement if the other party materially breaches or defaults in the performance

of its obligations. If we terminate the Verastem Agreement for Verastem's material breach, patent challenge, or insolvency, or if Verastem terminates for convenience, then, at our request and subject to our execution of a waiver of certain types of damages, Verastem will transition the duvelisib program back to us at Verastem's cost. If Verastem terminates for our breach or insolvency, Verastem will effect a more limited transition of the duvelisib program to us at our request and cost, subject to our execution of a waiver of certain types of damages, and we will thereafter pay to Verastem a low single-digit royalty on net sales of Licensed Products.

We and Verastem have made customary representations and warranties and have agreed to certain customary covenants, including confidentiality and indemnification.

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 IPI-549 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.

Under the terms of the Takeda Agreement, we are obligated to pay Takeda up to $5.0 million in remaining success-based milestone payments for the development of a product candidate other than duvelisib, which could include IPI-549. We are also obligated to pay Takeda up to $165.0 million in remaining success-based milestone payments related to the approval and commercialization of one product candidate other than duvelisib, which could be IPI-549.

Due to amendments to the Takeda Agreement, described below, we are no longer obligated to pay Takeda royalties on net sales of IPI-549, other products containing a selective inhibitor of PI3K-gamma, or duvelisib in oncology indications. However, we remain obligated to pay Takeda tiered royalties ranging from 7% to 11% on worldwide net sales of products containing a selective inhibitor of PI3K-delta or a selective dual inhibitor of PI3K delta and gamma, as described in the Takeda Agreement, including duvelisib if commercialized outside oncology indications. Such royalties are payable until the later to occur of (i) the expiration of specified patent rights and (ii) the expiration of non-patent regulatory exclusivities in a country, subject to reduction of the royalties and, in certain circumstances, limits on the number of products subject to a royalty obligation.

Under the September 2016 amendment to the Takeda Agreement, and in connection with our entry into the Verastem Agreement, we are no longer obligated to pay Takeda any remaining milestone payments for the development, approval or commercialization of duvelisib. In return, we became obligated to pay Takeda 50% of all revenue arising from certain qualifying transactions for duvelisib, including the Verastem Agreement, subject to certain exceptions including revenue we receive as reimbursement for duvelisib research and development expenses. We amended this obligation by entry into a fourth amendment to the Takeda Agreement on March 4, 2019, or Takeda Amendment. See Part II, Notes to Consolidated Financial Statements, Note 14, for details of the Takeda Amendment.

The July 2017 amendment to the Takeda Agreement terminated our obligation to pay royalties to Takeda with respect to worldwide net sales of products containing or comprised of a selective inhibitor of PI3K gamma, including but not limited to IPI-549. In consideration for such termination, we concurrently executed a convertible promissory note, which we refer to as the Takeda Note, which obligated us to pay Takeda, or its designated affiliate, the principal amount of $6.0 million together with interest accruing at a rate of 8% per annum on or before July 26, 2018 in cash or in shares of our common stock, at the election of Takeda. On March 12, 2018, we exercised our right to prepay in full the Takeda Note in the principal amount of $6.0 million together with interest of approximately $0.3 million. Takeda elected to receive $4.0 million of such payment in cash and approximately $2.3 million of such payment in shares of our common stock. Pursuant to the terms of the Takeda Note, we issued 1,134,689 shares of common stock, calculated using an average price of $2.028 per share, to Takeda's designated subsidiary, Millennium Pharmaceuticals, Inc.

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.

PellePharm

In June 2013, we entered into a license agreement with PellePharm, Inc., or PellePharm, under which we granted PellePharm exclusive global development and commercialization rights to our hedgehog inhibitor program, including IPI-926, a clinical-stage product candidate. We refer to our license agreement with PellePharm as the PellePharm Agreement and products covered by the PellePharm Agreement as Hedgehog Products.

Under the PellePharm Agreement, PellePharm is obligated to pay us up to $11.0 million in success-based milestone payments through the first commercial sale of a Hedgehog Product. We anticipate receiving a $2.0 million milestone payment for the initiation of a Phase 3 study of a Hedgehog Product in 2019. 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.

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.

PellePharm's royalty obligations to us expire on a country-by-country and Hedgehog Product-by-Hedgehog Product basis, and the PellePharm Agreement expires upon the expiration of the last royalty obligation owed by PellePharm to us, at which time the license to Hedgehog Products and licenses to our know-how as described in the PellePharm Agreement become fully-paid-up and non-royalty-bearing licenses. PellePharm has the right to terminate the PellePharm Agreement upon at least 180 days' prior written notice to us at any time, and we may terminate the PellePharm Agreement if PellePharm puts forth or actively assists a patent challenge related to our Hedgehog Product patent rights. Either party may terminate the PellePharm Agreement if the other party materially breaches or defaults in the performance of its obligations. Upon termination by either party, all rights and licenses granted by us to PellePharm under the PellePharm Agreement terminate and PellePharm shall, to the extent applicable, transfer and assign to us all rights, title, and interest in and to the trademark(s) used for Hedgehog Products in the territory covered under the PellePharm Agreement.

We and PellePharm have made customary representations and warranties and have agreed to certain customary covenants, including confidentiality and indemnification.

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 ten issued or allowed U.S. patents related to our PI3K-gamma program, which expire on various dates between 2033 and 2036, excluding any potential patent term extension. In addition, we have approximately 70 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 2036, 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. Many companies, including biotechnology and pharmaceutical 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. Many of these companies 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.

We believe that IPI-549 is the only PI3K-gamma selective inhibitor in clinical development. However, there are many competitors developing or commercializing therapies targeting macrophage biology, including the following competitors which we believe to be conducting clinical studies of product candidates targeting one or more aspects of macrophage biology: Array Biopharma, Inc., Deciphera Pharmaceuticals, Inc., Incyte Corporation (through its collaboration with Calithera Inc.), Bristol-Myers Squibb Company (through its collaboration with Five Prime Therapeutics, Inc.), Plexxikon Inc., GlaxoSmithKline plc, Eli Lilly and Company, Amgen Inc., F. Hoffmann-La Roche Ltd, Janssen Research & Development, LLC, a subsidiary of Johnson & Johnson, Forty Seven Inc., Surface Oncology, Inc., Celgene Corporation, Trillium Therapeutics Inc., Pfizer Inc., XBiotech, Inc., AbbVie Inc., Takeda Pharmaceuticals International, Inc., Novartis AG, Efranat Ltd., Seattle Genetics, Inc., AstraZeneca PLC, Apexigen Inc., X4 Pharmaceuticals, Inc., Syndax Pharmaceuticals, Inc., Syntrix Biosystems, Inc., Eisai Co., Ltd., Vaccinex, Inc., and Alligator Bioscience AB.

Further, the broader field of immuno-oncology is crowded with innovative therapies that may compete with IPI-549, including checkpoint inhibitor therapies such as PD-1 inhibitors nivolumab and pembrolizumab; PDL-1 inhibitors atezolizumab, avelumab, and durvalumab; and CTLA-4 inhibitors ipilimumab and tremelimumab. Many of these checkpoint inhibitor therapies are being evaluated in combination with other non-checkpoint inhibitor immuno-oncology product candidates. For example, nivolumab, which we are currently testing in combination with IPI-549, is being evaluated in multiple clinical trials by others in combination with non-checkpoint inhibitor candidates such as BMS-986016, an anti-LAG3 antibody; elotuzumab, a CD319 antibody; urelumab, a CD137 antibody; cabiralizumab, an anti-CSF1R antibody; and NKTR-214, an IL-2R agonist. The success of competing immuno-oncology therapies may limit the number of patients available for enrollment in our clinical trials.

Research and Development

As of March 1, 2019, our research and development group consisted of 10 employees, of whom six hold Ph.D. or M.D. degrees and three hold a masters degree. Our research and development group is focused on preclinical research, translational medicine, clinical trials and manufacturing technologies. Our research and development expense for the years ended December 31, 2018 and 2017 was approximately $19.8 million and $20.8 million, respectively.

Manufacturing and Supply

We rely primarily 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 the FDA and other regulations, and we plan to rely on third parties to manufacture commercial quantities of any products we successfully develop.

Sales and Marketing

We currently have no marketing, commercial sales, or distribution capabilities. We do, however, currently have worldwide commercialization rights for our PI3K-gamma inhibitor program, including IPI-549. In order to commercialize IPI-549, if and when it is approved for sale, we will need to, and we intend to, develop the necessary marketing, sales and distribution 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. The failure of an applicant to comply with the applicable regulatory requirements at any time during the product development process, including non-clinical testing, clinical testing, the approval process or post-approval process, may result in delays to the conduct of a study, regulatory review and approval and/or administrative or judicial sanctions. These sanctions may include, but are not limited to, the FDA's refusal to allow an applicant to proceed with clinical trials, refusal to approve pending applications, license suspension or revocation, withdrawal of an approval, warning letters, adverse publicity, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines and civil or criminal investigations and penalties brought by the FDA or Department of Justice, or DOJ, or other government entities, including state agencies.

An applicant seeking approval to market and distribute a new drug in the United States generally must satisfactorily complete each of the following steps before the product candidate will be licensed 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;
- 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 labelling 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 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;
- 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;
- payment of user fees and securing FDA approval of the NDA to allow marketing of the new drug product; and
- compliance with any post-approval requirements, including the potential requirement to implement a Risk Evaluation and Mitigation Strategy, or REMS, and the potential requirement to conduct any post-approval studies required by the FDA.

Preclinical Studies and Investigational New Drug Application

Before an applicant 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. 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, applicants must submit a protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical trials, among other things, must be submitted to the FDA as part of an IND. The FDA requires a 30-day waiting period after the filing of each IND before clinical trials may begin. This waiting period is designed to allow the FDA to review the IND to determine whether human research subjects will be exposed to unreasonable health risks. At any time during this 30-day period, or thereafter, the FDA may raise concerns or questions about the conduct of the trials as outlined in the IND and impose a clinical hold or partial clinical hold. In this case, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can begin.

Following commencement of a clinical trial under an IND, the FDA may also place a clinical hold or partial clinical hold on that trial. Clinical holds are imposed by the FDA whenever there is concern for patient safety and may be a result of new data, findings, or developments in clinical, nonclinical, and/or chemistry, manufacturing, and controls, 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. Specifically, on April 28, 2008, the FDA amended its regulations governing the acceptance of foreign clinical studies not conducted under an investigational new drug application as support for an IND or an NDA. The final rule provides that such studies must be conducted in accordance with GCP including review and approval by an independent ethics committee, or IEC, and informed consent from subjects. The GCP requirements in the final rule encompass both ethical and data integrity standards for clinical studies. The FDA's regulations are intended to help ensure the protection of human subjects enrolled in non-IND foreign clinical studies, as well as the quality and integrity of the resulting data. They further help ensure that non-IND foreign studies are conducted in a manner comparable to that required for IND studies.

In addition to the foregoing IND requirements, an IRB representing each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct continuing review and reapprove the 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. Similar requirements for posting clinical trial information are present in the European Union, through its EudraCT website: https://eudract.ema.europa.eu/, and in other countries.

Expanded Access to an Investigational Drug for Treatment Use

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

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

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

In addition, on May 30, 2018, the Right to Try Act was signed into law. The law, among other things, provides a federal framework for certain patients to access certain investigational new drug products that have completed a Phase 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."

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.

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. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB's requirements or if the product

has been associated with unexpected serious harm to patients. The FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the clinical data submitted.

Concurrent with clinical trials, companies often complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the drug as well as finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the drug candidate and, among other things, must develop methods for testing the identity, strength, quality, 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.

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, purity and potency of the drug product to the satisfaction of the FDA.

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

Following submission of an NDA, the FDA conducts a preliminary review of the application generally within 60 calendar days of its receipt and strives to inform the sponsor by the 74th day after the FDA's receipt of the submission whether the application is sufficiently complete to permit substantive review. The FDA may request additional information rather than accept the application for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA has agreed to specified performance goals in the review process of NDAs. 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. For applications seeking approval of products that are not NMEs, the ten-month and six-month review periods run from the date that the FDA receives the application. The review process and the Prescription Drug User Fee Act, or PDUFA, goal date may be extended by the FDA for three additional months to consider new information or clarification provided by the applicant to address an outstanding deficiency identified by the FDA following the original submission.

Before approving an application, the FDA typically will inspect the facility or facilities where the product is or will be manufactured. These pre-approval inspections may cover all facilities associated with an NDA 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 an applicant to develop a REMS. REMS use risk minimization strategies beyond the professional labeling to ensure that the benefits of the product outweigh the potential risks. To determine whether a REMS is needed, the FDA will consider the size of the population likely to use the product, seriousness of the disease, expected benefit of the product, expected duration of treatment, seriousness of known or potential adverse events and whether the product is a new molecular entity.

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.

Fast Track, Breakthrough Therapy, Priority Review and Regenerative Advanced Therapy Designations

The FDA is authorized to designate certain products for expedited review if they are intended to address an unmet medical need in the treatment of a serious or life-threatening disease or condition. These programs are referred to as fast track designation, breakthrough therapy designation, priority review designation and regenerative advanced therapy designation.

Specifically, the FDA may designate a product for Fast Track review if it is intended, whether alone or in combination with one or more other products, for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition. For Fast Track products, sponsors may have greater interactions with the FDA and the FDA may initiate review of sections of a Fast Track product's application before the application is complete. This rolling review may be available if the FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a Fast Track product may be effective. The sponsor must also provide, and the FDA must approve, a schedule for the submission of the remaining information and the sponsor must pay applicable user fees. However, the FDA's time period goal for reviewing a Fast Track application does not begin until the last section of the application is submitted. In addition, the Fast Track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

Second, a product may be designated as a Breakthrough Therapy if it is intended, either alone or in combination with one or more other products, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The FDA may take certain actions with respect to Breakthrough Therapies, including holding meetings with the sponsor throughout the development process; providing timely advice to the product sponsor regarding development and approval; involving more senior staff in the review process; assigning a cross-disciplinary project lead for the review team; and taking other steps to design the clinical trials in an efficient manner.

Third, the FDA may designate a product for priority review if it is a product that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. The FDA determines, on a case-by-case basis, whether the proposed product represents a significant improvement when compared with other available therapies. Significant improvement may be illustrated by evidence of increased effectiveness in the treatment of a condition, elimination or substantial reduction of a treatment-limiting product reaction, documented enhancement of patient compliance that may lead to improvement in serious outcomes, and evidence of safety and effectiveness in a new subpopulation. A priority designation is intended to direct overall attention and resources to the evaluation of such applications, and to shorten the FDA's goal for taking action on a marketing application from ten months to six months.

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 has the potential to address unmet medical needs for such disease or condition. The benefits of a regenerative advanced therapy designation include early interactions with FDA to expedite development and review, benefits available to breakthrough therapies, potential eligibility for priority review and accelerated approval based on surrogate or intermediate endpoints.

Accelerated Approval Pathway

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

For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit.

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

The accelerated approval pathway is most often used in settings in which the course of a disease is long and an extended period of time is required to measure the intended clinical benefit of a product, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly. Thus, accelerated approval has been used extensively in the development and approval of products for treatment of a variety of cancers in which the goal of therapy is generally to improve survival or decrease morbidity and the duration of the typical disease course requires lengthy and sometimes large trials to demonstrate a clinical or survival benefit. Thus, the benefit of accelerated approval derives from the potential to receive approval based on surrogate endpoints sooner than possible for trials with clinical or survival endpoints, rather than deriving from any explicit shortening of the FDA approval timeline, as is the case with priority review.

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

The FDA's Decision on an NDA

On the basis of the FDA's evaluation of the application and accompanying information, including the results of the inspection of the manufacturing facilities, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

If the FDA approves a new product, it may limit the approved indications for use of the product. The agency may also 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 healthcare professionals, and elements to assure safe use, or ETASU. ETASU can include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring and the use of 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, healthcare 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. It may be permissible, under very specific, narrow conditions, for a manufacturer to engage in nonpromotional, non-misleading communication regarding off-label information, such as distributing scientific or medical journal information.

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.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, and its implementing regulations, as well as the Drug Supply Chain Security Act, or DSCA, which regulate the distribution and tracing of prescription drug samples at the federal level, and set minimum standards for the regulation of distributors by the states. The PDMA, its implementing regulations and state laws limit the distribution of prescription pharmaceutical product samples, and the DSCA imposes requirements to ensure accountability in distribution and to identify and remove counterfeit and other illegitimate products from the market.

Pediatric Studies and Exclusivity

Under the Pediatric Research Equity Act of 2003, or PREA, an NDA or supplement thereto must contain data that are adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. Sponsors must also submit pediatric study plans prior to the assessment data. Those plans must contain an outline of the proposed pediatric study or studies the applicant plans to conduct, including study objectives and design, any deferral or waiver requests and other information required by regulation. The applicant, the FDA, and the FDA's internal review

committee must then review the information submitted, consult with each other and agree upon a final plan. The FDA or the applicant may request an amendment to the plan at any time.

For drugs intended to treat a serious or life-threatening disease or condition, the FDA must, upon the request of an applicant, meet to discuss preparation of the initial pediatric study plan or to discuss deferral or waiver of pediatric assessments. In addition, the FDA will meet early in the development process to discuss pediatric study plans with sponsors and the FDA must meet with sponsors by no later than the end-of-phase 1 meeting for serious or life-threatening diseases and by no later than ninety (90) days after the FDA's receipt of the study plan.

The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. Additional requirements and procedures relating to deferral requests and requests for extension of deferrals are contained in the FDA Safety and Innovation Act. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation.

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

Drug products that have received orphan designation are exempt from the requirements of PREA. Specifically, Section 505B(k) of the FDCA contains a statutory exemption from the requirement to conduct pediatric studies under PREA for certain drugs with orphan designation. Under this exemption, PREA does not apply to any application for a drug for an indication for which orphan designation has been granted when that application would otherwise trigger PREA because the application contains a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration. In July 2018, FDA issued draft guidance clarifying that it does not expect to grant any additional orphan-drug designation to drugs for pediatric subpopulations of common diseases. Pediatric-subpopulation designations that have already been granted will not be affected by this change.

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

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 a 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, or if the company with orphan drug exclusivity is not able to meet market demand. This is the case despite an earlier court opinion holding that the Orphan Drug Act unambiguously required the FDA to recognize orphan exclusivity regardless of a showing of clinical superiority.

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 applicant 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 applicant for approval of the application "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted."

Thus, Section 505(b)(2) authorizes the FDA to approve an NDA based on safety and effectiveness data that were not developed by the applicant. 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) applicant can establish that reliance on the FDA's previous approval is scientifically appropriate, the applicant 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) applicant.

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. To obtain approval of a generic drug, an applicant must submit an abbreviated new drug application, or ANDA, to the agency. An ANDA is a comprehensive submission that contains, among other things, data and information pertaining to the active pharmaceutical ingredient, bioequivalence, drug product formulation, specifications and stability of the generic drug, as well as analytical methods, manufacturing process validation data and quality control procedures. ANDAs are "abbreviated" because they generally do not include preclinical and clinical data to demonstrate safety and effectiveness. Instead, in support of such applications, a generic manufacturer may rely on the preclinical and clinical testing previously conducted for a drug product previously approved under an NDA, known as the reference-listed drug, or RLD.

Specifically, in order for an ANDA to be approved, the FDA must find that the generic version is identical to the RLD with respect to the active ingredients, the route of administration, the dosage form, the strength of the drug and the conditions of use of the drug. At the same time, the FDA must also determine that the generic drug is "bioequivalent" to the innovator drug. Under the statute, a generic drug is bioequivalent to a RLD if "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug." Upon approval of an ANDA, the FDA indicates whether the generic product is "therapeutically equivalent" to the RLD in its publication "Approved Drug Products with Therapeutic Equivalence Evaluations," also referred to as the "Orange Book." Physicians and pharmacists consider a therapeutic equivalent generic drug to be fully substitutable for the RLD. In addition, by operation of certain state laws and numerous health insurance programs, the FDA's designation of therapeutic equivalence often results in substitution of the generic drug without the knowledge or consent of either the prescribing physician or patient.

Under the Hatch-Waxman 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 applicant may submit its application four years following the original product approval. The FDCA also provides for a period of three years of exclusivity if the NDA includes reports of one or more new clinical investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the applicant and are essential to the approval of the application.

The FDCA also provides for a period of three years of exclusivity if the NDA includes reports of one or more new clinical investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the applicant and are essential to the approval of the application. This three-year exclusivity period often protects changes to a previously approved drug product, such as a new dosage form, route of administration, combination or indication. Three-year exclusivity would be available for a drug product that contains a previously approved active moiety, provided the statutory requirement for a new clinical investigation is satisfied. Unlike five-year NCE exclusivity, an award of three-year exclusivity does not block the FDA from accepting ANDAs seeking approval for generic versions of the drug as of the date of approval of the original drug product. The FDA typically makes decisions about awards of data exclusivity shortly before a product is approved.

The FDA must establish a priority review track for certain generic drugs, requiring the FDA to review a drug application within eight (8) months for a drug that has three (3) or fewer approved drugs listed in the Orange Book and is no longer protected by any patent or regulatory exclusivities, or is on the FDA's drug shortage list. The new legislation also authorizes the FDA to expedite review of ''competitor generic therapies'' or drugs with inadequate generic competition, including holding meetings with or providing advice to the drug sponsor prior to submission of the application.

Hatch-Waxman Patent Certification and the 30-Month Stay

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

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

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

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

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

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

Patent Term Restoration and Extension

A patent claiming a new drug product may be eligible for a limited patent term extension under the Hatch-Waxman Act, which permits a patent restoration of up to five years for patent term lost during product development and the FDA regulatory review. The restoration period granted on a patent covering a product is typically one-half the time between the effective date of a clinical investigation involving human beings is begun and the submission date of an application, plus the

time between the submission date of an application and the ultimate approval date. Patent term restoration cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date. Only one patent applicable to an approved product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent in question. A patent that covers multiple products for which approval is sought can only be extended in connection with one of the approvals. The USPTO reviews and approves the application for any patent term extension or restoration in consultation with the FDA.

Healthcare Law and Regulation

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

- the federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, paying, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made, in whole or in part, under a federal healthcare program such as Medicare and Medicaid;

- the federal civil and criminal false claims laws, including the civil False Claims Act, and civil monetary penalties laws, which prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false, fictitious or fraudulent or knowingly making, using or causing to made or used a false record or statement to avoid, decrease or conceal an obligation to pay money to the federal government.

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created additional federal criminal laws that prohibit, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, and their respective implementing regulations, including the Final Omnibus Rule published in January 2013, which impose obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;

- the federal false statements statute, which prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services;

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

- the federal transparency requirements known as the federal Physician Payments Sunshine Act, under the Patient Protection and Affordable Care Act, as amended by the Health Care Education Reconciliation Act, or the ACA, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report annually to the Centers for Medicare & Medicaid Services, or CMS, within the United States Department of Health and Human Services, information related to payments and other transfers of value made by that entity to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members; and

- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, which may apply to healthcare items or services that are reimbursed by non-government third-party payors, including private insurers.

Some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring manufacturers to report information related to payments to physicians and other healthcare 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.

Pharmaceutical Insurance Coverage and Healthcare 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.

There have been a number of federal and state proposals during the last few years regarding the pricing of pharmaceutical and biopharmaceutical products, limiting coverage and reimbursement for drugs and biologics and other medical products, government control and other changes to the healthcare system in the United States. In March 2010, the ACA was enacted, which includes measures that have significantly changed healthcare financing by both governmental and private insurers. The provisions of the ACA of importance to the pharmaceutical and biotechnology industry are, among others, the following:

- an annual, nondeductible fee on any entity that manufactures or imports certain branded prescription drug agents or biologic agents, which is apportioned among these entities according to their market share in certain government healthcare programs;
- an increase in the rebates a manufacturer must pay under the Medicaid Drug Rebate Program to 23.1% and 13% of the average manufacturer price for branded and generic drugs, respectively;
- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts to negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D;
- extension of manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations, unless the drug is subject to discounts under the 340B drug discount program;
- a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding new mandatory eligibility categories for certain individuals with

income at or below 133% of the federal poverty level, thereby potentially increasing manufacturers' Medicaid rebate liability;

- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;
- new requirements under the federal Physician Payments Sunshine Act for drug manufacturers to report information related to payments and other transfers of value made to physicians and teaching hospitals as well as ownership or investment interests held by physicians and their immediate family members;
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research;
- creation of the Independent Payment Advisory Board, which, if and when impaneled, will have authority to recommend certain changes to the Medicare program that could result in reduced payments for prescription drugs; and
- establishment of a Center for Medicare and Medicaid Innovation at CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending.

Other legislative changes have been proposed and adopted since the ACA was enacted. These changes include the Budget Control Act of 2011, which, among other things, led to aggregate reductions to Medicare payments to providers of up to 2% per fiscal year that started in 2013 and will stay in effect through 2024 unless additional congressional action is taken, and the American Taxpayer Relief Act of 2012, which, among other things, reduced Medicare payments to several types of providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used. Further, there have been several recent U.S. congressional inquiries and proposed state and federal legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products.

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

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

Further, there have been several recent U.S. congressional inquiries and proposed federal and proposed and enacted state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products. For example, there have been several recent U.S. congressional inquiries and proposed federal and proposed and enacted state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products. At the federal level, Congress and the Trump Administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. For example, on May 11, 2018, the Trump Administration issued a plan to lower drug prices. Under this blueprint for action, the Trump Administration indicated that the Department of Health and Human Services, or HHS, will: take steps to end the gaming of regulatory and patent processes by drug makers to unfairly protect monopolies; advance biosimilars and generics to boost price competition; evaluate the inclusion of prices in drug makers' ads to enhance price competition; speed access to and lower the cost of new drugs by clarifying policies for sharing information between insurers and drug makers; avoid excessive pricing by relying more on value-based pricing by expanding outcome-based payments in Medicare and Medicaid; work to give Part D plan sponsors more negotiation power with drug makers; examine which Medicare Part B drugs could be negotiated for a lower price by Part D plans, and improving the design of the Part B Competitive Acquisition Program; update Medicare's drug-pricing dashboard to increase transparency; prohibit Part D contracts that include "gag rules" that prevent pharmacists from informing patients when they could pay less out-of-pocket by not using insurance; and require that Part D plan members be provided with an annual statement of plan payments, out-of-pocket spending, and drug price increases.

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 healthcare authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other healthcare 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, an applicant 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

The Clinical Trials Directive 2001/20/EC, the Directive 2005/28/EC on Good Clinical Practice, or GCP, and the related national implementing provisions of the individual EU member states govern the system for the approval of clinical trials in the EU. Under this system, an applicant must obtain prior approval from the competent national authority of the EU member states in which the clinical trial is to be conducted. Furthermore, the applicant may only start a clinical trial at a specific study site after the competent ethics committee has issued a favorable opinion. The clinical trial application must be accompanied by, among other documents, an investigational medicinal product dossier (the Common Technical Document) with supporting information prescribed by Directive 2001/20/EC, Directive 2005/28/EC, where relevant the implementing national provisions of the individual EU member states and further detailed in applicable guidance documents.

In April 2014, the new Clinical Trials Regulation, (EU) No 536/2014, or the Clinical Trials Regulation, was adopted. The Clinical Trial Regulation was published on June 16, 2014 but is not expected to apply until sometime in 2019. The Clinical Trials Regulation will be directly applicable in all the EU member states, repealing the current Clinical Trials Directive 2001/20/EC and replacing any national legislation that was put in place to implement the Directive. Conduct of all clinical trials performed in the EU will continue to be bound by currently applicable provisions until the new Clinical Trials Regulation

becomes applicable. The extent to which on-going clinical trials will be governed by the Clinical Trials Regulation will depend on when the Clinical Trials Regulation becomes applicable and on the duration of the individual clinical trial. If a clinical trial continues for more than three years from the day on which the Clinical Trials Regulation becomes applicable the Clinical Trials Regulation will at that time begin to apply to the clinical trial.

The new Clinical Trials Regulation aims to simplify and streamline the approval of clinical trials in the EU. The main characteristics of the regulation include: a streamlined application procedure via a single entry point, the "EU Portal and Database"; a single set of documents to be prepared and submitted for the application as well as simplified reporting procedures for clinical trial sponsors; and a harmonized procedure for the assessment of applications for clinical trials, which is divided in two parts. Part I is assessed by the appointed reporting Member State, whose assessment report is submitted for review by the sponsor and all other competent authorities of all EU member states in which an application for authorization of a clinical trial has been submitted, or concerned member states. Part II is assessed separately by each concerned member state. Strict deadlines have been established for the assessment of clinical trial applications. The role of the relevant ethics committees in the assessment procedure will continue to be governed by the national law of the concerned member state. However, overall related timelines will be defined by the Clinical Trials Regulation.

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, an applicant must submit an MAA either under a centralized procedure administered by the EMA, or one of the procedures administered by competent authorities in the EU member states (decentralized procedure, national procedure or mutual recognition procedure). A marketing authorization may be granted only to an applicant established in the EU. Regulation (EC) No 1901/2006 provides that prior to obtaining a marketing authorization in the EU, applicants have to demonstrate compliance with all measures included in an EMA-approved 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 applicant 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 applicant 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 grant a so-called "marketing authorization under exceptional circumstances". Such authorization is intended for products for which the applicant can demonstrate that it is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or in the present state of scientific knowledge, comprehensive information cannot be provided, or it would be contrary to generally accepted principles of medical ethics to collect such information. Consequently, marketing authorization under exceptional circumstances may be granted subject to certain specific obligations, which may include the following:

- the applicant must complete an identified program of studies within a time period specified by the competent authority, the results of which form the basis of a reassessment of the benefit/risk profile;
- the medicinal product in question may be supplied on medical prescription only and may in certain cases be administered only under strict medical supervision, possibly in a hospital and in the case of a radiopharmaceutical, by an authorized person; and
- the package leaflet and any medical information must draw the attention of the medical practitioner to the fact that the particulars available concerning the medicinal product in question are as yet inadequate in certain specified respects.

A marketing authorization under exceptional circumstances is subject to annual review to reassess the risk-benefit balance in an annual reassessment procedure. Continuation of the authorization is linked to the annual reassessment and a negative assessment could potentially result in the marketing authorization being suspended or revoked. The renewal of a marketing authorization of a medicinal product under exceptional circumstances, however, follows the same rules as a "normal" marketing authorization. Thus, a marketing authorization under exceptional circumstances is granted for an initial five years, after which the authorization will become valid indefinitely, unless the EMA decides that safety grounds merit one additional five-year renewal.

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 applicant 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 applicants 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 applicant must demonstrate that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the EU or, if such method exists, the drug will be of significant benefit to those affected by that condition.

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

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

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

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

General Data Protection Regulation

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

will be a rigorous and time-intensive process that may increase the cost of doing business or require companies to change their business practices to ensure full compliance.

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 healthcare expenditures, especially in light of the severe fiscal and debt crises experienced by many countries in the EU. The downward pressure on healthcare costs in general, particularly prescription 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 1, 2019, we had 25 full-time employees, 10 of whom were engaged in research and development and 15 of whom were engaged in general business management, administration and finance. Approximately 72% of our employees hold advanced degrees. Our success depends, in part, on our ability to recruit and retain talented and trained scientific and business personnel and senior leadership. 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. We believe that relations with our employees are good.

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 784 Memorial Drive, Cambridge, Massachusetts 02139, and our telephone number at that address 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.

Executive Officers

The following table lists the positions, names and ages of our executive officers as of March 8, 2019:

Name	Age	Position
Adelene Q. Perkins	59	Chief Executive Officer
Samuel Agresta, M.D., M.P.H.	46	Chief Medical Officer
Lawrence E. Bloch, M.D., J.D.	53	President and Treasurer
Jeffery L. Kutok, M.D., Ph.D.	52	Senior Vice President, Chief Scientific Officer
Seth A. Tasker, J.D.	40	Vice President, General Counsel and Secretary

Adelene Q. Perkins, M.B.A., 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. Ms. Perkins was on the board of Padlock Therapeutics, a privately held biotechnology company, from 2015 to 2016 and was treasurer of the Massachusetts Life Sciences Center from 2014 to 2016. 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.

Samuel Agresta, M.D., M.P.H., has served as our Senior Vice President, Chief Medical Officer since August 2018. Prior to joining Infinity, Dr. Agresta held several positions at Agios Pharmaceuticals, Inc., or Agios, a publicly traded biopharmaceuticals company, from 2011 to July 2018, most recently serving as Vice President and Head of Clinical Development since 2013. In this capacity he oversaw the development and approval of enasidineb and ivosidenib for the treatment of patients with acute myeloid leukemia that harbor isocitrate dehydrogenase mutations. Before joining Agios, Dr. Agresta held positions of responsibility in oncology clinical development at Merrimack Pharmaceuticals and Genentech, Inc., both publicly traded pharmaceuticals companies. Prior to his industry experience, Dr. Agresta served on the oncology faculty at the H. Lee Moffitt Cancer Center and Research Institute where he specialized in adolescent sarcoma care and participated in numerous industry trials. Dr. Agresta received his medical degree, internal medicine training, and served as chief resident at Tulane University School of Medicine in New Orleans. While in medical school, he also received a master's degree in public health and tropical medicine from Tulane University School of Public Health. He completed his medical oncology fellowship at the University of South Florida and Moffitt Cancer Center and received a master's degree in clinical investigation from the University of South Florida.

Lawrence E. Bloch, M.D., J.D., M.B.A., 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.

Jeffery L. Kutok, M.D., Ph.D., has served as our Senior Vice President and Chief Scientific Officer since February 2017. He previously served as our Vice President of Biology and Translational Science from August 2013 to February 2017, our Senior Director of Biology and Translational Science from August 2012 to August 2013, our Senior Director of Molecular Pathology from March 2012 to August 2012, and our Director of Molecular Pathology from January 2011 to March 2012. Prior to joining Infinity, Dr. Kutok was an associate professor of pathology at Harvard Medical School and Brigham and Women's Hospital. His laboratory focused on translational medicine research and biomarker identification in cancer, and he is an author on over 200 journal articles, reviews and book chapters. Dr. Kutok is board certified in Anatomic Pathology and Hematology and had clinical duties in Hematopathology and Molecular Diagnostics at Brigham and Women's Hospital. Dr. Kutok received his B.S. in biology and his M.D., Ph.D. in medicine and molecular pathology from the State University of New York at Stony

Brook. His Ph.D. was earned working in the laboratory of Dr. Barry Coller, M.D. in the field of platelet pathobiology. He was also a post-doctoral fellow at Harvard University in the laboratory of Dr. Gary Gilliland, M.D., Ph.D.

Seth A. Tasker, J.D., M.B.A., has served as our Vice President, General Counsel and Secretary since July 2016. He previously served as 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., 784 Memorial Drive, Cambridge, Massachusetts 02139, 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 should be carefully considered. 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. Please see "Cautionary Note Regarding Forward Looking Information" on page 1 of 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

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, 2018, we had an accumulated deficit of $678.8 million. We expect to continue to spend significant resources to fund IPI-549, 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 or revenue from royalties owed to us under the Verastem Agreement, we expect to incur substantial operating losses over the next several years as our clinical trial and drug manufacturing activities continue. (For more about Verastem, Inc., or Verastem, and the Verastem Agreement, see *Part I Business — Collaborations — Verastem* in this Annual Report on Form 10-K.) In addition, if we proceed to seek and possibly obtain regulatory approval of IPI-549, 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.

IPI-549 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 IPI-549 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 IPI-549 or future efforts to commercialize IPI-549.

Developing pharmaceutical products, including conducting preclinical studies and clinical trials, is a very time consuming, expensive and uncertain process that takes years to complete. We will need substantial additional funds to support our planned operations. In the absence of additional funding or business development activities, we believe that our existing cash, cash equivalents and available-for-sale securities at December 31, 2018 will be adequate to satisfy our capital needs for at least the next twelve months.

Our estimate as to how long we expect our existing cash, cash equivalents and available-for-sale securities to be able to continue to fund our operations is based on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect. Further, changing circumstances, some of which may be beyond our control, could cause us to consume capital significantly faster than we currently anticipate, and we may need to seek additional funds sooner than planned. Our future 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 IPI-549, currently in clinical development;
- the timing of, and the costs involved in, obtaining regulatory approvals for IPI-549;
- subject to receipt of marketing approval, revenue, if any, received from commercial sales of IPI-549;
- 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, our product candidates 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.

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, it 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. For example, during the fiscal year ending December 31, 2018, we sold 4,461,893 shares of common stock at a weighted average price per share of $2.18 under our common stock sales facility for $9.3 million in net proceeds. Additionally, we sold 1,134,689 shares of common stock to Millennium Pharmaceuticals, Inc., the designated subsidiary of Takeda Pharmaceutical Company Limited, as partial repayment for the convertible promissory note, or the Takeda Note, we issued on July 26, 2017. We refer to our PI3K inhibitor program licensor, including its several subsidiaries, as Takeda.

If we incur additional indebtedness, there could be significant adverse consequences, including:

- requiring us to dedicate a portion of our cash resources to the payment of interest and principal, and prepayment and repayment fees and penalties, thereby reducing money available to fund working capital, capital expenditures, product development and other general corporate purposes;
- requiring us to grant security interests on our assets;
- subjecting us to restrictive covenants that may reduce our ability to incur additional debt, make capital expenditures, create liens, redeem stock, declare dividends, and acquire, sell or license intellectual property rights, or other operating restrictions that could adversely impact our ability to conduct our business;
- limiting our flexibility in planning for, or reacting to, changes in our business and the industry in which we compete;
- placing us at a competitive disadvantage compared to our competitors that have less debt or better debt servicing options; and

- increasing our vulnerability to adverse changes in general economic, industry and market conditions.

We may not have sufficient funds, and may be unable to arrange for additional financing, to pay the amounts due under any debt that we may incur. Failure to make payments or comply with other covenants under these debt instruments could result in an event of default and acceleration of amounts due. If an event of default occurs and the lenders accelerate the amounts due, we may not be able to make accelerated payments.

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 IPI-549 that we would otherwise prefer to develop and market ourselves, or to scale back, suspend, or terminate our business operations.

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 IPI-549 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 IPI-549 and Any Future Product Candidate

We are dependent on the success of IPI-549, our only product candidate.

Our prospects are substantially dependent on our ability to develop, obtain marketing approval for and successfully commercialize product candidates in one or more disease indications.

We currently have no products approved for sale and are investing substantially all of our efforts and financial resources in the development of IPI-549.

The success of IPI-549 will depend on several factors, including the following:

- our ability to raise additional capital;
- initiation, enrollment and successful completion of clinical trials, including in combination with other agents;
- a safety, tolerability and efficacy profile that is satisfactory to the U.S. Food and Drug Administration, or FDA, or any comparable foreign regulatory authority for marketing approval;
- timely receipt of marketing approvals from applicable regulatory authorities;
- the extent of any required post-marketing approval commitments to applicable regulatory authorities;
- establishment of supply arrangements with third-party raw materials suppliers and manufacturers;
- establishment of arrangements with third-party manufacturers to obtain finished drug product that is appropriately packaged for sale;
- adequate ongoing availability of raw materials and drug product for clinical development and any commercial sales;
- obtaining and maintaining patent, trade secret protection and regulatory exclusivity, both in the United States and internationally;
- protection of our rights in our intellectual property portfolio;
- successful launch of commercial sales following any marketing approval;
- a continued acceptable safety profile following any marketing approval;
- commercial acceptance by patients, the medical community and third-party payors; and
- our ability to compete with other therapies.

We also expect that the success of IPI-549 will depend primarily on its therapeutic potential in combination with other therapeutics, such as checkpoint inhibitor therapies, and not as a monotherapy.

Many of these factors are beyond our control, including clinical development, the regulatory submission process, potential threats to our intellectual property rights and the manufacturing, marketing and sales efforts of any collaborator. If we are unable to develop, receive marketing approval for and successfully commercialize IPI-549, on our own or with any collaborator, or experience delays as a result of any of these factors or otherwise, our business would be substantially harmed.

IPI-549 remains subject to clinical testing and regulatory approval. This process is highly uncertain, and we may never be able to obtain marketing approval for IPI-549.

To date, we have not obtained approval from the FDA or any foreign regulatory authority to market or sell any product candidates. IPI-549 and any future product candidates that we seek to advance will be subject to extensive governmental regulations relating to development, clinical trials, manufacturing and commercialization. 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.

For example, we are evaluating IPI-549, our only product candidate, in clinical development. If our current clinical trials 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 IPI-549. Satisfaction of these and other regulatory requirements is costly, time consuming, uncertain and subject to unanticipated delays. It is possible that IPI-549 will not obtain marketing approval. Even if IPI-549 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 IPI-549 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 IPI-549 or mistakenly believe that IPI-549 is toxic or not well tolerated when that is not in fact the case.

We may conduct clinical trials for IPI-549 or future product candidates at sites outside the United States. The FDA may not accept data from trials conducted in such locations and the conduct of trials outside the United States could subject us to additional delays and expense.

In the future we may conduct one or more of our clinical trials with one or more trial sites that are located outside the United States. Although the FDA may accept data from clinical trials conducted outside the United States, acceptance of these data is subject to certain conditions imposed by the FDA. For example, the clinical trial must be well designed and conducted and performed by qualified investigators in accordance with good clinical 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 IPI-549 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; and
- diminished protection of intellectual property in some countries.

IPI-549 must undergo rigorous clinical trials prior to receipt of regulatory approval. Any problems in these clinical trials could delay or prevent commercialization of IPI-549.

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. Any of the following could delay or disrupt the clinical development of IPI-549:

- unfavorable results of discussions with the FDA or comparable foreign authorities regarding the scope or design of our 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;
- 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;
- inadequate supply, delays in distribution or deficient quality of, or inability to purchase or manufacture drug product, comparator drugs or other materials necessary to conduct our 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;
- serious and unexpected drug-related side effects experienced by participants in our 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;
- the placement by the FDA or a foreign regulatory authority of a clinical hold on a trial; or
- any restrictions on, or post-approval commitments with regard to, any regulatory approval we ultimately obtain that render the product candidate not commercially viable.

We may suspend, or the FDA or other applicable regulatory authorities may require us to suspend, clinical trials of IPI-549 at any time if we or they believe the patients participating in such clinical trials, or in independent third-party clinical trials for drugs based on similar technologies, are being exposed to unacceptable health risks or for other reasons.

The delay, suspension or discontinuation of any of our clinical trials, or a delay in the analysis of clinical data for IPI-549, for any of the foregoing reasons, could adversely affect our ability to obtain regulatory approval for and to commercialize IPI-549, increase our operating expenses and have a material adverse effect on our financial results.

Adverse events or undesirable side effects caused by, or other unexpected properties of, IPI-549, alone or in combination with other agents, may be identified during development and could delay or prevent IPI-549 marketing approval or limit its use.

Adverse events or undesirable side effects caused by, or other unexpected properties of, IPI-549, 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 IPI-549 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 IPI-549 is associated with adverse events or undesirable side effects or has properties that are unexpected, we, or any collaborators, may need to abandon development or limit development of IPI-549 to certain uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective. Many compounds that initially showed promise in clinical or earlier stage testing have later been found to cause undesirable or unexpected side effects that prevented further development of the compound. Combining two or more agents may increase the instances of or severity of adverse events or undesirable effects.

If the market opportunities for IPI-549 or product candidates we may develop in the future are smaller than we believe they are, even assuming approval of a drug candidate, our business may suffer.

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 IPI-549 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 number of patients may turn out to be lower than expected. Likewise, the potentially addressable patient population for our product candidate may be limited or may not be amenable to treatment with our product candidate, and new patients may become increasingly difficult to identify or gain access to, which would adversely affect our results of operations and our business.

If we, or any future collaborators, experience any of a number of possible unforeseen events in connection with clinical trials of IPI-549, potential clinical development, marketing approval or commercialization of IPI-549 could be delayed or prevented.

We, or any future collaborators, may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent clinical development, marketing approval or commercialization of IPI-549, including:

- regulators or institutional review boards may not authorize us, any collaborators or our or their investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- we, or any collaborators, may have delays in reaching or fail to reach agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites;
- clinical trials of IPI-549 may produce unfavorable or inconclusive results;
- we, or any collaborators, may decide, or regulators may require us or them, to conduct additional clinical trials or abandon IPI-549;
- the number of patients required for clinical trials of IPI-549 may be larger than we, or any collaborators, anticipate; patient enrollment in these clinical trials may be slower than we, or any collaborators, anticipate; or participants may drop out of these clinical trials at a higher rate than we, or any collaborators, anticipate;
- the cost of planned clinical trials of IPI-549 may be greater than we anticipate;
- our third-party contractors or those of any collaborators, including those manufacturing IPI-549, comparator or combination drugs, or components or ingredients thereof or conducting clinical trials on our behalf or on behalf of any collaborators, may fail to comply with regulatory requirements or meet their contractual obligations to us or any collaborators in a timely manner or at all;
- patients that enroll in a clinical trial may misrepresent their eligibility to do so or may otherwise not comply with the clinical trial protocol, resulting in the need to drop the patients from the clinical trial, increase the needed enrollment size for the clinical trial or extend the clinical trial's duration;
- we, or any collaborators, may have to delay, suspend or terminate clinical trials of IPI-549 for various reasons, including a finding that the participants are being exposed to unacceptable health risks, undesirable side effects or other unexpected characteristics of IPI-549;
- regulators or institutional review boards may require 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 IPI-549 or findings of undesirable effects caused by a chemically or mechanistically similar product or product candidate;
- the FDA or comparable foreign regulatory authorities may disagree with our, or any collaborators', clinical trial designs or our or their interpretation of data from preclinical studies and clinical trials;
- the FDA or comparable foreign regulatory authorities may fail to approve or subsequently find fault with the manufacturing processes or facilities of third-party manufacturers with which we, or any collaborators, enter into agreements for clinical and commercial supplies;
- the supply or quality of raw materials or manufactured product candidates and combination or comparator drugs or other materials necessary to conduct clinical trials of IPI-549 may be insufficient, inadequate or not available at an acceptable cost, or we may experience interruptions in supply; and
- the approval policies or regulations of the FDA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient to obtain marketing approval.

Product development costs for us, 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 IPI-549. We do not know whether any 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 IPI-549 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 IPI-549 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 IPI-549, 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.

Results of preclinical studies and early clinical trials may not be successful, and even if they are successful, may not be predictive of results of future late-stage clinical trials.

We are in early-stage clinical development for IPI-549. 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. The design of a clinical trial can determine whether its results will support approval of a product and flaws in the design of a clinical trial may not become apparent until the clinical trial is well advanced. We may be unable to design and execute a clinical trial to support marketing approval. In addition, preclinical and clinical data are often susceptible to varying interpretations and analyses. Many companies that believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval for the product candidates. Even if we, or any collaborators, believe that the results of clinical trials for IPI-549 warrant marketing approval, the FDA or comparable foreign regulatory authorities may disagree and may not grant marketing approval of IPI-549.

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 IPI-549, the development timeline and regulatory approval and commercialization prospects for IPI-549 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, which is a function of many factors, including:

- the size and nature of the patient population;
- the severity of the disease under investigation;
- the nature and complexity of the trial protocol, including eligibility criteria for the trial;
- the number of clinical trial sites and the proximity of patients to those sites;
- standard of care in disease under investigation;
- the commitment of clinical investigators to identify eligible patients;
- competing studies or trials; and
- clinicians' and patients' perceptions as to the potential advantages and risks of the drug being studied in relation to other available therapies, including any new drugs that may be approved for the indications we are investigating.

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 foreign regulatory authorities could require us to conduct clinical trials with a larger number of patients than has been projected for IPI-549 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, which could impair the validity or statistical significance of the clinical trial. A number of factors can influence the patient discontinuation rate, including, but not limited to:

- the inclusion of a placebo or comparator arm in a trial;
- possible inactivity or low activity of the product candidate being tested at one or more of the dose levels being tested;
- the occurrence of adverse side effects, whether or not related to the product candidate; and
- the availability of numerous alternative treatment options, including clinical trials evaluating competing product candidates, that may induce patients to discontinue their participation in the trial.

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.

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

We have never obtained marketing approval for a product candidate. It is possible that the FDA may refuse to accept for substantive review any new drug applications, or NDAs, that we may in the future submit for any product candidate or may conclude after review of our data that our application is insufficient to obtain marketing approval. If the FDA does not accept or

approve any future NDAs we may submit, it may require that we conduct additional clinical trials, preclinical studies or manufacturing validation studies and submit that data before it will reconsider our applications. Depending on the extent of these or any other FDA-required trials or studies, approval of any application that we submit may be delayed by several years, or may require us to expend more resources than we have available. It is also possible that additional trials or studies, if performed and completed, may not be considered sufficient by the FDA to approve our NDAs.

Any delay in obtaining, or an inability to obtain, marketing approvals would prevent us from commercializing IPI-549 or any product candidates we may develop in the future, or any companion diagnostics, generating revenues and achieving and sustaining profitability. If any of these outcomes occurs, we may be forced to abandon our development efforts for one or more product candidates, which could significantly harm our business.

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 IPI-549. 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 safety concerns with respect to such product may also result in a significant drop in the potential sales of such product, damage to our reputation in the marketplace, or result in our and our collaborators' becoming subject to lawsuits, including class actions. 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 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 IPI-549, 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 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 do not have a sales, marketing or distribution infrastructure and have no experience in the sale, marketing or distribution of pharmaceutical products. 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. This may be costly, and our investment could be lost if we cannot retain or reposition our sales and marketing personnel. In addition, we may not be able to hire or retain a sales force in the United States that is sufficient in size or has adequate expertise in the medical markets that we 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. If a potential partner has development or commercialization expertise that we believe is particularly relevant to one of our products, then we may seek to collaborate with that potential partner even if we believe we could otherwise develop and commercialize the product independently.

As a result of entering into any such arrangements with third parties to perform sales, marketing and distribution services, 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.

If we do not establish sales, marketing and distribution capabilities, either on our own or in collaboration with third parties, we will not be successful in commercializing IPI-549 or any of product candidates we may develop in the future that receive marketing approval.

Our competitors and potential competitors may develop products that make IPI-549 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.

IPI-549 is an inhibitor of the gamma isoform of PI3K, and we believe it is the only PI3K-gamma selective inhibitor in clinical development. However, there are many competitors developing or commercializing therapies targeting macrophage biology, including the following competitors, which we believe to be conducting clinical studies of product candidates targeting one or more aspects of macrophage biology: Array Biopharma, Inc., Deciphera Pharmaceuticals, Inc., Incyte Corporation (through its collaboration with Calithera Inc.), Bristol-Myers Squibb Company (through its collaboration with Five Prime Therapeutics, Inc.), Plexxikon Inc., GlaxoSmithKline plc, Eli Lilly and Company, Amgen Inc., F. Hoffmann-La Roche Ltd, Janssen Research & Development, LLC, a subsidiary of Johnson & Johnson, Forty Seven Inc., Surface Oncology, Inc., Celgene Corporation, Trillium Therapeutics Inc., Pfizer Inc., XBiotech, Inc., AbbVie Inc., Takeda Pharmaceuticals International, Inc., Novartis AG, Efranat Ltd., Seattle Genetics, Inc., AstraZeneca PLC, Apexigen Inc., X4 Pharmaceuticals, Inc., Syndax Pharmaceuticals, Inc., Syntrix Biosystems, Inc., Eisai Co., Ltd., Vaccinex, Inc., and Alligator Bioscience AB.

Further, the broader field of IO is crowded with innovative therapies that may compete with IPI-549, including checkpoint inhibitor therapies such as PD-1 inhibitors nivolumab and pembrolizumab; PDL-1 inhibitors atezolizumab, avelumab, and durvalumab; and CTLA-4 inhibitors ipilimumab, and tremelimumab. Many of these checkpoint inhibitor therapies are being evaluated in combination with other non-checkpoint inhibitor IO product candidates. For example, nivolumab, which we are currently testing in combination with IPI-549, is being evaluated by others in multiple clinical trials in combination with non-checkpoint inhibitor candidates such as BMS-986016, an anti-LAG3 antibody; elotuzumab, a CD319 antibody; urelumab, a CD137 antibody; cabiralizumab, an anti-CSF1R antibody; and NKTR-214, an IL-2R agonist. The success of competing IO therapies may limit the number of patients available for enrollment in our clinical trials.

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 IPI-549. These competitive products may have superior safety or efficacy, have more attractive pharmacologic properties, or be manufactured less expensively than IPI-549. 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 IPI-549 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 IPI-549 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 IPI-549, 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 IPI-549 will depend substantially, both domestically and abroad, on the extent to which the costs of IPI-549 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 IPI-549. 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 IPI-549 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 IPI-549, even if IPI-549 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 IPI-549 will depend in part on the extent to which coverage and adequate reimbursement for IPI-549 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 IPI-549 profitably. These payors may not view IPI-549 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 IPI-549 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 IPI-549, which could result in lower than anticipated product revenues. If the prices for IPI-549 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, increasingly, third-party payors are requiring higher levels of evidence of the benefits and clinical outcomes of new technologies and are challenging the prices charged. Further, the net reimbursement for drug products may be subject to additional reductions if there are changes to laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. An inability to promptly obtain coverage and adequate payment rates from both government-funded and private payors for IPI-549 could significantly harm our operating results, our ability to raise capital needed to commercialize IPI-549 and our overall financial condition.

If the FDA or comparable foreign regulatory authorities grant generic versions of IPI-549 marketing approval, or such authorities do not grant IPI-549 appropriate periods of data exclusivity before approving generic versions of IPI-549, the sales of IPI-549 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 Federal Food, Drug, and Cosmetic Act, or FDCA, provides a period of five years of non-patent exclusivity for a new drug containing a new chemical entity, or NCE. 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 IPI-549 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:

- 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.

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 IPI-549 or any future product candidates we may develop could be delayed or terminated.

We currently have worldwide development and commercialization rights to IPI-549. We license certain patent and other intellectual property rights under our agreement with Takeda, which we refer to as the Takeda Agreement, to discover, develop and commercialize pharmaceutical products targeting the delta and/or gamma isoforms of PI3K, including IPI-549 and duvelisib. We have also licensed or sublicensed certain of our intellectual property rights to third parties, including our exclusive license of worldwide rights to develop and commercialize duvelisib to Verastem, Inc., or Verastem, pursuant to an agreement we entered into with Verastem in November 2016 and which we refer to as the Verastem 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 one or more other collaborators for the development and commercialization of IPI-549 or any product candidate that we may develop in the future. 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 IPI-549 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.

Additional collaborations would be complex and time consuming to negotiate and document.

Any collaboration agreements that we enter into in the future may contain restrictions on our ability to enter into potential collaborations or to otherwise develop IPI-549 or any product candidate that we may develop in the future.

Further, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators. We may not be able to negotiate collaborations on a timely basis, on acceptable terms, or at all. If we are unable to do so, 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 IPI-549 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 IPI-549.

IPI-549 requires precise, high quality manufacturing. The third-party manufacturers on which we rely may not be able 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 IPI-549 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 IPI-549, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of IPI-549, operating restrictions and/or criminal prosecution, any of which could significantly and adversely affect supply of IPI-549 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, our manufacturers cannot perform as agreed, we may be unable to replace such third-party manufacturers in a timely manner, and the production of IPI-549 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, IPI-549 has been manufactured for preclinical testing and clinical trials primarily by third-party manufacturers. If the FDA or other regulatory agencies approve IPI-549 for commercial sale, we expect that we would continue to rely, at least initially, on third-party manufacturers to produce commercial quantities of IPI-549. These manufacturers may

not be able to successfully increase the manufacturing capacity for IPI-549 in a timely or economical manner, or at all. 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 IPI-549, 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 IPI-549 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 IPI-549 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 Verastem pursuant to the Verastem 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 IPI-549 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 IPI-549 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 IPI-549 and duvelisib. We may enter into additional license agreements in the future. 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 IPI-549 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 IPI-549 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 Verastem materially breaches the Verastem Agreement, we could lose our license rights under the Takeda Agreement, including rights to IPI-549.

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 IPI-549.

We own or hold exclusive licenses to a number of U.S. and foreign patents and patent applications directed to IPI-549. Our success depends on our ability to obtain patent protection both in the United States and in other countries for IPI-549, our methods of manufacture and our methods of use. Our ability to protect IPI-549 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 IPI-549. 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 IPI-549.

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, IPI-549 or its therapeutic use. In the event that a third party has also filed a U.S. patent application relating to IPI-549 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 IPI-549 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 Verastem 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 IPI-549. 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 IPI-549, even when we are aware of third-party patents that may be relevant to IPI-549, 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 IPI-549.

While we are not currently aware of any litigation or third-party claims of intellectual property infringement related to IPI-549 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 Verastem's technologies infringes these patents or that we or Verastem are employing their proprietary technology without authorization. We or Verastem 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 Verastem's technologies infringes any patents, or defending against any claim that we or Verastem 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 Verastem may be required to:

- pay substantial damages;
- stop developing, manufacturing and/or commercializing IPI-549 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 Verastem paying substantial royalties or the granting of cross-licenses to our or Verastem's technologies.

If any of the foregoing were to occur, we may be unable to commercialize IPI-549, or we may elect to cease certain of our business operations, either of which could severely harm our business. Similarly, Verastem may be unable to commercialize duvelisib, therefore reducing or eliminating the royalties owed to us under the Verastem Agreement.

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 IPI-549 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 IPI-549 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 IPI-549. 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 IPI-549, and our ability to generate revenue will be materially impaired.

IPI-549 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 IPI-549 will prevent us from commercializing IPI-549. We and our collaborators have not received approval to market IPI-549 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 to the various regulatory authorities for each therapeutic indication to establish the product candidate's safety and efficacy. Securing regulatory approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the relevant regulatory authority. IPI-549 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 IPI-549. 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 IPI-549, the commercial prospects for IPI-549 may be harmed, and our ability to generate revenues will be materially impaired.

Failure to obtain marketing approval in foreign jurisdictions would prevent IPI-549 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 IPI-549 in any market.

Additionally, on June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the European Union, commonly referred to as Brexit. On March 29, 2017, the country formally notified the European Union of its intention to withdraw pursuant to Article 50 of the Lisbon Treaty. Since a significant proportion of the regulatory framework in the United Kingdom is derived from European Union directives and regulations, Brexit could materially impact the regulatory regime with respect to the approval of IPI-549 or any future product candidates we may develop in the United Kingdom or the European Union. For example, the British government has begun negotiating the terms of the UK's withdrawal from the EU. It is unclear what impact Brexit may have, if any, on the development and commercialization of IPI-549, although the first practical effects of Brexit on healthcare were felt in November 2017 when EU member states voted to move the European Medicines Agency, or the EMA, the EU's regulatory body, from London to Amsterdam. Operations in Amsterdam are slated to commence by March 30, 2019, although the move itself could cause significant disruption to the regulatory approval process in Europe.

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

Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would prevent us from commercializing IPI-549, or any future product candidates we may develop, in the United Kingdom and/or the European Union and restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek regulatory approval in the United Kingdom and/or European Union for our product candidates, which could significantly and materially harm our business.

Even if we or our collaborators obtain marketing approvals for IPI-549, the terms of approvals and ongoing regulation of IPI-549 may limit how we manufacture and market IPI-549, 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 IPI-549. 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 IPI-549, 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.

IPI-549 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 IPI-549, 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 IPI-549 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 healthcare 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.

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

Under the CURES Act and the Trump Administration's regulatory reform initiatives, the FDA's policies, regulations and guidance may be revised or revoked and that could prevent, limit or delay regulatory approval of IPI-549 or any future product candidates we may develop, which would impact our ability to generate revenue.

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

We also cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative or executive action, either in the United States or abroad. For example, certain policies of the Trump Administration may impact our business and industry. Namely, the Trump Administration has taken several executive actions, including the issuance of a number of Executive Orders, that could impose significant burdens on, or otherwise materially

delay, the FDA's ability to engage in routine regulatory and oversight activities such as implementing statutes through rulemaking, issuance of guidance, and review and approval of marketing applications. An under-staffed FDA could result in delays in the FDA's responsiveness or in its ability to review submissions or applications, issue regulations or guidance, or implement or enforce regulatory requirements in a timely fashion or at all. Moreover, on January 30, 2017, President Trump issued an Executive Order, applicable to all executive agencies, including the FDA, which requires that for each notice of proposed rulemaking or final regulation to be issued in fiscal year 2017, the agency shall identify at least two existing regulations to be repealed, unless prohibited by law. These requirements are referred to as the "two-for-one" provisions. This Executive Order includes a budget neutrality provision that requires the total incremental cost of all new regulations in the 2017 fiscal year, including repealed regulations, to be no greater than zero, except in limited circumstances. For fiscal years 2018 and beyond, the Executive Order requires agencies to identify regulations to offset any incremental cost of a new regulation and approximate the total costs or savings associated with each new regulation or repealed regulation. In interim guidance issued by the Office of Information and Regulatory Affairs within the Office of Management and Budget on February 2, 2017, the administration indicates that the "two-for-one" provisions may apply not only to agency regulations, but also to significant agency guidance documents. In addition, on February 24, 2017, President Trump issued an executive order directing each affected agency to designate an agency official as a "Regulatory Reform Officer" and establish a "Regulatory Reform Task Force" to implement the two-for-one provisions and other previously issued executive orders relating to the review of federal regulations, however it is difficult to predict how these requirements will be implemented, and the extent to which they will impact the FDA's ability to exercise its regulatory authority. If these executive actions impose constraints on the FDA's ability to engage in oversight and implementation activities in the normal course, our business may be negatively impacted.

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

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

- the federal Anti-Kickback Statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order or recommendation or arranging of, any good or service, for which payment may be made under a federal healthcare program such as Medicare and Medicaid;
- the federal False Claims Act imposes criminal and civil penalties, including through civil whistleblower or qui tam actions, against individuals or entities for, among other things, knowingly presenting, or causing to be presented, false or fraudulent claims for payment by a federal healthcare program or making a false statement or record material to payment of a false claim or avoiding, decreasing or concealing an obligation to pay money to the federal government, with potential liability including mandatory treble damages and significant per-claim penalties, currently set at $5,500 to $11,000 per false claim;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;
- the federal Physician Payments Sunshine Act requires applicable manufacturers of covered drugs to report payments and other transfers of value to 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 healthcare 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 healthcare 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 IPI-549, 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 IPI-549 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 healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, imprisonment, exclusion of products from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any of the physicians or other healthcare providers or entities with whom we expect to do business is found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

Recently enacted and future legislation may increase the difficulty and cost for us and any future collaborators to obtain marketing approval of and commercialize IPI-549 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 the United States, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or Medicare Modernization Act, changed the way Medicare covers and pays for pharmaceutical products. The legislation expanded Medicare coverage for drug purchases by the elderly and introduced a new reimbursement methodology based on average sales prices for physician administered drugs. In addition, this legislation provided authority for limiting the number of drugs that will be covered in any therapeutic class. Cost reduction initiatives and other provisions of this legislation could decrease the coverage and price that we receive for any approved products. While the Medicare Modernization Act applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own reimbursement rates. Therefore, any reduction in reimbursement that results from the Medicare Modernization Act may result in a similar reduction in payments from private payors.

In March 2010, then-President Obama signed into law the ACA. Among the provisions of the ACA of potential importance to our business and IPI-549, including, without limitation, our ability to commercialize and the prices we may obtain for IPI-549 or any future product candidates we may develop and that are approved for sale, are the following:

- an annual, non-deductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic products;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program;
- expansion of federal healthcare fraud and abuse laws, including the False Claims Act and the Anti-Kickback Statute, new government investigative powers and enhanced penalties for noncompliance;
- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices;
- extension of manufacturers' Medicaid rebate liability;
- expansion of eligibility criteria for Medicaid programs;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;

- new requirements to report financial arrangements with physicians and teaching hospitals;
- a new requirement to annually report drug samples that manufacturers and distributors provide to physicians; and
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. These changes included aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2024 unless additional congressional action is taken. The American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for IPI-549 or any future product candidates we may develop for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used.

Since enactment of the ACA, there have been numerous legal challenges and congressional actions to repeal and replace provisions of the law. For example, with enactment of the TCJA, which was signed by the President on December 22, 2017, Congress repealed the "individual mandate." The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, will become effective in 2019. According to the Congressional Budget Office, the repeal of the individual mandate will cause 13 million fewer Americans to be insured in 2027 and premiums in insurance markets may rise. Further, each chamber of the Congress has put forth multiple bills designed to repeal or repeal and replace portions of the ACA. Although none of these measures has been enacted by Congress to date, Congress may consider other legislation to repeal and replace elements of the ACA. The Congress may likely consider other legislation to replace elements of the ACA, during the next congressional session. It is possible that repeal and replacement initiatives, if enacted into law, could ultimately result in fewer individuals having health insurance coverage or in individuals having insurance coverage with less generous benefits. While the timing and scope of any potential future legislation to repeal and replace ACA provisions is highly uncertain in many respects, it is also possible that some of the ACA provisions that generally are not favorable for the research-based pharmaceutical industry could also be repealed along with ACA coverage expansion provision. We will continue to evaluate the effect that the ACA and its possible repeal and replacement could have on our business.

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

We will continue to evaluate the effect that the ACA and its possible repeal and replacement could have on our business. It is possible that repeal and replacement initiatives, if enacted into law, could ultimately result in fewer individuals having health insurance coverage or in individuals having insurance coverage with less generous benefits. While the timing and scope of any potential future legislation to repeal and replace ACA provisions is highly uncertain in many respects, it is also possible that some of the ACA provisions that generally are not favorable for the research-based pharmaceutical industry could also be repealed along with ACA coverage expansion provisions. 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 commercialize product candidates.

The costs of prescription pharmaceuticals in the United States has also been the subject of considerable discussion in the United States, and members of Congress and the Administration have stated that they will address such costs through new legislative and administrative measures. The pricing of prescription pharmaceuticals is also subject to governmental control

outside the United States. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost effectiveness of IPI-549 or future product candidates we may develop 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 ability to generate revenues and become profitable could be impaired. In the European Union, similar political, economic and regulatory developments may affect our ability to profitably commercialize our products. In addition to continuing pressure on prices and cost containment measures, legislative developments at the European Union or member state level may result in significant additional requirements or obstacles that may increase our operating costs.

Specifically, there have been several recent U.S. congressional inquiries and proposed federal and proposed and enacted state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products. At the federal level, Congress and the Trump Administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. For example, on May 11, 2018, the Trump Administration issued a plan to lower drug prices. Under this blueprint for action, the Trump Administration indicated that the HHS will: take steps to end the gaming of regulatory and patent processes by drug makers to unfairly protect monopolies; advance biosimilars and generics to boost price competition; evaluate the inclusion of prices in drug makers' ads to enhance price competition; speed access to and lower the cost of new drugs by clarifying policies for sharing information between insurers and drug makers; avoid excessive pricing by relying more on value-based pricing by expanding outcome-based payments in Medicare and Medicaid; work to give Part D plan sponsors more negotiation power with drug makers; examine which Medicare Part B drugs could be negotiated for a lower price by Part D plans, and improving the design of the Part B Competitive Acquisition Program; update Medicare's drug-pricing dashboard to increase transparency; prohibit Part D contracts that include "gag rules" that prevent pharmacists from informing patients when they could pay less out-of-pocket by not using insurance; and require that Part D plan members be provided with an annual statement of plan payments, out-of-pocket spending, and drug price increases.

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 healthcare authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other healthcare 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 IPI-549 or future product candidates we may develop or additional pricing pressures.

Moreover, legislative and regulatory proposals have also been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical drugs. We cannot be sure whether additional legislative changes will be enacted, or whether the FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our drug candidates, if any, may be. In addition, increased scrutiny by the United States Congress of the FDA's approval process may significantly delay or prevent marketing approval, as well as subject us and any future collaborators to more stringent drug labeling and post-marketing testing and other requirements.

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

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

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.

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.

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. 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 IPI-549 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.

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 attackscyber-attacks, computer viruses, unauthorized access, sabotage, natural disasters, terrorism, war, and telecommunication and electrical failures and other disruptions. System failures, accidents. Any system failure, accident or security breaches could causebreach that causes interruptions in our operations, for us or those third parties with which we contract, and could result in a material disruption of our clinical and commercialization activitiesproduct development programs and business operations, in addition to possibly requiring substantial expenditures of resources to remedy. TheFor 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 were to resultresults in a loss of, or damage to, our data or applications, or inappropriate public disclosure of confidential or proprietary information, we could incur liability and our product development and commercialization efforts could be delayed. Such delay could have a material adverse impact on our business, operating results and financial condition.may incur liabilities and the further development of IPI-549, 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 healthcare 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 healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable foreign regulatory authorities, report financial information or data accurately or disclose unauthorized activities to us. 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 in an effort 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 IPI-549;
- future sales of, and the trading volume in, our common stock;
- 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 Verastem Agreement;
- the results and timing of regulatory reviews relating to the approval of IPI-549;
- 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 IPI-549, if approved, to achieve commercial success;
- the results of clinical trials conducted by others on drugs that would compete with IPI-549;
- the regulatory approval of drugs that would compete with IPI-549;
- issues in manufacturing IPI-549;
- 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;
- healthcare reform measures, including changes in the structure of healthcare 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. If our bid price falls below $1.00 per share for 30 consecutive business days, we will receive a deficiency notice from Nasdaq advising us that we have 180 days to regain compliance by maintaining a minimum bid price of at least $1.00 for a minimum of ten consecutive business days. Under certain circumstances, Nasdaq could require that the minimum bid price exceed $1.00 for more than ten consecutive days before determining that a company complies.

If we fail to satisfy the Nasdaq Global Select Market's continued listing requirements, 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 and requires our independent auditors to attest to the effectiveness of our internal control over financial reporting. 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 our restructuring or 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 Section 382 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 may experience 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. If we determine that an ownership change has occurred and our ability to use our historical net operating loss and tax credit carryovers is materially limited, or if our research and development credit carryforwards are adjusted, our use of those attributes to offset future income tax liabilities would be limited.

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

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

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.

Our executive officers, directors and major shareholders may be able to exert significant control over the company, which may make an acquisition of us difficult.

To our knowledge, based on the number of shares of our common stock outstanding on March 1, 2019, stockholders beneficially owning 5% or more of our common stock, as well as our executive officers, directors, and their respective affiliates, beneficially owned in the aggregate approximately 32% of our common stock. These stockholders have the ability to influence our company through this ownership position. For example, as a result of this concentration of ownership, these stockholders, if acting together, may have the ability to affect the outcome of matters submitted to our stockholders for approval, including the election and removal of directors, changes to our equity compensation plans and any merger or similar transaction. This concentration of ownership may, therefore, harm the market price of our common stock by:

- delaying, deferring or preventing a change in control of our company;
- impeding a merger, consolidation, takeover or other business combination involving us; or
- discouraging a potential acquirer from making a tender offer or otherwise attempting to obtain control of us.

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, 2018, we had $58.6 million in cash and cash equivalents. We historically have invested these amounts in money market funds, corporate obligations, U.S. government-sponsored enterprise obligations, U.S. Treasury securities and mortgage-backed 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 September 1, 2017, we entered into a lease covering 6,091 square feet of office space located at 784 Memorial Drive. The lease expires on August 31, 2019.

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 8, 2019, there were 48 holders of record of our common stock.

Item 6. Selected Financial Data

Not applicable.

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 report for a discussion of important factors that could cause actual results to differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

Overview

We are an 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 our efforts on advancing 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 IPI-549 is the only selective inhibitor of PI3K-gamma being investigated in clinical trials. We have worldwide development and commercialization rights to IPI-549, 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—Business Overview—Collaborations—Takeda.

MARIO-1: MAcrophage Reprogramming in Immuno-Oncology, or MARIO-1, is our ongoing Phase 1/1b, first-in-human clinical trial designed to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of IPI-549 as a monotherapy and in combination with nivolumab, also known as Opdivo®, in approximately 220 patients with advanced solid tumors. Nivolumab is a checkpoint inhibitor therapy commercialized by Bristol-Myers Squibb Company, or BMS, that targets a receptor in the human body called programmed death receptor 1, or PD-1. Data from the dose-escalation components of MARIO-1, which are complete, demonstrate that IPI-549 is well tolerated as a monotherapy at all doses studied up to the recommended monotherapy expansion dose of 60 mg once daily, or QD, and in combination with the standard dose of

nivolumab up to the recommended combination expansion dose of 40 mg once daily, or QD. The combination therapy expansion includes: cohorts of patients with non-small cell lung cancer, melanoma, and squamous cell carcinoma of the head and neck whose tumors have shown initial resistance or subsequently have developed resistance to immune checkpoint therapy; a cohort of patients with triple negative breast cancer who have not been previously treated with a checkpoint inhibitor; a cohort of patients with mesothelioma; and a cohort of patients who have a high baseline level of myeloid-derived suppressor cells, the presence of which correlates to a poor response to PD-1 and PD-L1 inhibitors.

We reported data from the combination expansion cohorts of the MARIO-1 trial in a late-breaking poster presentation at the 33rd Annual Meeting of the Society for Immunotherapy of Cancer, or SITC, on November 10, 2018. The data demonstrated that IPI-549 in combination with the standard dose of nivolumab is well-tolerated with no treatment-related deaths among the 82 patients evaluable for safety as of the October 14, 2018 data-cutoff date. Among the 44 patients evaluable for activity, 15 patients showed a best response of stable disease or better, including one partial response in an advanced melanoma patient who progressed on immediate prior nivolumab therapy. In addition, a patient with chemotherapy-resistant triple-negative breast cancer, or TNBC, showed a 26% reduction in tumor target lesions at the first assessment. Reductions in elevated baseline levels of myeloid-derived suppressor cells, or MDSCs, as well as corresponding increases in the proliferative fraction of previously exhausted memory cytotoxic T cells were seen in these patients. The data included long-term follow up on additional partial responses in two patients from the combination dose escalation. One patient with microsatellite stable gallbladder cancer and another with adrenocortical carcinoma maintained a partial response for over 12 months and 17 months, respectively. These patients also demonstrated sustained inhibition of MDSCs during the period in which the partial response was maintained.

We plan to expand our IPI-549 clinical development in the first half of 2019 with initiation of MARIO-275, a global randomized study in immuno-oncology naïve patients with urothelial cancer, and a study with Arcus investigating IPI-549 in a triple therapy combination in previously treated patients with advanced triple-negative breast cancer, or TNBC. In the second half of 2019 we intend to complete enrollment in the MARIO-1 combination expansion cohorts and to initiate a combination study of IPI-549 in front-line advanced cancer patients.

We have primarily incurred operating losses since inception. Our net loss was $11.3 million and $41.8 million for the years ended December 31, 2018 and 2017, respectively. As of December 31, 2018, we had an accumulated deficit of $678.8 million. As we have no approved products, we have not generated any revenue from product sales and, 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. As of December 31, 2018, we had approximately $58.6 million in cash, cash equivalents and available-for-sale securities. We will need substantial additional funds to support our planned operations. In the absence of additional funding or business development activities, we believe that our existing cash, cash equivalents and available-for-sale securities will be adequate to satisfy our capital needs for at least the next twelve months based on planned levels of spending.

We expect to continue to spend significant resources to fund the development and potential commercialization of IPI-549, and we expect to incur significant operating losses for the foreseeable future. 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 IPI-549 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.

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 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 infrastructure, corporate communications, corporate development 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 represents expense associated with amounts owed to third parties as a result of royalty revenue recognized.

Other Income and Expense

Other income and expense typically consists of interest earned on cash, cash equivalents and available-for-sale securities, gain or loss on sale of property and equipment and interest expense.

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 revenue recognition, accrued expenses 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. The terms of these collaboration agreements may include payment 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.

Effective January 1, 2018, we adopted Financial Accounting Standards Board Accounting Standard Codification Topic 606, *Revenue from Contracts with Customers,* or ASC 606. The standard requires a company to recognize revenue when it transfers goods or services to customers in an amount that reflects the consideration that the company expects to receive for those goods or services. The standard allows for two transition methods - full retrospective, in which the standard is applied to each prior reporting period presented, or modified retrospective, in which the cumulative effect of initially applying the standard is recognized at the date of initial adoption. We elected the modified retrospective approach and applied it to contracts

not completed at the date of adoption. Therefore, comparative prior periods have not been adjusted. The adoption of the standard did not have a material impact on our financial position and results of operations when applied to our out-licensing arrangements. See Note 10 to our consolidated financial statements included elsewhere in this Annual Report on Form 10-K for additional details on these arrangements.

The principles in the new standard 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.

Stock-Based Compensation

We expense the fair value of employee stock options and other equity compensation. We use our judgment in determining the fair value of our equity instruments, including selecting the inputs we use for the Black-Scholes valuation model. Equity instrument valuation models are by their nature highly subjective. Any significant changes in any of our judgments, including those used to select the inputs for the Black-Scholes valuation model, could have a significant impact on the fair value of the equity instruments granted and the associated compensation charge we record in our financial statements.

Results of Operations

The following table summarizes our results of operations for the years ended December 31, 2018 and 2017, in thousands, together with the change in each item as a percentage.

	2018	2017	% Change
Collaboration revenue	$ 22,000	$ 6,000	267 %
Royalty revenue	146	—	— %
Research and development expense	(19,758)	(20,830)	(5)%
General and administrative expense	(14,248)	(21,615)	(34)%
Royalty expense	(69)	—	— %
Investment and other income	769	1,787	(57)%
Interest expense	(93)	(1,010)	(91)%
Other expense (note 9)	—	(6,882)	(100)%
Income taxes benefit (expense)	—	720	(100)%

Revenue

Our revenue during the year ended December 31, 2018 consisted of approximately:

- $22.0 million of revenue related to a payment from Verastem upon approval by the U.S. Food and Drug Administration, or FDA, of duvelisib for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma after at least two prior therapies, as well as adult patients with relapsed or refractory follicular lymphoma after at least two prior systemic therapies.
- $0.1 million of revenue related to royalties from Verastem on net sales of duvelisib following the FDA approval in the third quarter of 2018.

Our revenue during the year ended December 31, 2017 consisted of:

- $6.0 million of revenue related to the achievement by Verastem of the successful completion of the DUO clinical study of duvelisib and our receipt of the associated payment under our agreement with Verastem.

Research and Development Expense

Research and development expenses represented approximately 58% and 49% of our total operating expenses for the years ended December 31, 2018 and 2017, respectively.

Research and development expense is comparable for the years ended December 31, 2018 and 2017.

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, 2018 and 2017 and from January 1, 2006 through December 31, 2018, we estimate that we incurred $19.8 million, $20.8 million and $629.5 million, respectively, on our PI3K inhibitor program, including IPI-549 and duvelisib.

We expect our research and development expense to increase as a result of our continued clinical development of IPI-549. 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 IPI-549 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; and
- the effect of competing technological and market developments.

General and Administrative Expense

The decrease in general and administrative expense for the year ended December 31, 2018 as compared to the year ended December 31, 2017 was primarily attributable to a decrease of $5.0 million in compensation, related to a reduction in bonus and stock compensation, and a decrease of $1.7 million related to the exit of our previous facility lease effective August 31, 2017.

Royalty Expense

Royalty expense represents the 4% royalty on net sales of duvelisib to cover the reimbursement of research and development costs owed by us to Mundipharma International Corporation Limited and Purdue Pharmaceutical Products L.P.

Investment and Other Income

Investment and other income decreased in the year ended December 31, 2018 as compared to the year ended December 31, 2017 primarily as a result of a gain on the sale of personal property, computer equipment, and furniture and fixtures during 2017 and decreased income from subleases at 784 Memorial Drive which ended during the third quarter of 2017.

Interest Expense

Interest expense for the year ended December 31, 2018 decreased as compared to December 31, 2017 due to the termination of the financing obligation in connection with the August 31, 2017 termination of our previous lease (see Note 9 of the notes to our consolidated financial statements included elsewhere in this Annual Report on Form 10-K) and the prepayment of the Takeda Note (see Note 10 of the notes to our consolidated financial statements included elsewhere in this Annual Report on Form 10-K).

Other Expense

Other expense for the year ended December 31, 2017 represents the loss incurred to terminate the financing obligation in connection with the August 31, 2017 termination of our previous lease. This loss was comprised of: (i) $1.9 million representing the difference between the estimated carrying value of the building and building improvements and the related financing obligation and deferred rent at August 31, 2017; and (ii) the $5.0 million termination payment. Further information regarding the lease termination is described in Note 9 of the notes to our consolidated financial statements included elsewhere in this Annual Report on Form 10-K.

Income Taxes

We did not incur any income tax expense during the year ended December 31, 2018. Income tax benefit for December 31, 2017 is a result of monetizing our alternative minimum tax credit carryforwards as permitted by the Tax Cut and Jobs Act that was enacted on December 22, 2017.

Liquidity and Capital Resources

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, debt, interest on investments, up-front license fees, expense reimbursement, milestones, royalties and cost sharing under our collaborations to fund our operations. Our available-for-sale debt securities primarily trade in liquid markets, and the average days to maturity of our portfolio, as of December 31, 2018, is less than six months. Because IPI-549 is in an early stage of 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 IPI-549 or whether, or when, we may achieve profitability.

The following table summarizes the components of our financial condition:

	December 31, 2018	December 31, 2017
	(in thousands)	
Cash, cash equivalents and available-for-sale securities	$ 58,591	$ 57,609
Working capital	52,100	46,791

	Year Ended December 31,	
	2018	2017
	(in thousands)	
Cash (used in) provided by:		
Operating activities	$ (4,714)	$ (36,711)
Investing activities	13,104	(4,278)
Financing activities	5,619	(146)

Cash Flows

The principal use of cash in operating activities in all periods presented was related to our research and development programs. Our cash flow used in operating activities for the year ended December 31, 2018 decreased compared to the year ended December 31, 2017 primarily due to the receipt of $22.0 million from Verastem upon approval by the FDA of duvelisib for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma after at least two prior therapies, as well as adult patients with relapsed or refractory follicular lymphoma after at least two prior systemic therapies.

Our cash flow 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 investing activities for the years ended December 31, 2018 and 2017 included purchases and proceeds from maturities and purchases and proceeds from sales of property and equipment. Our investing activities for the year ended December 31, 2018 included $15.7 million in purchases of available-for-sale securities and proceeds of $28.8 million from maturities of available-for-sale securities.

Net cash from financing activities for the year ended December 31, 2018 included net proceeds from our common stock sales facility of $9.3 million, which was partially offset by the prepayment of the Takeda Note (see Note 10 of the notes to our consolidated financial statements included elsewhere in this Annual Report on Form 10-K). Net cash from financing activities for the year ended December 31, 2017 included $0.3 million of payments on the financing obligation related to our previous lease.

We will need substantial additional funds to support our planned operations. In the absence of additional funding or business development activities, we believe that our existing cash, cash equivalents and available-for-sale securities will be adequate to satisfy our capital needs for at least the next twelve months. 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 need to raise additional funds may also be accelerated for other reasons, including, without limitation, if:

- the scope, progress, results and costs of developing IPI-549, currently in clinical development;
- the timing of, and the costs involved in, obtaining regulatory approvals for IPI-549;
- subject to receipt of marketing approval, revenue, if any, received from commercial sales of IPI-549;
- 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, IPI-549 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, 2018, we have received $254.1 million of net proceeds from our public stock offerings, including our common stock sales facility. 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.

Common Stock Sales Facility

In May 2016, we entered into a controlled equity offering sales agreement, or Sales Agreement, with Cantor Fitzgerald & Co., or Cantor Fitzgerald pursuant to which we may from time to time, at our option, offer and sell shares of our common stock having an aggregate offering price of up to $50.0 million through Cantor Fitzgerald, acting as our sales agent. Cantor Fitzgerald will be entitled to a commission of 3.0% of the aggregate gross proceeds from sales of shares of our common stock under the Sales Agreement. Sales of shares of our common stock under the Sales Agreement may be made by any method permitted by law that is deemed an "at the market" offering as defined in Rule 415 under the Securities Act of 1933, as amended, including sales made through the Nasdaq Global Select Market, on any other existing trading market for our common stock or to or through a market maker. We may also authorize Cantor Fitzgerald to sell shares in privately negotiated transactions. During the year ended December 31, 2018, we sold 4,461,893 shares of common stock at a weighted average price per share of $2.18 at-the-market pursuant to the Sales Agreement for an additional $9.3 million in net proceeds. During the year ended December 31, 2017, we issued and sold 10,958 shares of common stock at a weighted average price per share of $2.54 at-the-market pursuant to the Sales Agreement for approximately $27,000 in net proceeds. We have no obligation to sell shares of our common stock and cannot provide any assurances that we will issue any additional shares pursuant to the Sales Agreement. We may also suspend the offering of shares of our common stock upon notice and subject to other conditions.

Off-Balance Sheet Arrangements

Since inception, we have not engaged in any off-balance sheet financing activities, including the use of structured finance, special purpose entities or variable interest entities.

Inflation

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

New Accounting Pronouncements

See Note 2 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 a description of recent accounting pronouncements applicable to our business.

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, 2018 and 2017, 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, 2018, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2018 and 2017, and the results of its operations and its cash flows for each of the two years in the period ended December 31, 2018, in conformity with U.S. generally accepted accounting principles.

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

Basis for Opinion

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

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

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2001.
Boston, Massachusetts
March 14, 2019

INFINITY PHARMACEUTICALS, INC.

Consolidated Balance Sheets

(in thousands, except share and per share amounts)

	December 31,	
	2018	2017
Assets		
Current assets:		
Cash and cash equivalents	$ 48,616	$ 34,607
Available-for-sale securities	9,975	23,002
Prepaid expenses and other current assets	1,227	777
Total current assets	59,818	58,386
Property and equipment, net	28	219
Other assets	369	748
Total assets	$ 60,215	$ 59,353
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 1,197	$ 459
Accrued expenses	6,521	5,136
Note payable (note 10)	—	6,000
Total current liabilities	7,718	11,595
Other liabilities	38	28
Total liabilities	7,756	11,623
Commitments and contingencies (note 9)		
Stockholders' equity:		
Preferred Stock, $0.001 par value; 1,000,000 shares authorized, no shares issued and outstanding at December 31, 2018 and 2017	—	—
Common Stock, $0.001 par value; 100,000,000 shares authorized, 56,907,096 and 50,761,039 shares issued and outstanding at December 31, 2018 and December 31, 2017, respectively	57	51
Additional paid-in capital	731,178	715,213
Accumulated deficit	(678,772)	(667,519)
Accumulated other comprehensive loss	(4)	(15)
Total stockholders' equity	52,459	47,730
Total liabilities and stockholders' equity	$ 60,215	$ 59,353

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,	
	2018	2017
Revenue:		
Collaboration revenue	$ 22,000	$ 6,000
Royalty revenue	146	—
Total revenues	22,146	6,000
Operating expenses:		
Research and development	19,758	20,830
General and administrative	14,248	21,615
Royalty expense	69	—
Total operating expenses	34,075	42,445
Loss from operations	(11,929)	(36,445)
Other income (expense):		
Investment and other income	769	1,787
Interest expense	(93)	(1,010)
Other expense (note 9)	—	(6,882)
Total other income (expense)	676	(6,105)
Loss before income taxes	(11,253)	(42,550)
Income taxes benefit	—	720
Net loss	$ (11,253)	$ (41,830)
Basic and diluted loss per common share	$ (0.20)	$ (0.83)
Basic and diluted weighted average number of common shares outstanding	55,411,370	50,560,195
Other comprehensive loss:		
Net unrealized holding gains (losses) on available-for-sale securities arising during the period	$ 11	$ (12)
Comprehensive loss	$ (11,242)	$ (41,842)

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,	
	2018	2017
Operating activities		
Net loss	$ (11,253)	$ (41,830)
Adjustments to reconcile net loss to net cash used in operating activities:		
Note payable (note 10)	—	6,000
Depreciation	191	1,715
Stock-based compensation, including 401(k) match	3,448	6,972
Non-cash adjustment to financing obligation	—	1,882
Gain on sale of fixed assets	—	(736)
Other, net	138	(25)
Changes in operating assets and liabilities:		
Prepaid expenses and other assets	(71)	7,110
Accounts payable, accrued expenses and other liabilities	2,833	(17,799)
Net cash used in operating activities	(4,714)	(36,711)
Investing activities		
Purchases of property and equipment	—	(43)
Proceeds from sale of assets	—	750
Purchases of available-for-sale securities	(15,686)	(23,985)
Proceeds from maturities of available-for-sale securities	28,790	19,000
Net cash provided by (used in) investing activities	13,104	(4,278)
Financing activities		
Proceeds from common stock sales facility, net of issuance costs	9,330	—
Proceeds from issuances of common stock, net	289	146
Repayment of note payable	(4,000)	—
Payments on financing obligation	—	(292)
Net cash provided by (used in) financing activities	5,619	(146)
Net increase (decrease) in cash and cash equivalents	14,009	(41,135)
Cash, cash equivalents and restricted cash at beginning of period	34,607	75,742
Cash, cash equivalents and restricted cash at end of period	$ 48,616	$ 34,607
Supplemental cash flow information		
Cash paid for interest	$ —	$ 802
Supplemental schedule of noncash activities		
Issuance of common stock for repayment of note payable, including interest	$ 2,301	$ —
Issuance of common stock for compensation	$ 493	$ —

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, 2016	50,374,871	$ 50	$ 708,096	$ (625,689)	$ (3)	$ 82,454
Stock-based compensation expense			6,526			6,526
401(k) plan match issued in common stock	111,235		136			136
Issuance of common stock related to employee stock purchase plan	38,648		56			56
Vesting of restricted stock and other, net	236,285	1	399			400
Unrealized loss on marketable securities					(12)	(12)
Net loss				(41,830)		(41,830)
Balance at December 31, 2017	50,761,039	$ 51	$ 715,213	$ (667,519)	$ (15)	$ 47,730
Exercise of stock options	135,000		199			199
Stock-based compensation expense			3,323			3,323
Issuance of common stock related to sales facility, net of issuance costs	4,461,893	5	9,325			9,330
Issuance of common stock related to repayment of note payable	1,134,689	1	2,300			2,301
Issuance of common stock, net	414,475		818			818
Unrealized gain on marketable securities					11	11
Net loss				(11,253)		(11,253)
Balance at December 31, 2018	56,907,096	$ 57	$ 731,178	$ (678,772)	$ (4)	$ 52,459

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

1. Organization

Infinity Pharmaceuticals, Inc., is an 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.

Cash Equivalents and Available-For-Sale Securities

Cash equivalents and available-for-sale securities primarily consist of money market funds and U.S. government-sponsored enterprise obligations. 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, corporate obligations and U.S. government-sponsored enterprise obligations, 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, 2018 and 2017 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 securities 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 income (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, 2018, our cash, cash equivalents and available-for-sale securities balance was $58.6 million. We have primarily incurred operating losses since inception and have relied on our ability to fund our operations through collaboration and license arrangements and through the sale of stock. We expect to continue to spend significant resources to fund the development and potential commercialization of 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, cash equivalents and available-for-sale securities will be adequate to satisfy our forecasted operating needs for at least the next twelve months. For more information, refer to the section titled "Liquidity and Capital Resources" in Item 7, Management's Discussion and Analysis of Financial Condition and Results of Operations.

Concentration of 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 and U.S. government-sponsored enterprise obligations. 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.

Segment Information

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

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 capital 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
Building and building improvements	10 to 50 years, less estimated residual value at the end of the financing obligation term
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.

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.

Effective January 1, 2018, we adopted Financial Accounting Standards Board, or FASB, Accounting Standard Codification, or ASC, Topic 606, *Revenue from Contracts with Customers,* or ASC 606. The standard requires a company to recognize revenue when it transfers goods or services to customers in an amount that reflects the consideration that the company expects to receive for those goods or services. The standard allows for two transition methods - full retrospective, in which the standard is applied to each prior reporting period presented, or modified retrospective, in which the cumulative effect of initially applying the standard is recognized at the date of initial adoption. We elected the modified retrospective approach and applied it to contracts not completed at the date of adoption. Therefore, comparative prior periods have not been adjusted. The adoption of the standard did not have a material impact on our financial position and results of operations when applied to our out-licensing arrangements. See Note 10 for additional details on these arrangements.

The principles in the new standard 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.

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, 2018 and 2017.

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 such 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,	
	2018	2017
Stock options	8,151,608	7,460,722
Warrants	1,000,000	1,000,000

Comprehensive Loss

Comprehensive loss is comprised of net loss and other comprehensive income (loss). Other comprehensive income (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, 2018, there were no material reclassifications out of accumulated other comprehensive income (loss).

Stock-based Compensation Expense

For awards granted to employees and directors, including 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. Following the adoption of Accounting Standards Update, or ASU, No. 2018-07, *Compensation—Stock Compensation: Improvements to Nonemployee Share-Based Payment Accounting,* or ASU No. 2018-07, the accounting for non-employee awards will be generally consistent with that of employee awards. The measurement date for non-employee awards is the date of grant without changes in the fair value of the award. Stock-based compensation costs for non-employees are recognized as expense over the vesting period on a straight-line 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.

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 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.

Reclassifications

Certain amounts in the prior years' financial statements have been reclassified to conform to the current year presentation. Adjustments have been made to the Consolidated Statements of Cash Flows to aggregate certain items. These reclassifications have no impact on previously reported net income, net loss or cash flows.

New Accounting Pronouncements

In February 2016, the FASB, issued ASU No. 2016-02, *Leases,* or ASU No. 2016-02*,* which requires lessees to recognize the assets and liabilities arising from leases on the balance sheet. ASU No. 2016-02 is effective for fiscal years beginning after December 15, 2018, including interim periods within those fiscal years, requiring the use of a modified retrospective transition approach applied at the beginning of the earliest comparative period presented in the financial statements. Early adoption is permitted. In July 2018, the FASB issued ASU No. 2018-10, *Codification Improvements to Topic 842, Leases,* or ASU No. 2018-10, and ASU No. 2018-11, *Leases (Topic 842) Targeted Improvements*, or ASU No. 2018-11. ASU No. 2018-10 provides certain amendments that affect narrow aspects of the guidance issued in ASU No. 2016-02. ASU No. 2018-11 allows all entities adopting ASU No. 2016-02 to choose an additional (and optional) transition method of adoption under the modified retrospective approach, which an entity initially applies the new leases standard at the adoption date and recognizes a cumulative-effect adjustment to the opening balance of retained earnings in the period of adoption. We expect to use the optional transition method presented in ASU No. 2018-11 and the available practical expedients permitted under the transition guidance within the new standard on adoption. The adoption of ASU No. 2016-02 is not expected to have a material impact on our consolidated financial statements.

Recently Adopted Accounting Pronouncements

Effective January 1, 2018, we adopted ASC Topic 606. The new standard requires a company to recognize revenue when it transfers goods or services to customers in an amount that reflects the consideration that the company expects to receive for those goods or services. The standard allows for two transition methods - full retrospective, in which the standard is applied to each prior reporting period presented, or modified retrospective, in which the cumulative effect of initially applying the standard is recognized at the date of initial adoption. We elected the modified retrospective approach and applied it to contracts not completed at the date of adoption. Therefore, comparative prior periods have not been adjusted. The adoption of the standard did not have a material impact on our financial position and results of operations when applied to our out-licensing arrangements. See Note 10 for additional details on these arrangements.

In January 2016, the FASB issued ASU No. 2016-01, *Financial Instruments: Recognition and Measurement of Financial Assets and Financial Liabilities*, or ASU No. 2016-01, which amends certain aspects of accounting and disclosure requirements for financial instruments, including the requirement that equity investments with readily determinable fair values be measured at fair value with any changes in fair value recognized in a company's results of operations. Equity investments that do not have readily determinable fair values may be measured at fair value or at cost minus impairment adjusted for changes in observable prices. We adopted ASU No. 2016-01 as of January 1, 2018. The adoption of ASU No. 2016-01 did not have an impact on our consolidated financial statements.

In August 2016, the FASB issued ASU No. 2016-15, *Statement of Cash Flows: Classification of Certain Cash Receipts and Cash Payments*, or ASU No. 2016-15, which clarifies classification of certain cash receipts and cash payments on the statement of cash flows to reduce existing diversity in practice. We adopted ASU No. 2016-15 as of January 1, 2018. The adoption of ASU No. 2016-15 did not have a material impact on our consolidated financial statements.

In November 2016, the FASB issued ASU No. 2016-18, *Statement of Cash Flows, Restricted Cash,* or ASU No. 2016-18, which provides guidance on the presentation of restricted cash and restricted cash equivalents in the statement of cash flows. Under the new standard, the statement of cash flows explains the change during the period in the total of cash, cash equivalents, and amounts generally described as restricted cash or restricted cash equivalents. Amounts generally described as restricted cash and restricted cash equivalents are now included with cash and cash equivalents when reconciling the beginning-of-period and end-of-period amounts shown in the statements of cash flows. We adopted ASU No. 2016-18 as of January 1,

2018 on a retrospective basis which resulted in a $1.7 million change in financing activities. We have no restricted cash equivalents at December 31, 2018 or 2017.

The cash, cash equivalents and restricted cash at the beginning and end of each period presented in our consolidated statements of cash flows for the years ended December 31, 2018 and 2017 consisted of the following balances from our consolidated balance sheets:

	Year Ended December 31, 2018		Year Ended December 31, 2017	
	Beginning of period	End of period	Beginning of period	End of period
	(in thousands)			
Cash and cash equivalents	$ 34,607	$ 48,616	$ 74,060	$ 34,607
Restricted cash	—	—	1,152	—
Restricted cash, less current portion	—	—	530	—
Cash, cash equivalents and restricted cash per statement of cash flows	$ 34,607	$ 48,616	$ 75,742	$ 34,607

In May 2017, the FASB issued ASU No. 2017-09, *Compensation—Stock Compensation: Scope of Modification Accounting*, or ASU No. 2017-09, which clarifies when changes to the terms and conditions of a share-based payment award must be accounted for as modifications. The new guidance will result in fewer changes to the terms of an award being accounted for as modifications and reduce diversity in practice for when changes are accounted for as modifications. It does not change the accounting for modifications. We adopted ASU No. 2017-09 as of January 1, 2018, using a prospective approach to awards modified on or after the adoption date, and adoption did not have an impact on our financial statement presentation or disclosures.

In June 2018, the FASB issued ASU No. 2018-07, which expands the scope of ASC Topic 718 to include share-based payment transactions for acquiring goods and services from nonemployees. ASU No. 2018-07 is effective for fiscal years beginning after December 15, 2018, including interim periods within those fiscal years. Early adoption is permitted. We adopted ASU No. 2018-07 as of July 1, 2018. The adoption of ASU No. 2018-07 did not have a material impact on our consolidated financial statements.

In August 2018, the FASB issued ASU No. 2018-13, *Fair Value Measurement: Disclosure Framework—Changes to the Disclosure Requirements for Fair Value Measurement,* or ASU No. 2018-13, which eliminates, adds and modifies certain disclosure requirements for fair value measurements as part of the FASB's disclosure framework project. ASU No. 2018-13 is effective for fiscal years beginning after December 15, 2019, including interim periods within those fiscal years. Early adoption is permitted. We adopted ASU No. 2018-13 as of September 30, 2018. The adoption of ASU No. 2018-13 did not have a material impact on our disclosure to 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.

2010 Stock Incentive Plan

Our 2010 Stock Incentive Plan, or the 2010 Plan, was approved by our stockholders in May 2010. The 2010 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 9,785,000 shares of our common stock may be issued pursuant to awards granted under the 2010 Plan, plus an additional amount of our common stock underlying awards issued under the 2000 Stock Incentive Plan, or the 2000 Plan, that expire or are canceled without the holders receiving any shares under those awards. As of December 31, 2018, an aggregate of 7,734,425 shares of our common stock were reserved for issuance upon the exercise of outstanding awards, and up to 1,410,363 shares of common stock may be issued pursuant to awards granted under the 2010 Plan.

2000 Stock Incentive Plan

The 2000 Stock Incentive Plan, or the 2000 Plan, provided for the grant of stock options intended to qualify as incentive stock options under the IRC, as well as nonstatutory stock options and restricted stock. As of December 31, 2018, an aggregate of 417,183 shares of our common stock were reserved for issuance upon the exercise of outstanding awards granted under the 2000 Plan. The 2000 Plan was terminated upon approval of the 2010 Plan; therefore, no further grants may be made under the 2000 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 2018, 73,822 shares of common stock were purchased for total proceeds of approximately $0.1 million. During 2017, 38,648 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,	
	2018	2017
	(in thousands)	
Research and development	$ 553	$ 1,756
General and administrative	2,895	5,216
Total stock-based compensation expense	$ 3,448	$ 6,972

As of December 31, 2018, we had approximately $2.0 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 1.6 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,	
	2018	2017
Risk-free interest rate	2.5%	1.9%
Expected annual dividend yield	—	—
Expected stock price volatility	96.9%	90.1%
Expected term of options	5.7 years	5.6 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.

Following the adoption of ASU No. 2016-09, we recognize forfeitures related to employee share-based payments as they occur.

All options granted to employees during the years ended December 31, 2018 and 2017 were granted with exercise prices equal to the fair market value of our common stock on the date of grant. We consider the closing price of our common stock as reported on the Nasdaq Global Select Market to be the fair market value.

A summary of our stock option activity for the year ended December 31, 2018 is as follows:

	Stock Options	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Life (years)	Aggregate Intrinsic Value (in millions)
Outstanding at January 1, 2018	7,460,722	$ 6.02		
Granted	1,649,750	2.04		
Exercised	(135,000)	1.47		
Forfeited	(244,578)	2.44		
Expired	(579,286)	6.63		
Outstanding at December 31, 2018	8,151,608	$ 5.36	7.1	$ —
Exercisable at December 31, 2018	6,397,882	$ 6.21	6.6	$ —

The weighted-average fair value per share of options granted during the years ended December 31, 2018 and 2017 was $1.57 and $1.17, respectively.

The aggregate intrinsic value of options outstanding at December 31, 2018 was calculated based on the positive difference, if any, between the closing fair market value of our common stock on December 31, 2018 and the exercise price of the underlying options. The aggregate intrinsic value of options exercised during the year ended December 31, 2018 was approximately $0.1 million. During the year ended December 31, 2017, there were no options exercised. The total cash received from employees and non-employees as a result of stock option exercises during the year ended December 31, 2018 was $0.2 million.

No related income tax benefits were recorded during the years ended December 31, 2018 or 2017.

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, 2018			
	Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
	(in thousands)			
Cash and cash equivalents	$ 48,616	$ —	$ —	$ 48,616
Available-for-sale securities:				
U.S. Treasury securities due in one year or less	4,988	—	(2)	4,986
U.S. government-sponsored enterprise obligations due in one year or less	4,991	—	(2)	4,989
Total available-for-sale securities	9,979	—	(4)	9,975
Total cash, cash equivalents and available-for-sale securities	$ 58,595	$ —	$ (4)	$ 58,591

	December 31, 2017			
	Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
	(in thousands)			
Cash and cash equivalents	$ 34,607	$ —	$ —	$ 34,607
Available-for-sale securities:				
U.S. Treasury securities due in one year or less	3,497	—	(3)	3,494
U.S. government-sponsored enterprise obligations due in one year or less	19,520	—	(12)	19,508
Total available-for-sale securities	23,017	—	(15)	23,002
Total cash, cash equivalents and available-for-sale securities	$ 57,624	$ —	$ (15)	$ 57,609

We held two debt securities at December 31, 2018 that had been in an unrealized loss position for less than twelve months. The fair value of these securities was $10.0 million. As of December 31, 2018, we held no securities in foreign financial institutions. We evaluated our securities for other-than-temporary impairments based on quantitative and qualitative factors. We considered the decline in market value for these two securities to be primarily attributable to current economic and market conditions. It is not more likely than not that we will be required to sell these securities, and we do not intend to sell these securities before the recovery of their amortized cost bases. Based on our analysis, we do not consider these investments to be other-than-temporarily impaired as of December 31, 2018.

We had no material realized gains or losses on our available-for-sale securities for the years ended December 31, 2018 and 2017. There were no other-than-temporary impairments recognized for the years ended December 31, 2018 and 2017.

5. Fair Value

The following table provides the assets carried at fair value measured on a recurring basis as of December 31, 2018 and 2017:

	Level 1	Level 2
	(in thousands)	
December 31, 2018		
Assets:		
Cash and cash equivalents	$ 48,616	$ —
U.S. Treasury securities	—	4,986
U.S. government-sponsored enterprise obligations	—	4,989
Total	$ 48,616	$ 9,975
December 31, 2017		
Assets:		
Cash and cash equivalents	$ 34,607	$ —
U.S. Treasury securities	—	3,494
U.S. government-sponsored enterprise obligations	—	19,508
Total	$ 34,607	$ 23,002

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

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

There have been no changes to our valuation methods during the year ended December 31, 2018. We had no available-for-sale securities that were classified as Level 3 at any point during the year ended December 31, 2018.

6. Prepaid Expenses and Other Current Assets

Prepaid expenses and other current assets consist of the following:

	December 31,	
	2018	2017
	(in thousands)	
Prepaid expenses	$ 641	$ 563
Other current assets	586	214
Total prepaid expenses and other current assets	$ 1,227	$ 777

7. Property and Equipment

Property and equipment consist of the following:

	December 31,	
	2018	2017
	(in thousands)	
Computer equipment and software	$ 1,814	$ 1,814
Leasehold improvements	16	16
	1,830	1,830
Less accumulated depreciation	(1,802)	(1,611)
	$ 28	$ 219

During the year ended December 31, 2017, we retired or sold certain personal property, computer equipment, and furniture and fixtures that had a net book value of approximately $0.2 million for proceeds of $0.9 million resulting in a net gain of $0.7 million.

8. Accrued Expenses

Accrued expenses consisted of the following:

	December 31,	
	2018	2017
	(in thousands)	
Accrued compensation and benefits	$ 2,630	$ 2,002
Accrued clinical and development	2,656	1,736
Other	1,235	1,398
Total accrued expenses	$ 6,521	$ 5,136

9. Commitments and Contingencies

We currently sublease 6,091 square feet of office space at 784 Memorial Drive, Cambridge, Massachusetts. The term of the lease commenced on September 1, 2017 and will expire on August 31, 2019. From September 1, 2017 through August 31, 2018, the base rent of the lease was $19,796 per month. From September 1, 2018 until the expiration date, the base rent of the lease is $20,303 per month. In addition to the base rent, we are also responsible for our share of the operating expenses, utility costs and real estate taxes, in accordance with the terms of the lease.

At December 31, 2018, future minimum payments under the lease are approximately $0.1 million.

Rent expense of $0.2 million and $0.4 million was incurred during the years ended December 31, 2018 and 2017, respectively.

We previously leased approximately 61,000 square feet of office space in Cambridge, Massachusetts, under a lease agreement, or the Lease. We were deemed the owner of the building for accounting purposes, and we recorded the building in our property and equipment balance, although legal ownership remained with the landlord. Our balance sheet reflected a financing obligation related to the building.

In 2017, we and the landlord entered into amendments to the Lease to early terminate the Lease subject to the satisfaction of specified contingencies and a termination payment of $5.0 million. The contingencies were satisfied on June 15, 2017, and the Lease, as amended, terminated effective August 31, 2017.

During the year ended December 31, 2017, we recorded other expense of $6.9 million which represents the loss incurred to terminate the financing obligation in connection with the August 31, 2017 lease termination. This loss was comprised of: (i) $1.9 million representing the difference between the estimated carrying value of the building and building improvements and the related financing obligation and deferred rent at August 31, 2017; and (ii) the $5.0 million termination payment.

10. Collaborations

Verastem

On October 29, 2016, we and Verastem entered into a license agreement, which we and Verastem amended and restated on November 1, 2016, effective as of October 29, 2016. We refer to the amended and restated license agreement as the Verastem Agreement. Under the Verastem Agreement, 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. Upon entry into the Verastem Agreement, Verastem assumed financial responsibility for activities that were part of our ongoing duvelisib program, including a randomized, Phase 3 monotherapy clinical study in patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma which we refer to as the DUO Study. Verastem is obligated to use diligent efforts, as defined in the Verastem Agreement, to develop and commercialize one Licensed Product. During the term of the Verastem Agreement, we have agreed not to research, develop, manufacture or commercialize duvelisib in any indication in humans or animals.

Following a short transition period, which terminated December 31, 2016, Verastem assumed all financial and operational responsibility for the duvelisib program except for the clinical shutdown costs and certain clinical close-out activities that we agreed to retain. We assessed this arrangement in accordance with ASC 606 and concluded that at the date of contract inception this arrangement contained two performance obligations, consisting of the license and transition activities. We satisfied the license at contract inception and transition activities over the transition period which ended in December 2016.

On September 6, 2017, Verastem notified us that the DUO Study met certain pre-specified criteria at completion triggering a $6.0 million payment under the Verastem Agreement, which we received in cash on October 13, 2017. On September 24, 2018, we earned a $22.0 million payment from Verastem upon approval by the U.S. Food and Drug Administration of duvelisib for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma after at least two prior therapies, as well as adult patients with relapsed or refractory follicular lymphoma after at least two prior systemic therapies. We received the $22.0 million payment in cash on November 2, 2018. We recorded the $6.0 million and $22.0 million payments as revenue during the years ended December 31, 2017 and 2018, respectively.

Verastem is also obligated to pay us royalties on worldwide net sales of Licensed Products ranging from the mid-single digits to the high-single digits. The royalty obligation will continue on a product-by-product and country-by-country basis until the latest to occur of (i) the last-to-expire patent right covering the applicable Licensed Product in the applicable country, (ii) the last-to-expire patent right covering the manufacture of the applicable Licensed Product in the country of manufacture of such Licensed Product, (iii) the expiration of non-patent regulatory exclusivity for such Licensed Product in the applicable country and (iv) ten years following the first commercial sale of a Licensed Product in the applicable country, provided that upon the expiration of the last-to-expire patent right covering the Licensed Product in the United States, the applicable royalty on net sales for such Licensed Product in the United States will be reduced by 50%. The royalties are also subject to reduction by 50% of certain third-party royalty payments or patent litigation damages or settlements which might be required to be paid by Verastem if litigation were to arise, with any such reductions capped at 50% of the amounts otherwise payable during the applicable royalty payment period. On March 5, 2019, we and HealthCare Royalty Partners III, L.P., or HCR, entered into a purchase and sale agreement, or the HCR Agreement, 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 Verastem Agreement. See Note 14 for details of the transaction.

In addition to the foregoing, Verastem is obligated to pay us a royalty of 4% on worldwide net sales of Licensed Products to cover the reimbursement of research and development costs owed by us to Mundipharma International Corporation Limited, or Mundipharma, and Purdue Pharmaceutical Products L.P., or Purdue. We refer to these royalty obligations as the Trailing Mundipharma Royalties. Once we have fully reimbursed Mundipharma and Purdue, the Trailing Mundipharma Royalties will be reduced to 1% of net sales in the United States. The Trailing Mundipharma Royalties are payable on a product-by-product basis until the latest to occur of (i) the last-to-expire patent right covering the applicable Licensed Product in the United States, (ii) the last-to-expire patent right covering the manufacture of the applicable Licensed Product in the country of manufacture of such Licensed Product, (iii) the expiration of non-patent regulatory exclusivity for such Licensed Product in the United States and (iv) ten years following the first commercial sale of such Licensed Product in the United States, provided that, upon the expiration of the last-to-expire patent right covering a Licensed Product in the United States, the applicable royalty on net sales for such Licensed Product in the United States will be reduced by 50%. In addition, the Trailing Mundipharma Royalties are subject to reduction by 50% of certain third-party royalty payments or patent litigation damages or settlements which might be required to be paid by Verastem if litigation were to arise, with any such reductions capped at 50% of the amounts otherwise payable during the applicable royalty payment period. We recognize total royalties received from Verastem as royalty revenue. We recognize amounts owed to Mundipharma and Purdue as royalty expense.

The Verastem Agreement expires when each party no longer has any obligations to the other party under the Verastem Agreement. Verastem has the right to terminate the Verastem Agreement upon at least 180 days' prior written notice to us at any time. Either party may terminate the Verastem Agreement if the other party materially breaches or defaults in the performance of its obligations. If we terminate the Verastem Agreement for Verastem's material breach, patent challenge, or insolvency, or if Verastem terminates for convenience, then, at our request and subject to our execution of a waiver of certain types of damages, Verastem will transition the duvelisib program back to us at Verastem's cost. If Verastem terminates for our breach or insolvency, Verastem will effect a more limited transition of the duvelisib program to us at our request and cost, subject to our execution of a waiver of certain types of damages, and we will thereafter pay to Verastem a low single-digit royalty on net sales of Licensed Products.

We and Verastem have made customary representations and warranties and have agreed to certain customary covenants, including confidentiality and indemnification.

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 IPI-549 and duvelisib, an oral, dual inhibitor of PI3K delta and gamma. In January 2012, Intellikine was acquired by Takeda Pharmaceutical Company Limited, or 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.

Under the terms of the Takeda Agreement, we are obligated to pay Takeda up to $5.0 million in remaining success-based milestone payments for the development of a product candidate other than duvelisib, which could include IPI-549. We are also obligated to pay Takeda up to $165.0 million in remaining success-based milestone payments related to the approval and commercialization of one product candidate other than duvelisib, which could be IPI-549.

Due to amendments to the Takeda Agreement described below, we are no longer obligated to pay Takeda royalties on net sales of IPI-549, other products containing a selective inhibitor of PI3K-gamma, or duvelisib in oncology indications. However, we remain obligated to pay Takeda tiered royalties ranging from 7% to 11% on worldwide net sales of products containing a selective inhibitor of PI3K-delta or a selective dual inhibitor of PI3K delta and gamma, as described in the Takeda Agreement, including duvelisib if commercialized outside oncology indications. Such royalties are payable until the later to occur of (i) the expiration of specified patent rights and (ii) the expiration of non-patent regulatory exclusivities in a country, subject to reduction of the royalties and, in certain circumstances, limits on the number of products subject to a royalty obligation.

Under the September 2016 amendment to the Takeda Agreement, and in connection with our entry into the Verastem Agreement, we are no longer obligated to pay Takeda any remaining milestone payments for the development, approval or commercialization of duvelisib. In return, we became obligated to pay Takeda 50% of all revenue arising from certain qualifying transactions for duvelisib, including those under the Verastem Agreement, subject to certain exceptions including revenue we receive as reimbursement for duvelisib research and development expenses. On March 4, 2019, we entered into a fourth amendment, or Takeda Amendment, to the Takeda Agreement. The Takeda Amendment amends our obligation to pay Takeda 50% of all revenue under the Verastem Agreement, defined below. See Note 14 for details of the Takeda Amendment.

The July 2017 amendment to the Takeda Agreement terminated our obligations to pay royalties to Takeda with respect to worldwide net sales of products containing or comprised of a selective inhibitor of PI3K gamma, including but not limited to IPI-549. In consideration for such termination, we concurrently executed a convertible promissory note, which we refer to as the Takeda Note, pursuant to which we were obligated to pay Takeda, or its designated affiliate, the principal amount of $6.0 million together with interest accruing at a rate of 8% per annum on or before July 26, 2018 in cash or in shares of our common stock, at the election of Takeda. The $6.0 million has been included in our accompanying consolidated balance sheets as a current liability titled Note Payable as of December 31, 2017. We recorded the $6.0 million in research and development expense and $0.2 million of interest expense related to the Takeda Note during the year ended December 31, 2017.

On March 12, 2018, we exercised our right to prepay in full the Takeda Note in the principal amount of $6.0 million together with interest of approximately $0.3 million. Takeda elected to receive $4.0 million of such payment in cash and approximately $2.3 million of such payment in shares of our common stock. Pursuant to the terms of the Takeda Note, we issued 1,134,689 shares of common stock to Takeda at a price of $2.028 per share to Takeda's designated subsidiary, Millennium Pharmaceuticals, Inc.

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.

PellePharm

In June 2013, we entered into a license agreement with PellePharm, Inc., or PellePharm, under which we granted PellePharm exclusive global development and commercialization rights to our hedgehog inhibitor program, including IPI-926, a clinical-stage product candidate. We refer to our license agreement with PellePharm as the PellePharm Agreement and products covered by the PellePharm Agreement as Hedgehog Products.

Under the PellePharm Agreement, PellePharm is obligated to pay us up to $11.0 million in clinical, 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. As of December 31, 2018, we did not recognize revenue related to the milestones 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 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 clinical, 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 milestones, including royalties, will be recognized when the related sales occur as these amounts have been determined to relate predominantly to the license granted to PellePharm and therefore are recognized at the later of when the performance obligation is satisfied, or the related sales occur.

PellePharm's royalty obligations to us expire on a country-by-country and Hedgehog Product-by-Hedgehog Product basis, and the PellePharm Agreement expires upon the expiration of the last royalty obligation owed by PellePharm to us, at which time the license to Hedgehog Products and licenses to our know-how as described in the PellePharm Agreement become fully-paid-up and non-royalty-bearing licenses. PellePharm has the right to terminate the PellePharm Agreement upon at least 180 days' prior written notice to us at any time, and we may terminate the PellePharm Agreement if PellePharm puts forth or actively assists a patent challenge related to our Hedgehog Product patent rights. Either party may terminate the PellePharm Agreement if the other party materially breaches or defaults in the performance of its obligations. Upon termination by either party, all rights and licenses granted by us to PellePharm under the PellePharm Agreement terminate and PellePharm shall, to the extent applicable, transfer and assign to us all rights, title, and interest in and to the trademark(s) used for Hedgehog Products in the Territory.

We and PellePharm have made customary representations and warranties and have agreed to certain customary covenants, including confidentiality and indemnification.

11. Income Taxes

We did not have any income tax expense for the year ended December 31, 2018. We recognized an income tax benefit of $0.7 million for the year ended December 31, 2017 as a result of monetizing our alternative minimum tax credit carryforwards as permitted by the Tax Cut and Jobs Act, or the Act, that was enacted on December 22, 2017.

Our income tax expense for the years ended December 31, 2018 and 2017 differed from the expected U.S. federal statutory income tax expense as set forth below:

	Years Ended December 31,	
	2018	2017
	(in thousands)	
Expected federal tax benefit	$ (2,363)	$ (14,467)
Permanent differences	337	673
State taxes, net of the deferred federal benefit	(621)	(2,150)
Tax credit carryforwards	(450)	—
Adjustments to deferred tax assets and deferred tax liabilities	1,073	5,291
Tax Cut and Jobs Act impact	—	74,455
Other	(24)	—
Change in valuation allowance	2,048	(64,522)
Income tax expense (benefit)	$ —	$ (720)

On December 22, 2017, the Securities Exchange Commission staff issued Staff Accounting Bulletin No. 118, Income Tax Accounting Implications of the Tax Cuts and Jobs Act, or SAB 118, which allows the recording of provisional amounts during a measurement period not to extend beyond one year of the enactment date. In accordance with SAB 118, we

determined the provisional impacts of the Act and recorded the provisional amounts in the period ending December 31, 2017. There have been no changes to the provisional amounts recorded at December 31, 2017 and the Company considers the accounting related to the Act complete.

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

	Years Ended December 31,	
	2018	2017
	(in thousands)	
Deferred tax assets (liabilities):		
Net operating loss carryforwards	$ 139,690	$ 135,787
Tax credit carryforwards	40,977	40,539
Intangible assets	20,336	22,206
Accrued expenses	48	88
Stock-based compensation	5,698	6,056
Other	366	391
Valuation allowance	(207,115)	(205,067)
Net deferred tax assets	$ —	$ —

We have recorded a valuation allowance against our deferred tax assets in each of the years ended December 31, 2018, and 2017 because we believe that it is more likely than not that these assets will not be realized. The valuation allowance increased by approximately $2.0 million during the year ended December 31, 2018 primarily as a result of the increase in our unbenefited net operating loss for the current period. This is reduced by the reduction in the intangible asset deferred tax asset resulting from amortization deductions in the current period. The valuation allowance decreased by approximately $57.7 million during the year ended December 31, 2017 primarily as a result of the re-measurement of our deferred tax balance following the Act.

Subject to the limitations described below, at December 31, 2018, we have cumulative net operating loss carryforwards of approximately $538.8 million and $419.9 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. The state net operating loss carryforwards begin to expire in 2031 and continue to expire through 2038. In addition, we have cumulative federal and state tax credit carryforwards of $33.1 million and $10.0 million, respectively, available to reduce federal and state income taxes which expire through 2038 and 2030, 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.

At December 31, 2018 and 2017, we had no unrecognized tax benefits. As of December 31, 2018 and 2017, we had no accrued interest or penalties related to uncertain tax positions and no amounts have been recognized in our consolidated statements of operations. We will recognize interest and penalties related to uncertain tax positions in income tax expense. For all years through December 31, 2016, 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 2015, although carryforward attributes that were generated prior to tax year 2015 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.

12. Stockholders' Equity

Common Stock Sales Facility

In May 2016, we entered into a controlled equity offering sales agreement, or Sales Agreement, with Cantor Fitzgerald & Co., or Cantor Fitzgerald pursuant to which we may from time to time, at our option, offer and sell shares of our common stock having an aggregate offering price of up to $50.0 million through Cantor Fitzgerald, acting as our sales agent. Cantor Fitzgerald will be entitled to a commission of 3.0% of the aggregate gross proceeds from sales of shares of our common stock under the Sales Agreement. Sales of shares of our common stock under the Sales Agreement may be made by any method permitted by law that is deemed an "at the market" offering as defined in Rule 415 under the Securities Act of 1933, as amended, including sales made through the Nasdaq Global Select Market, on any other existing trading market for our common stock or to or through a market maker. We may also authorize Cantor Fitzgerald to sell shares in privately negotiated transactions. During the year ended December 31, 2018, we sold 4,461,893 shares of common stock at a weighted average price per share of $2.18 at-the-market pursuant to the Sales Agreement for an additional $9.3 million in net proceeds. During the year ended December 31, 2017, we issued and sold 10,958 shares of common stock at a weighted average price per share of $2.54 at-the-market pursuant to the Sales Agreement for approximately $27,000 in net proceeds. We have no obligation to sell shares of our common stock and cannot provide any assurances that we will issue any additional shares pursuant to the Sales Agreement. We may also suspend the offering of shares of our common stock upon notice and subject to other conditions.

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. As of December 31, 2018, no warrants have been exercised.

13. 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, 2018 and 2017, we matched 50% of the participant's contribution up to 6% of the participant's pre-tax salary with shares of our common stock. Our matching contributions for each of the years ended December 31, 2018 and 2017 were $0.1 million.

14. Subsequent Events

Transaction with HealthCare Royalty Partners

Purchase and Sale Agreement

On March 5, 2019, we and HealthCare Royalty Partners III, L.P., or HCR, entered into a purchase and sale agreement, or the HCR Agreement, providing for the acquisition by HCR, of our interest in certain royalty payments, or the Purchased Assets, based on worldwide annual net sales of products containing IPI-145, or Licensed Product, pursuant to the Verastem Agreement. We refer to the acquisition of such interests as the Transaction. Following satisfaction of customary closing conditions, we received $30.0 million, or the Closing Date Payment, less certain transaction expenses, on March 11, 2019. After sharing with Takeda in accordance with the Takeda Amendment, defined above, we retain $22.5 million in gross proceeds or approximately $20.0 million in net proceeds. We will also be entitled to receive up to $15.0 million in milestone payments based on the achievement of certain pre-specified net sales levels of the Licensed Product in the United States in the calendar year 2019 and up to an additional $5.0 million milestone payment based on the achievement of a certain pre-specified net sales level of the Licensed Product in the United States in the calendar year 2020. We refer to the milestone payments collectively as the Sales Milestone Payments. The Sales Milestone Payments, if paid, together with the Closing Date Payment are collectively referred to herein as the Investment Amount.

Pursuant to the HCR Agreement, our sale of the Purchased Assets shall be subject to an increasing cap amount equal to, for each applicable time period specified below, a multiple, as set forth below, of (a) the Investment Amount plus (b) 100% of the reasonably incurred Applicable Purchaser Expenditures (as defined below), or the Cap Amount:

Time Period	Cap Amount
From the Closing 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%

On any date that aggregate payments made to HCR with respect to the Purchased Assets based on worldwide, annual net sales of the Licensed Product equal the Cap Amount applicable to such date, or the Cap Date, the HCR Agreement will automatically terminate and all rights to the royalty stream with respect to the Licensed Product will revert back to us, or the Reversion; provided, however, that if the Cap Date has not been achieved by June 30, 2025, there shall be no Cap Date, and the term of the HCR Agreement shall continue through the term of the Verastem Agreement. Prior to June 30, 2025, we shall have the right, but not the obligation, at any time prior to the Cap Date, if applicable, to cause the occurrence of the Cap Date (including for the purpose of determining the termination date of the HCR Agreement) by paying to HCR an amount equal to (i) the then-applicable Cap Amount less (ii) 100% of all payments made in respect of the Purchased Assets received by HCR pursuant to the Verastem Agreement or the HCR Agreement through the date of such payment.

We will retain in full our obligations to make payments to Takeda, pursuant to the Takeda Agreement, as amended. Verastem will continue to pay Infinity royalties with respect to net sales of the Licensed Product that we are obligated to pay to Purdue and Mundipharma and Infinity will retain in full its obligations to make the royalty payments to those entities pursuant to our separate agreements with those entities.

If the Verastem Agreement is terminated prior to the Cap Date, we shall use commercially reasonable efforts, at HCR's request, in consultation and cooperation with HCR, for a prespecified time period, or the Initial Search Period, to locate, negotiate and secure a license of the intellectual property rights with respect to the Licensed Product. We refer to any such license as a New Arrangement. HCR shall have the right to consent in writing to any New Arrangement, which approval shall not be unreasonably withheld or delayed. Following the expiration or termination of the Initial Search Period, we shall use commercially reasonable efforts to provide cooperation and assistance to HCR in connection with HCR's efforts to locate, negotiate and secure a New Arrangement; provided, that we shall have the right to consent in writing to any New Arrangement, which approval shall not be unreasonably withheld or delayed.

The Purchaser shall bear all expenses in connection with any obligations set forth in the HCR Agreement regarding protection and enforcement of certain intellectual property underlying the Licensed Product and efforts in connection with the location, negotiation and securing of a New Arrangement, including the reimbursement to us for all out-of-pocket third-party expenses, including reasonable attorney's fees, we incurred in connection with such activities, which we refer to collectively as the Applicable Purchaser Expenditures.

The HCR Agreement contains other customary terms and conditions, including representations and warranties, conditions precedent, indemnities and covenants, including covenants that, among other things, require us to provide certain information to HCR with respect to the Verastem Agreement and the Licensed Product and to cooperate with HCR, at HCR's expense, to take certain actions under the Verastem Agreement and otherwise with respect to the Licensed Product to protect HCR's rights to receive the royalty payments. These covenants are subject to a number of important exceptions and qualifications.

In addition to the Cap Date, the HCR Agreement (a) may be terminated (i) by mutual agreement of us and HCR and (ii) by either of us or HCR, if the Transaction does not close within 30 days of the date of the HCR Agreement, and (b) shall automatically terminate upon the expiration of our and Verastem's obligations to each other under the Verastem Agreement (for a reason other than early termination thereof).

Protective Rights Agreement

As part of the Transaction, on the Closing Date, we are obligated to enter into a Protective Rights Agreement, or the PRA, with HCR Collateral Management, LLC, as agent for HCR, or the Agent. Under the PRA, we are obligated to grant to the Agent, among other things, a security interest in all of the our right, title and interest in, to and under the Purchased Assets, certain patents owned by us and underlying the Licensed Product, and certain related rights and proceeds thereof. The PRA will not give a security interest in any of our other assets and terminates upon termination of the HCR Agreement, at which time all rights will revert back to us.

The rights of the Agent under the PRA are exercisable (a) in the event that the Transaction is characterized by a court of competent jurisdiction as a loan, rather than a sale; (b) upon the occurrence of certain insolvency events with respect to, or

breaches of the HCR Agreement by, us that have caused or would reasonably be expected to cause: (i) the invalidity of the security interest pursuant to the PRA or the HCR Agreement, (ii) impairment of a material portion of the collateral or (iii) termination of the Verastem Agreement; and (c) upon any breach by us of our obligations to locate, negotiate and secure a New Arrangement or to provide cooperation and assistance to HCR in connection therewith.

Takeda Amendment

On March 4, 2019, the Takeda Amendment Effective Date, we entered into a fourth amendment, or Takeda Amendment, to the Takeda Agreement. Under the Takeda Agreement, defined in Note 10, we are obligated to pay Takeda 50% of the royalties otherwise payable to us pursuant to the Verastem Agreement, subject to certain exceptions. Pursuant to the Takeda Amendment, Takeda has consented to the sale of the Purchased Assets, has agreed to forego its rights to 50% of the royalties during the period prior to the Reversion, and has agreed not to seek any payment from HCR with respect to the royalties owed to Takeda in exchange for payments equal to (a) 25% of the Investment Amount, net of 25% of the expenses incurred by us in connection with the Transaction (the aggregate amount of such expenses shall be capped at $4.0 million), within 15 days of receipt of any portion of the Investment Amount by us and (b) 25% of the royalties that would have been payable to us but for the consummation of the Transaction, no later than the date such payments would have been received by us under the Verastem Agreement, or the Interim Obligation. We also have the right to extinguish the Interim Obligation by payment to Takeda of an amount equal to (i) the amount paid to Takeda under clause (a) of the foregoing sentence multiplied by the multiple set forth in the table below corresponding to the time period in which such extinguishing payment is made, minus (ii) all 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 occurrence of the Reversion, at which time our obligations under the Takeda Agreement to pay to Takeda 50% of the royalties payable under the Verastem Agreement shall be reinstated.

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, 2018. In designing and evaluating our disclosure controls and procedures, management recognized that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives, and our management necessarily applied its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on this evaluation, our principal executive officer and principal financial officer concluded that as of December 31, 2018, 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.

No change in our internal control over financial reporting occurred during the fiscal quarter ended December 31, 2018 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Internal Control Over Financial Reporting

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

Our management is responsible for establishing and maintaining adequate internal control over financial reporting. Internal control over financial reporting is defined in Rules 13a-15(f) and 15d-15(f) promulgated under the Exchange Act as a process designed by, or under the supervision of, 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, 2018. 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, 2018, our internal control over financial reporting is effective based on those criteria.

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

(b) Report of Independent Registered Public Accounting Firm

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

Opinion on Internal Control over Financial Reporting

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

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the consolidated balance sheets of the Company as of December 31, 2018 and 2017, the related consolidated statements of operations and comprehensive loss, stockholders' equity and cash flows for each of the two years in the period ended December 31, 2018, and the related notes and our report dated March 14, 2019 expressed an unqualified opinion thereon.

Basis for Opinion

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

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

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

Definition and Limitations of Internal Control Over Financial Reporting

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

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

/s/ Ernst & Young LLP

Boston, Massachusetts
March 14, 2019

(c) 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 year ended December 31, 2018 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

PART III

Item 10. Directors, Executive Officers and Corporate Governance

The sections titled "Proposal 1—Election of Directors," "Board and Committee Meetings," "Section 16(a) Beneficial Ownership Reporting Compliance" and "Corporate Governance Guidelines; Code of Conduct and Ethics" appearing in the definitive proxy statement we will file in connection with our Annual Meeting of Stockholders to be held on June 13, 2019 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—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 Annual Meeting of Stockholders to be held on June 13, 2019 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 Annual Meeting of Stockholders to be held on June 13, 2019 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 Annual Meeting of Stockholders to be held on June 13, 2019 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 Annual Meeting of Stockholders to be held on June 13, 2019 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.	10-Q	8/9/2007	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	
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	Convertible Promissory Note, dated as of July 26, 2017, by and between Registrant and Intellikine LLC.	10-Q	11/7/2017	10.2	
10.6†	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	
10.7	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	
10.8	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					
10.9	Form of Warrant to Purchase Common Stock of Infinity Pharmaceuticals, Inc., issued to the Deerfield Entities, together with a schedule of holders and amounts (issued February 24, 2014).	10-Q	5/6/2014	10.2	
Leases					
10.10	Lease Agreement, dated as of September 25, 2014, between Registrant and BHX, LLC, as trustee of 784 Realty Trust.	10-Q	11/10/2014	10.4	
10.11	Amendment to Lease, dated as of March 27, 2017, between Registrant and BHX, LLC as trustee of 784 Realty Trust.	8-K	3/29/2017	10.1	
10.12	Second Amendment of Lease, dated as of May 1, 2017, between Registrant and BHX, LLC as trustee of 784 Realty Trust.	8-K	5/22/2017	10.1	
10.13	Third Amendment of Lease, dated as of May 31, 2017, between Registrant and BHX, LLC as trustee of 784 Realty Trust.	8-K	6/2/2017	10.1	

Exhibit No.	Description	Incorporated by Reference			Filed with this 10-K
		Form	SEC Filing date	Exhibit Number	
Equity Plans					
10.19*	2000 Stock Incentive Plan.	S-1	5/9/2000	10.59	
10.20*	Amendment No. 1 to 2000 Stock Incentive Plan;Amendment No. 2 to 2000 Stock Incentive Plan;Amendment No. 3 to 2000 Stock Incentive Plan.	8-K	9/18/2006	10.32	
10.21*	Amendment No. 4 to 2000 Stock Incentive Plan.	10-Q	8/9/2007	10.1	
10.22*	Amendment No. 5 to 2000 Stock Incentive Plan.	S-8	5/23/2008	99.4	
10.23*	Form of Incentive Stock Option Agreement under 2000 Stock Incentive Plan.	8-K	9/18/2006	10.33	
10.24*	Form of Nonstatutory Stock Option Agreement under 2000 Stock Incentive Plan.	8-K	9/18/2006	10.34	
10.25*	2010 Stock Incentive Plan.	8-K	5/28/2010	10.1	
10.26*	Form of Incentive Stock Option Agreement under 2010 Stock Incentive Plan.	8-K	5/28/2010	10.2	
10.27*	Form of Nonstatutory Stock Option Agreement under 2010 Stock Incentive Plan.	8-K	5/28/2010	10.3	
10.28*	Form of Restricted Stock Agreement under 2010 Stock Incentive Plan	10-K	3/14/2017	10.23	
10.29*	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	
10.30*	Amendment No. 1 to 2010 Stock Incentive Plan.	8-K	12/14/2010	99.2	
10.31*	Amendment No. 2 to 2010 Stock Incentive Plan.	8-K	5/18/2012	99.1	
10.32*	Amendment No. 3 to 2010 Stock Incentive Plan.	8-K	6/13/2013	10.1	
10.33*	Amendment No. 4 to 2010 Stock Incentive Plan.	8-K	6/13/2013	10.1	
10.34*	Amendment No. 5 to 2010 Stock Incentive Plan.	8-K	6/16/2015	10.1	
10.35*	Amendment No. 6 to 2010 Stock Incentive Plan.	10-Q	5/4/2016	10.1	
10.36*	2013 Employee Stock Purchase Plan, as amended.	8-K	6/13/2013	99.1	

Exhibit No.	Description	Incorporated by Reference			Filed with this 10-K
		Form	SEC Filing date	Exhibit Number	
Agreements With Executive Officers					
10.37*	Offer Letter between the Registrant and Lawrence E. Bloch, M.D., J.D. dated May 15, 2012.	8-K	7/25/2012	10.1	
10.38*	Offer Letter between IDI and Adelene Perkins dated as of February 6, 2002.	8-K	9/18/2006	10.11	
10.39*	Amendment to Offer Letter between IDI and Adelene Perkins dated as of October 25, 2007.	8-K	10/30/2007	99.5	
10.40*	Offer Letter between the Registrant and Seth A. Tasker, J.D. dated February 22, 2008	10-K	3/14/2017	10.34	
10.41*	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	
10.42*	Offer Letter between the Registrant and Jeffery Kutok, M.D., Ph.D. dated October 26, 2010	10-K	3/14/2017	10.36	
10.43*	Employment Retention Incentive Package Letter Agreement between the Registrant and Jeffery Kutok, M.D., Ph.D. dated July 1, 2016	10-K	3/14/2017	10.37	
10.44*	Offer Letter between the Registrant and Samuel Agresta, M.D., dated July 19, 2018.	10-Q	11/5/2018	10.1	
10.45*	Infinity Pharmaceuticals, Inc. Executive Severance Benefits Plan effective February 6, 2013.	8-K	2/12/2013	10.1	
10.46*	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. Filed herewith.				X
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	The following materials from the Registrant's Annual Report on Form 10-K for the year ended December 31, 2018, formatted in XBRL (eXtensible Business Reporting Language): (i) the Consolidated Balance Sheets, (ii) the Consolidated Statements of Operations and Comprehensive Loss, (iii) the Consolidated Statements of Cash Flows, (iv) the Consolidated Statements of Stockholders' Equity, and (v) Notes to Consolidated Financial Statements.				X

* Indicates management contract or compensatory plan

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

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 14, 2019

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 14, 2019
/s/ LAWRENCE E. BLOCH, M.D., J.D. **Lawrence E. Bloch, M.D., J.D.**	President; Treasurer *(Principal Financial Officer, Principal Accounting Officer)*	March 14, 2019
/s/ DAVID BEIER, J.D. **David Beier, J.D.**	Director	March 12, 2019
/s/ JEFFREY BERKOWITZ, J.D. **Jeffrey Berkowitz, J.D.**	Director	March 12, 2019
/s/ ANTHONY B. EVNIN, PH.D. **Anthony B. Evnin, Ph.D.**	Director	March 12, 2019
/s/ MICHAEL G. KAUFFMAN, M.D., Ph.D. **Michael G. Kauffman, M.D., Ph.D.**	Director	March 12, 2019
/s/ NORMAN C. SELBY **Norman C. Selby**	Director	March 12, 2019
/s/ MICHAEL C. VENUTI, PH.D. **Michael C. Venuti, Ph.D.**	Director	March 12, 2019

This report contains forward-looking statements regarding our expectations with respect to our plans and strategy for our business, the possible achievement of discovery, development, and regulatory goals and milestones in 2019 and beyond, our future discovery and development efforts, our collaborations, and our future operating results and financial position. 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 discovery and clinical 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. Please refer to the section entitled "Risk Factors" in Part I of the accompanying annual report on Form 10-K for a description of these risks and uncertainties. Unless required by law, we do not undertake any obligation to update any forward-looking statements.

Infinity is a clinical-stage biopharmaceutical company focused on developing novel anti-cancer therapies. We are advancing a unique approach to treating cancer with IPI-549, a potentially transformative, first-in-class immunotherapy candidate for the treatment of solid tumors.

EXECUTIVE LEADERSHIP

Samuel Agresta, M.D., M.P.H.
Chief Medical Officer

Lawrence Bloch, M.D., J.D.
President

Jeffery Kutok, M.D., Ph.D.
Chief Scientific Officer

Adelene Perkins
Chair and Chief Executive Officer

Seth Tasker
General Counsel and Secretary

BOARD OF DIRECTORS

David Beier, J.D.
Managing Director,
Bay City Capital

Jeffrey Berkowitz
Chief Executive Officer,
Real Endpoints, LLC

Anthony Evnin, Ph.D.
Partner, Venrock Associates

Michael Kauffman, M.D., Ph.D.
Chief Executive Officer,
Karyopharm Therapeutics

Adelene Perkins
Chair and Chief Executive Officer,
Infinity Pharmaceuticals, Inc.

Norman Selby
Chairman, RealEndpoints

Michael Venuti, Ph.D.
Industry Consultant

ANNUAL MEETING

The Annual Meeting of Stockholders will be held at 8:30 a.m. EDT on June 13, 2019, at
Infinity Pharmaceuticals, Inc.
784 Memorial Drive
Cambridge, MA 02139

INDEPENDENT AUDITORS

Ernst & Young LLP; Boston, MA

INVESTOR INQUIRIES

617.453.1015
irpr_info@infi.com

STOCK LISTING

NASDAQ: INFI

TRANSFER AGENT

The transfer agent is responsible, among other things, for handling stockholder questions regarding lost stock certificates, address changes, including duplicate mailings, and changes in ownership or name in which shares are held. These requests may be directed to the transfer agent at the following address:

American Stock Transfer & Trust Company, LLC
6201 15th Avenue
Brooklyn, NY 11219
www.amstock.com

SEC FORM 10-K

A copy of Infinity's annual report on Form 10-K filed with the Securities and Exchange Commission is available free of charge from the company's Investor Relations Department by calling 617.453.1015, sending a request by email to irpr_info@infi.com or sending a written request to:

Investor Relations
Infinity Pharmaceuticals, Inc.
784 Memorial Drive
Cambridge, MA 02139

Footnotes:
1 Kaneda M., Messer K., Ralainirina N., Li H., et al. PI3K-gamma is a molecular switch that controls immune suppression. *Nature*, 2016 Nov;539:437-442.
2 De Henau O., Rausch M., Winkler D., Campesato L., et al. Overcoming resistance to checkpoint blockade therapy by targeting PI3K-gamma in myeloid cells. *Nature*, 2016 Nov;539:443-447.
3 OPDIVO® is a registered trademark of Bristol-Myers Squibb.
4 Sullivan et al., ASCO Annual Meeting 2018
5 Chmielowski et al., SITC Annual Meeting 2018
6 Tecentriq® and Avastin® are registered trademarks of Roche
7 Abraxane® is a registered trademark of Celgene

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