INFINITY PHARMACEUTICALS, INC.
Form 10-K
February 23, 2016
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

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

For the fiscal year ended: December 31, 2015

¨ **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, $.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 x

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 x

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 x No ¨

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted 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 and post such files). Yes x 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. x

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

Large accelerated filer x	Accelerated filer ¨	Non-accelerated filer ¨ (Do not check if a smaller reporting company)	Smaller reporting company ¨

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

The aggregate market value of voting Common Stock held by non-affiliates of the registrant as of June 30, 2015 was $528,764,262 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 February 16, 2016: 49,339,647

Documents incorporated by reference:

Portions of our definitive proxy statement to be filed with the Securities and Exchange Commission no later than April 29, 2016 in connection with our 2016 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 strategy for our business, the possible achievement of discovery and development goals and milestones in 2016, our future discovery and 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 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 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 discovering, developing and delivering best-in-class medicines to patients with difficult-to-treat diseases. We combine proven scientific expertise with a passion for developing novel small molecule drugs that target disease pathways for potential applications in oncology. Our most advanced product candidate is duvelisib, also known as IPI-145, an oral, dual-inhibitor of the delta and gamma isoforms of phosphoinositide-3-kinase, or PI3K, which is currently being evaluated for the treatment of hematologic malignancies, or blood cancers. We believe that duvelisib is the only inhibitor of PI3K-delta and gamma being investigated in Phase 3 clinical trials. We are pursuing duvelisib in oncology through a strategic collaboration with AbbVie Inc., or AbbVie. For information regarding our collaboration, please see below under the heading *AbbVie* in the section entitled Strategic Alliances.

Through the efforts of our dedicated discovery research program, during 2016 we expanded our pipeline with the addition of IPI-549, an orally administered, clinical-stage, immuno-oncology product candidate that selectively inhibits the gamma isoform of PI3K. In addition to duvelisib and IPI-549, we are working to generate new product candidates for potential investigation in oncology.

Product Development Pipeline

Historically, our product development programs have arisen from a combination of internally developed programs and strategic licensing arrangements. We focus on targets that have the potential to fundamentally change how disease is treated and where we believe we can use our scientific capabilities to identify differentiated product candidates with well-defined development paths. We seek to leverage what we believe to

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be our innovative approaches to drug discovery and translational medicine and our robust internal capabilities across all of the relevant scientific disciplines, including medicinal chemistry, cell biology, biochemistry, pharmacology and molecular pathology. Our goal is to integrate these disciplines to rapidly identify product candidates and to better understand which populations of patients may benefit most from our product candidates.

The table and descriptions below summarize key information about our product candidates, duvelisib and IPI-549. None of our product candidates are approved for any indication by the United States Food and Drug Administration or any other regulatory agency.

Duvelisib: Dual Inhibitor of PI3K Delta and Gamma

	Indication	Status
Indolent non-Hodgkin Lymphoma		
DYNAMO	Refractory indolent non-Hodgkin lymphoma	Phase 2, open-label, single-arm clinical study Designed with potential to support accelerated approval Primary endpoint: response rate according to the International Working Group, or IWG, criteria Enrollment complete: 129 patients Expect to report topline data in the third quarter of 2016
CONTEMPO	Previously untreated follicular lymphoma	Phase 1b/2 open label, two-arm clinical study Duvelisib plus obinutuzumab or rituximab Targeting approximately 100 patients Primary endpoint: Safety; complete response rate according to IWG criteria Enrollment ongoing Expect to report initial data from this study in the second half of 2016
BRAVURA	Relapsed indolent non-Hodgkin lymphoma	Phase 3, double-blind, placebo-controlled clinical study Duvelisib plus rituximab and bendamustine compared to placebo plus rituximab and bendamustine Targeting approximately 600 patients Primary endpoint: progression-free survival Enrollment ongoing
FRESCO	Relapsed or refractory follicular lymphoma	Phase 2 randomized clinical study Duvelisib in combination with rituximab compared to chemotherapy in combination with rituximab Targeting 230 patients

		Primary endpoint: progression-free survival Enrollment ongoing
DYNAMO+R	Previously treated follicular lymphoma	Phase 3 randomized, placebo-controlled clinical study Duvelisib plus rituximab compared to placebo plus rituximab Study identified for closure

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	Indication	Status
Chronic Lymphocytic Leukemia		
DUO	Relapsed or refractory chronic lymphocytic leukemia	Phase 3, randomized, monotherapy clinical study Duvelisib compared to ofatumumab Primary endpoint: progression-free survival Enrollment complete: 319 patients Expect to report topline data in the second half of 2016
SYNCHRONY	Patients with chronic lymphocytic leukemia whose disease has progressed following treatment with a Bruton s tyrosine kinase inhibitor	Phase 1b open-label clinical study Duvelisib in combination with obinutuzumab Primary endpoint: Safety Targeting approximately 64 patients Enrollment ongoing
Advanced Hematologic Malignancies		
Duvelisib + Venetoclax	Relapsed or refractory indolent or aggressive non-Hodgkin lymphoma, chronic lymphocytic leukemia, or small lymphocytic lymphoma	Phase 1b/2 open label clinical study Duvelisib in combination with venetoclax Targeting approximately 174 patients Initiated, not yet recruiting
IPI-549: PI3K Gamma-Selective Inhibitor		
Solid Tumors	Patients with a range of solid tumors, including melanoma and non-small cell lung cancer	Phase 1 clinical study Includes a dose-escalation phase and an expansion phase, and is designed to evaluate IPI-549 as a monotherapy as well as in combination with an anti-PD-1 antibody therapy Enrollment ongoing

PI3 Kinase Inhibitor Program

The PI3Ks are a family of enzymes involved in multiple cellular functions, including cell proliferation and survival, cell differentiation, cell migration, and immunity. PI3K-delta and PI3K-gamma are two proteins with distinct and mostly non-overlapping roles believed to support the growth and survival of malignant B-cells. Specifically, preclinical data suggest that PI3K-delta signaling can lead to the proliferation of malignant B-cells, and that both PI3K-gamma and PI3K-delta play an important role in the formation and maintenance of the supportive tumor microenvironment.

Duvelisib: Targeting Hematologic Malignancies by Dual Inhibition of PI3K Delta and Gamma Isoforms

We believe that dual inhibition of PI3K-delta and PI3K-gamma may provide multiple opportunities to develop a differentiated therapy for the treatment of certain hematologic malignancies. Our lead product candidate, duvelisib, is an oral, dual inhibitor of PI3K-delta and PI3K-gamma, which we believe is the only dual inhibitor of PI3K-delta and PI3K-gamma being investigated in Phase 3 clinical trials. Duvelisib is an investigational compound, and its safety and efficacy have not yet been evaluated by the FDA or any other health authority.

Hematologic malignancies are cancers of the blood or bone marrow such as non-Hodgkin lymphoma, or NHL, and chronic lymphocytic leukemia, or CLL. It is estimated that there will be approximately 134,650 newly diagnosed cases of NHL in the seven major pharmaceutical markets (United States, France, Germany, Italy,

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Japan, Spain, and United Kingdom) in 2016. The distribution of NHL subtypes differs by country. In the United States and major European countries in 2012, diffuse large B-cell lymphoma, or DLBCL, accounted for 37-43% of NHL cases while CLL accounted for 25-33% and follicular lymphoma for 17-22%. Even with advances in treatment options for these diseases, the clinical outlook for patients still remains poor. A significant proportion of patients relapse following treatment and become refractory to current agents, representing a significant unmet medical need.

To address this need, we are conducting DUETTS (Duvelisib Trials in Hematologic Malignancies), a worldwide clinical investigation of duvelisib in blood cancers initially focusing on lymphoma and CLL. The investigation of duvelisib in our DUETTS trials, discussed below in detail, is supported by data from our Phase 1, open-label, dose-escalation study designed to evaluate the safety, pharmacokinetics and clinical activity of duvelisib in patients with advanced hematologic malignancies. The maximum tolerated dose of duvelisib was defined at 75 mg twice daily, or BID, and we have closed the trial to further enrollment. Data from this study, presented in December 2014 at the Annual Meeting of the American Society for Hematology, or ASH 2014, showed that duvelisib is clinically active in CLL, iNHL, aggressive NHL, or aNHL, and T-cell lymphoma, as well as other hematologic malignancies. We are continuing to evaluate duvelisib in 14 patients with hematologic malignancies across multiple dose levels from 10 mg BID to 75 mg BID with eight patients (57%) continuing to receive 25 mg bid. These 14 remaining patients represent several hematology indications: four patients with iNHL, mantle cell lymphoma, or MCL, or CLL; seven treatment-naïve, high-risk CLL patients, with high-risk defined as patients aged 65 or older or having either of two genetic abnormalities known as a 17p- deletion or a p53 mutation; two patients with cutaneous T-cell lymphoma, or CTCL, or noncutaneous T-cell lymphoma; and one patient with aNHL.

Indolent Non-Hodgkin Lymphoma

As part of the DUETTS program in lymphoma, we are conducting DYNAMO , a Phase 2, open-label, single arm monotherapy study evaluating the safety and efficacy of duvelisib dosed at 25 mg twice daily in 129 patients with iNHL. DYNAMO enrollment criteria include patients with follicular lymphoma, the most common subtype of iNHL, marginal zone lymphoma, and small lymphocytic lymphoma, or SLL, whose disease is refractory to rituximab, a monoclonal antibody treatment, and to either chemotherapy or radioimmunotherapy and who must have progressed within six months of receiving their last therapy. The primary endpoint of the study is response rate according to the International Working Group, or IWG, Criteria. We completed enrollment in DYNAMO in September 2015 and expect to report topline data in the third quarter of 2016.

The DYNAMO study is designed with the potential to support accelerated approval of duvelisib in patients with follicular lymphoma and SLL, assuming we are able to generate positive safety and efficacy data from the study and on the condition that we conduct a confirmatory study. The FDA has granted orphan drug designation to duvelisib for the potential treatment of follicular lymphoma, and has granted fast track designation to the investigation of duvelisib for the treatment of patients with follicular lymphoma who have received at least two prior therapies. The availability of accelerated approval is uncertain, and is dependent on a number of factors including whether duvelisib has demonstrated a meaningful benefit relative to available therapies. For a further discussion of the FDA s accelerated approval pathway, and certain risks related to our ability to seek accelerated approval for duvelisib, see Government Regulation and Product Approvals Review and Approval of Drugs in the United States and Risk Factors Risks Related to Regulatory Approval and Marketing of Our Product Candidates and Other Legal Compliance Matters elsewhere in this report.

The investigation of duvelisib in DYNAMO is supported by preliminary data from our Phase 1, open-label, dose-escalation study designed to evaluate the safety, pharmacokinetics and clinical activity of duvelisib in patients with advanced hematologic malignancies, discussed in more detail below. Data presented at ASH 2014 from our Phase 1 study have demonstrated that duvelisib administered at 25 mg BID is clinically active in patients with iNHL, with a 72% (13 of 18 evaluable patients) overall response rate and a 33% (6 of 18 evaluable

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patients) complete response rate. Among patients with follicular lymphoma, the overall response rate was 69% (9 of 13 evaluable patients), including a 38% complete response rate (5 of 13 evaluable patients). As of the time of ASH 2014, the median progression free survival and median overall survival had not yet been reached, with 69% of patients progression-free and with an 89% overall survival rate at 24 months. Duvelisib was generally well tolerated, and the majority of side effects were low-grade, asymptomatic and transient. The majority of adverse events were Grade 1 or 2, reversible and/or clinically manageable. At the 25 mg BID dose, the most common Grade 3 side effects were an increase in alanine aminotransferase, or ALT, or aspartate aminotransferase, or AST (32%), diarrhea (16%), neutropenia and pneumonia (11% each). Grade 4 neutropenia was 11% (two patients), Grade 4 ALT or AST increase was 5% (one patient) and Grade 4 pneumonia was 5% (one patient).

Additional DUETTS clinical studies in lymphoma include CONTEMPO, BRAVURA, and FRESCO. CONTEMPO is a Phase 1b/2 clinical study of duvelisib in combination with obinutuzumab, a monoclonal antibody treatment, or rituximab in patients with previously untreated follicular lymphoma. We expect to report initial data from CONTEMPO in the second half of 2016. BRAVURA is a Phase 3, double-blind, placebo-controlled study in patients with relapsed iNHL designed to evaluate the safety and efficacy of duvelisib plus rituximab and bendamustine, a chemotherapy, compared to placebo plus rituximab and bendamustine in approximately 600 patients. The primary endpoint is progression-free survival. We requested advice from the FDA to determine if BRAVURA, as designed, can serve as a confirmatory study if DYNAMO supports an accelerated approval. FRESCO is a Phase 2 randomized study in patients with relapsed or refractory follicular lymphoma that is designed to evaluate the safety and efficacy of duvelisib plus rituximab compared to rituximab plus a combination of chemotherapies referred to as CHOP in approximately 230 patients. The chemotherapies included in CHOP are cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone. The primary endpoint of FRESCO is progression-free survival. DYNAMO+R, a Phase 3 randomized, placebo-controlled study evaluating duvelisib dosed at 25 mg BID in combination with rituximab compared to placebo plus rituximab in patients with previously treated follicular lymphoma has been identified for closure and is no longer enrolling patients.

Chronic Lymphocytic Leukemia

As part of the DUETTS investigation in CLL, we are conducting DUO™ and SYNCHRONY. DUO is a randomized, Phase 3 monotherapy study designed to evaluate the safety and efficacy of duvelisib dosed at 25 mg BID compared to ofatumumab, a monoclonal antibody treatment, in 319 patients with relapsed or refractory CLL. The primary endpoint of the study is progression-free survival. Enrollment of DUO was completed in November 2015, and we expect to report topline data in the second half of 2016 if supported by the interim analysis. SYNCHRONY is a Phase 1b trial of duvelisib in combination with obinutuzumab in CLL patients whose disease has progressed following treatment with a Bruton s tyrosine kinase, or BTK, inhibitor. This study is supported by Phase 1 data of duvelisib in six CLL patients previously treated with ibrutinib, a BTK inhibitor, presented at ASH 2014. Early clinical activity was observed, with partial responses in one CLL patient and stable disease in five CLL patients. The safety profile of duvelisib in these patients appeared consistent with the safety profile observed in other patients with advanced hematologic malignancies treated with duvelisib in the Phase 1 study. The FDA and the European Medicines Agency, or EMA, have granted orphan drug designation to duvelisib for the potential treatment of CLL and SLL. The FDA has granted fast track designation to the investigation of duvelisib for the potential treatment of patients with CLL who have received at least one prior therapy.

The investigation of duvelisib in DUO and SYNCHRONY is supported by preliminary data from our Phase 1 study that demonstrated that duvelisib administered at 25 mg BID is clinically active in patients with relapsed or refractory CLL, with a 57% overall response rate (17 of 30 evaluable patients), including one complete response. At the time of ASH 2014, the median progression free survival and median overall survival in the 31 patients who received the 25 mg BID dose had not yet been reached with a median time on treatment of 7.6 months (range: 0.9 months to 34.1 months). The majority of side effects were Grade 1-2, reversible and/or clinically manageable. Across all doses evaluated in the study (N = 55), the most common Grade 3 side effects were pneumonia (24%), neutropenia (18%) and anemia (16%). Grade 4 pneumonia was 2% (one patient), Grade 4 neutropenia was 24% (13 patients) and Grade 4 anemia was 2% (one patient).

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Additional data from our Phase 1 study has demonstrated clinical activity of duvelisib dosed at 25 mg BID in previously untreated patients with CLL, with an 88% overall response rate (15 partial responses out of 17 evaluable patients, with two additional patients exhibiting stable disease) based on International Workshop on Chronic Lymphocytic Leukemia, or iwCLL, criteria. The study included 18 treatment-naïve CLL patients who were high-risk, defined as age 65 or over and/or having certain genetic abnormalities known as 17p deletions or p53 mutations. Data presented at the annual meeting of the American Society of Clinical Oncology, or ASCO, in June 2015, showed that the median time to response was 3.7 months, and the median progression-free survival and median overall survival had not yet been reached. The majority of adverse events were grade 1 or grade 2 and clinically manageable. The most common Grade 3 side effects among the 18 enrolled patients were diarrhea (22%), an increase in ALT and AST (17%), and rash (11%). Five patients (28%) had Grade 4 neutropenia or decreases in neutrophil count. There were no Grade 4 events of diarrhea, increases in ALT or AST or rash. Six patients discontinued treatment due to an adverse event.

Investigating Duvelisib in Combination with Venetoclax

As part of our collaboration, AbbVie has initiated the first clinical study investigating duvelisib in combination with venetoclax, a first-in-class, investigational, selective B-cell lymphoma 2, or BCL-2, inhibitor. This Phase 1b/2 trial is designed to evaluate the safety and activity of duvelisib in combination with venetoclax in approximately 174 patients with relapsed or refractory, iNHL, aNHL, CLL or SLL. Preclinical data for duvelisib presented at ASCO in June 2015 demonstrates synergy with standards-of-care and emerging therapeutics in development for hematologic malignancies, including duvelisib in combination with venetoclax. For information regarding our collaboration with AbbVie, please see below under the heading *AbbVie* in the section entitled Strategic Alliances.

T-Cell Lymphoma, aNHL and Other Lymphomas

Data from our Phase 1 study presented at ASH 2014 and at the 7th Annual T-cell Lymphoma Forum held in January 2015 demonstrates that duvelisib is clinically active in advanced T-cell lymphomas. Treatment with duvelisib in heavily pre-treated patients with relapsed or refractory T-cell lymphoma resulted in an overall response rate of 42% (14 of 33 patients evaluable for response), including two complete responses and twelve partial responses. Among the 15 patients with peripheral T-cell lymphoma, or PTCL, who were evaluable for response, treatment with duvelisib resulted in two complete responses and six partial responses, for an overall response rate of 53%. Among the 18 patients with CTCL evaluable for response, treatment with duvelisib resulted in to six partial responses for an overall response rate of 33%. Stable disease was observed in one patient with PTCL and six patients with CTCL. The Grade 3 side effects in patients with T-cell lymphoma included increases in ALT or AST in 11 patients (31%), rash in six patients (17%) and pneumonia in five patients (14%). Two patients (6%) had Grade 4 ALT or AST increases, and one patient (3%) had Grade 4 pneumonia. The majority of patients (27 of 35) received duvelisib dosed at 75 mg BID.

Duvelisib Global Regulatory Filings

We expect to report topline data from our DYNAMO study in the third quarter of 2016, and if supported by the DYNAMO data, we anticipate that we will submit a New Drug Application, or NDA, in the fourth quarter of 2016 seeking accelerated approval of duvelisib from the FDA for the treatment of follicular lymphoma and SLL. In addition, we expect to conduct a planned interim analysis of data from our DUO study in the second half of 2016. If supported by the interim analysis of data from our DUO study, we expect to report topline data from our DUO study in the second half of 2016 and submit an NDA in the fourth quarter of 2016 seeking regular approval of duvelisib from the FDA for the treatment of certain patients with CLL. Additionally, if supported by an interim analysis of data from the DUO study and data from our DYNAMO study, we expect that AbbVie will submit a Marketing Authorization Application, or MAA, in the fourth quarter of 2016 seeking approval from the EMA to market duvelisib for certain patients with follicular lymphoma and CLL.

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IPI-549: Targeting Solid Tumors by Selective Inhibition of the PI3K Gamma Isoform

In 2015, we expanded our pipeline to include IPI-549, an orally administered, selective PI3K-gamma inhibitor that we intend to evaluate as a potential treatment in solid tumors. Preclinical data from studies investigating IPI-549 indicates that IPI-549 has the potential to heighten an anti-cancer response by targeting macrophages in the immune-suppressive tumor microenvironment and may have the potential to treat a broad range of solid tumors. IPI-549 has demonstrated dose-dependent, single-agent, anti-tumor activity in multiple solid tumor models, including mouse models of lung cancer, colon cancer and breast cancer. Additionally, mice treated with IPI-549 in combination with a type of therapy called a checkpoint inhibitor showed greater tumor growth inhibition than treatment with either IPI-549 or the checkpoint inhibitor alone. Preclinical in vivo data also demonstrated that T-cells, a type of cell that plays a role in the human immune system, are required for the anti-tumor activity of IPI-549. These data were presented at CRI-CIMT-EATI-AACR - The Inaugural International Cancer Immunotherapy Conference in September 2015.

Based on our preclinical data generated to date, we have initiated a Phase 1 first-in-human study that includes a dose-escalation phase to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of IPI-549 as a monotherapy, as well as a dose-escalation phase evaluating IPI-549 in combination with a checkpoint inhibitor therapy that targets a receptor in the human body called programmed death receptor 1, or PD-1. If supported by data from the initial portion of the study, a Phase 1b portion would investigate IPI-549 in patients with selected solid tumors, including non-small cell lung cancer and melanoma.

Strategic Alliances

Since our inception, corporate alliances have been integral to our strategy. 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. All of our revenues to date have been generated under research collaborative agreements including our corporate alliances.

AbbVie

On September 2, 2014, we entered into a collaboration and license agreement with AbbVie, which we refer to as the AbbVie Agreement. Under the AbbVie Agreement, we are collaborating with AbbVie to develop and commercialize products containing duvelisib, which we refer to as Duvelisib Products, in oncology indications. IPI-549 is excluded from the collaboration. Under the terms of the AbbVie Agreement, we have granted to AbbVie licenses under applicable patents, patent applications, know-how and trademarks to develop, commercialize and manufacture Duvelisib Products in oncology indications. These licenses are generally co-exclusive with rights we retain, except that we have granted AbbVie exclusive licenses to commercialize Duvelisib Products outside the United States. We and AbbVie retain the rights to perform our respective obligations and exercise our respective rights under the AbbVie Agreement, and we and AbbVie may each grant sublicenses to affiliates or third parties.

Under the AbbVie Agreement, we and AbbVie have created a governance structure, including committees and working groups to manage the development, manufacturing and commercialization responsibilities for Duvelisib Products. Generally, we and AbbVie must mutually agree on decisions, although in specified circumstances either we or AbbVie would be able to break a deadlock.

We and AbbVie share oversight of development and have each agreed to use diligent efforts, as defined in the AbbVie Agreement, to carry out our development activities under an agreed upon development plan. We have primary responsibility for the conduct of development of Duvelisib Products, unless otherwise agreed, and AbbVie has responsibility for the conduct of certain contemplated combination clinical studies, including those examining duvelisib and venetoclax, which we refer to as the AbbVie Studies. We have the responsibility to manufacture Duvelisib Products until we transition manufacturing responsibility to AbbVie, which we expect to

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occur as promptly as practicable while ensuring continuity of supply. Excluding the AbbVie Studies, we are responsible for all costs to develop and manufacture Duvelisib Products up to a maximum amount of $667 million after which we will share Duvelisib Product development and manufacturing costs equally with AbbVie. The development and manufacturing costs of the AbbVie Studies will be shared equally.

We and AbbVie share operational responsibility and decision making authority for commercialization of Duvelisib Products in the United States. Specifically, we have the primary responsibility for advertising, distribution, and booking sales, and we share certain other commercialization functions with AbbVie. Assuming regulatory approval, we and AbbVie are obligated to each provide half of the sales representative effort to promote Duvelisib Products in the United States. Outside the United States, AbbVie has, with limited exceptions, operational responsibility and decision making authority to commercialize Duvelisib Products. We and AbbVie will share the cost of manufacturing and supply for commercialization of Duvelisib Products in the United States, and AbbVie will bear the cost of manufacturing and supply for commercialization of Duvelisib Products outside the United States.

AbbVie paid us a non-refundable $275 million upfront payment in 2014 and a $130 million milestone payment in November 2015 associated with the completion of enrollment of DYNAMO in September 2015. Further, AbbVie has agreed to pay us up to an additional $400 million in potential future milestone payments comprised of $125 million associated with the acceptance by the FDA of the first NDA submission for duvelisib, $75 million associated with the acceptance of the first MAA submission for duvelisib, up to $75 million associated with the achievement of specified regulatory approval milestones, and up to $125 million associated with the achievement of specified commercialization milestones. Under the terms of the AbbVie Agreement, we and AbbVie will equally share commercial profits or losses of Duvelisib Products in the United States, including sharing equally the existing royalty obligations to Mundipharma International Corporation Limited, or Mundipharma, and Purdue Pharmaceutical Products L.P., or Purdue, for sales of Duvelisib Products in the United States, as well as sharing equally the existing U.S. milestone payment obligations to Takeda Pharmaceutical Company Limited, or Takeda. For more information about such obligations, refer to the sections below titled Takeda and Mundipharma and Purdue.

Additionally, AbbVie has agreed to pay us tiered royalties on net sales of Duvelisib Products outside the United States ranging from 23.5% to 30.5%, depending on annual net sales of Duvelisib Products by AbbVie, its affiliates and its sublicensees. We are responsible for the existing royalty obligations to Mundipharma and Purdue outside the United States, and AbbVie has agreed to reimburse us for our existing Duvelisib Product milestone payment obligations to Takeda outside the United States. The tiered royalty from AbbVie is subject to a reduction of 4% at each tier if our royalties to Mundipharma and Purdue are reduced according to the terms of our respective agreements with Mundipharma and Purdue. This tiered royalty can further be reduced based on specified factors, including patent expiry, generic entry, and royalties paid to third parties with blocking intellectual property. These royalties are payable on a product-by-product and country-by-country basis until AbbVie ceases selling the product in the country.

Subject to limited exceptions, we have agreed that we and our affiliates will not commercialize, or assist others in commercializing, in oncology indications any product that is a PI3K delta, gamma inhibitor that meets certain agreed-to criteria, other than Duvelisib Products, and AbbVie has agreed to similar restrictions. Registration-directed clinical trials and commercialization of Duvelisib Products for uses outside of oncology indications would require our and AbbVie s mutual consent.

The AbbVie Agreement will remain in effect until all development, manufacturing and commercialization of Duvelisib Products cease, unless terminated earlier. Either we or AbbVie may terminate the AbbVie Agreement if the other party is subject to certain insolvency proceedings or if the other party materially breaches the AbbVie Agreement and the breach remains uncured for a specified period, which may be extended in certain circumstances. However, we may terminate the AbbVie Agreement only on a country-by-country basis in the event AbbVie is not using diligent efforts to obtain regulatory approval or to commercialize Duvelisib Products

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in a country outside the United States. AbbVie may also terminate the AbbVie Agreement for convenience after a specified notice period. In the event there is a material uncured breach by either us or AbbVie of development or commercialization obligations, the non-breaching party may also have the right to assume and conduct such applicable development or commercialization obligations. If AbbVie or any of its affiliates or sublicensees challenges the patents we have licensed to AbbVie, we can terminate the AbbVie Agreement if the challenge is not withdrawn after a specified notice period.

If the AbbVie Agreement is terminated, we would receive all rights to the regulatory filings related to duvelisib upon our request, our license to AbbVie would terminate, and AbbVie would grant us a perpetual, irrevocable license to develop, manufacture and commercialize products containing duvelisib, excluding any compound which is covered by patent rights controlled by AbbVie or its affiliates. This license would be royalty-free, unless the AbbVie Agreement is terminated for material breach, in which case, depending on the breaching party and the timing of the material breach, a royalty rate may be payable by us ranging from a low single-digit percentage to a low double-digit percentage of net sales, and, in some cases, subject to a payment cap.

If the AbbVie Agreement is terminated, we would not be entitled to receive payment for any milestone achieved after notice of termination but before the effective date of termination. Further, if the AbbVie Agreement is terminated, there are certain wind-down obligations to ensure a smooth transition of the responsibilities of the parties including, unless the AbbVie Agreement is terminated by AbbVie for our material breach, the continued conduct of certain development and commercialization activities by AbbVie for a limited transition period and the continued funding by AbbVie of its half of the cost of the AbbVie Studies ongoing at the time of termination, except for those AbbVie Studies that may be transitioned to Infinity following termination.

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 delta and/or gamma isoforms of PI3K, including duvelisib and IPI-549, and we paid Intellikine a $13.5 million upfront license fee. In January 2012, Intellikine was acquired by Takeda, acting through its Millennium business unit. We refer to our PI3K inhibitor program licensor as Takeda. In December 2012, we amended and restated our development and license agreement with Takeda.

Under the terms of the amended and restated agreement, we retained worldwide development rights and, in exchange for an agreement to pay Takeda $15 million in installments, we regained commercialization rights for products arising from the agreement for all therapeutic indications, and we are solely responsible for research conducted under the agreement.

We are obligated to pay to Takeda up to $5 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 an aggregate of $450 million in success-based milestone payments for the approval and commercialization of two distinct products, of which one could be a Duvelisib Product and the other could be a product containing IPI-549. In February 2014, we paid Takeda a $10 million milestone payment in connection with the initiation of DUO, our Phase 3 study of duvelisib in patients with relapsed or refractory CLL. On March 31, 2015, we paid a $52.5 million fee to exercise an option that we purchased from Takeda in July 2014 for a one-time upfront payment of $5 million. As a result of our exercise of this option, we are no longer obligated under the amended and restated development and license agreement to pay to Takeda tiered royalties with respect to worldwide net sales in oncology indications of products containing or comprised of duvelisib.

Except for duvelisib products in oncology indications, we are obligated to pay Takeda tiered royalties ranging from 7% to 11% on worldwide net sales of products described in the agreement, which could include IPI-549 if successfully developed and commercialized. Such royalties are payable until the later to occur of the

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expiration of specified patent rights and 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.

The amended and restated 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. Either party may terminate the 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 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 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 agreement also provides for customary reciprocal indemnification obligations of the parties.

Mundipharma and Purdue

On July 17, 2012, we terminated our strategic alliance with Mundipharma and Purdue, and we entered into termination and revised relationship agreements with each of those entities, which we refer to as the 2012 Termination Agreements. The strategic alliance was previously governed by strategic alliance agreements that we entered into with each of Mundipharma and Purdue in November 2008. The strategic alliance agreement with Purdue was focused on the development and commercialization in the United States of products targeting fatty acid amide hydrolase, or FAAH. The strategic alliance agreement with Mundipharma was focused on the development and commercialization outside the United States of all products and product candidates that inhibit or target the Hedgehog pathway, FAAH, PI3K and product candidates arising out of our early discovery projects in all disease fields.

Under the terms of the 2012 Termination Agreements:

All intellectual property rights that we had previously licensed to Mundipharma and Purdue to develop and commercialize products under the previous strategic alliance agreements terminated resulting in the return to us of worldwide rights to all product candidates that had previously been covered by the strategic alliance.

We have no further obligation to provide research and development services to Mundipharma and Purdue as of July 17, 2012.

Mundipharma and Purdue have no further obligation to provide research and development funding to us. Under the strategic alliance, Mundipharma was obligated to reimburse us for research and development expenses we incurred, up to an annual aggregate cap for each strategic alliance program other than FAAH. We did not record a liability for amounts previously funded by Purdue and Mundipharma as this relationship was not considered a financing arrangement.

We are obligated to pay Mundipharma and Purdue a 4% royalty in the aggregate, subject to reduction as described below, on worldwide net sales of products that were covered by the alliance until such time as they have recovered approximately $260 million, representing the research and development funding paid to us for research and development services performed by us through the termination of the strategic alliance. After this cost recovery, our royalty obligations to Mundipharma and Purdue will be reduced to a 1% royalty on net sales in the United States of products that were previously subject to the strategic alliance. All payments are contingent upon the successful commercialization of products that were subject to the alliance, which products require significant further development. As such, there is significant uncertainty about whether any such products will ever be approved or commercialized. If no products are commercialized, no payments will be due by us to Mundipharma and Purdue; therefore, no amounts have been accrued.

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Royalties are payable under these agreements until the later to occur of the last-to-expire of specified patent rights and the expiration of non-patent regulatory exclusivities in a country, provided that if royalties are payable solely on the basis of non-patent regulatory exclusivity, each of the royalty rates is reduced by 50%. In addition, royalties payable under these agreements after Mundipharma and Purdue have recovered all research and development expenses paid to us are subject to reduction on account of third-party royalty payments or patent litigation damages or settlements which might be required to be paid by us if litigation were to arise, with any such reductions capped at 50% of the amounts otherwise payable during the applicable royalty payment period.

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 eight issued or allowed U.S. patents related to our duvelisib program, which expire on various dates between 2029 and 2032, excluding any patent term extension. We have three issued or allowed U.S. patents related to our PI3K gamma program, which expire on various dates between 2033 and 2034, excluding any patent term extension. In addition, we have approximately 275 patents and patent applications pending worldwide related to our PI3K programs. Any patents that may issue from our pending patent applications would expire between 2029 and 2035, excluding any patent term extension. These patents and patent applications disclose compositions of matter, pharmaceutical compositions, methods of use and synthetic methods.

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 protect our proprietary technology and processes, in part, by confidentiality agreements with our employees, consultants, collaborators and contractors.

Competition

The pharmaceutical and biotechnology industries are intensely competitive. Many companies, including biotechnology, chemical 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.

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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.

PI3K Inhibitor Program

We believe that the following companies, among others, have developed or are in the clinical stage of development of compounds targeting the delta and/or gamma isoforms of PI3K:

- Gilead Sciences, Inc., or Gilead, has received approval from the FDA of idelalisib for the treatment of people with CLL, SLL, or follicular lymphoma, and which we believe is conducting a Phase 1b clinical trial of acalisib;
- Bayer AG, which we believe is conducting Phase 2 and Phase 3 clinical trials of copanlisib;
- TG Therapeutics, Inc., which we believe is conducting Phase 1, Phase 2, and Phase 3 clinical trials of TGR-1202;
- Novartis, which we believe is conducting a Phase 2 clinical trial of buparlisib;
- Acerta Pharma BV, which we believe is conducting Phase 1 clinical trials of ACP 319;
- Genentech, which we believe is conducting a Phase 1 clinical trial of apitolisib;
- Incyte Corporation, which we believe is conducting a Phase 1 clinical trial of INCB-050465, and which we also believe is conducting a Phase 1 clinical trial of INCB-040093; and
- Rhizen Pharmaceuticals S.A., which we believe is conducting Phase 1 clinical trials of RP-6530.

In addition, many companies are developing product candidates directed to disease targets such as Bruton s tyrosine kinase (or BTK), B-cell lymphoma 2 (or BCL-2), Janus Kinase (or JAK), B-lymphocyte antigen CD-19, and programmed death 1/ligand 1 (or PD-1/PD-L1), Cluster of Differentiation 79B antibody-drug conjugate (or CD79B ADC), and pleiotropic pathways in the fields of hematology-oncology, including in the specific diseases for which we are currently developing duvelisib, or for which we may develop duvelisib or other PI3K inhibitors in the future. Such companies include:

- Pharmacyclics LLC, a wholly-owned subsidiary of AbbVie, through its collaboration with Janssen Biotech, which has received approval from the FDA of ibrutinib, a BTK inhibitor, for the treatment of people with MCL, CLL, or Waldenström s macroglobulinemia, and is conducting multiple late stage clinical studies of ibrutinib in additional hematologic malignancies;
- AbbVie, which we believe is conducting a Phase 3 and multiple Phase 1 and Phase 2 clinical trials of venetoclax, a BCL-2 inhibitor, in hematologic malignancies;

Celgene Corporation, which has received FDA approval of lenalidomide, an immunomodulator, for the treatment of people with multiple myeloma, MCL, and myelodyplastic syndromes, and is conducting late stage clinical studies of lenalidomide in additional hematologic malignancies; we also believe that Celgene is conducting a Phase 1 clinical trial of CC-292, a BTK inhibitor, in patients with CLL;

Acerta Pharma BV, which we believe is conducting a Phase 3 clinical trial of ACP-196, a BTK inhibitor, in patients with CLL;

Incyte Corporation, which has received FDA approval of ruxolitinib, a JAK inhibitor, in patients with intermediate or high-risk myelofibrosis, and which we believe is conducting a Phase 2 clinical trial in CLL;

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Novartis AG, which we believe is conducting a Phase 2 trial of CTL-019, which targets CD-19, in a trial that includes iNHL and CLL and acute lymphocytic leukemia, or ALL, patients;

Novartis AG, which we believe is conducting a Phase 1b trial of BCL-201, a BCL-2 inhibitor, in combination with idelalisib in patients with follicular lymphoma or MCL;

Genentech, which we believe is conducting a Phase 2 trial of polatuzumab vedotin, which targets CD79b ADC, in patients with follicular lymphoma or DLBCL;

MorphoSys, which we believe is conducting Phase 2 clinical trials of MOR208, a B-lymphocyte antigen CD-19 inhibitor, in patients with NHL, CLL, and ALL;

Celgene, which we believe is conducting Phase 1/2 and Phase 1 clinical trials of CC-122, a pleiotropic pathway modifier, in patients with CLL, and NHL;

BeiGene Co., Ltd, which we believe is conducting Phase 1 clinical trials of BGB-3111, a BTK inhibitor, in patients with B-cell malignancies;

Gilead Sciences, Inc./Ono Pharmaceutical Group, which we believe is conducting Phase 1 clinical trials of ONO-4059, a BTK inhibitor, in patients with NHL and CLL; and

Bristol-Myers Squibb Company, Roche Group and its subsidiary Genentech, and AstraZeneca PLC, each of which we believe is conducting clinical trials of anti-PD-1 or anti-PD-L1 antibodies, in patients with hematologic malignancies.

Research and Development

As of February 1, 2016, our research and development group consisted of 164 employees, of whom 34% hold Ph.D. or M.D. degrees and an additional 13% hold other advanced degrees. Our research and development group is focusing on drug discovery, preclinical research, translational medicine, clinical trials and manufacturing technologies. Our research and development expense for the years ended December 31, 2015, 2014 and 2013 was approximately $199.1 million, $143.6 million and $99.8 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. As required by our agreement with AbbVie, we are in the process of transitioning the responsibility to manufacture Duvelisib Products to AbbVie as promptly as is practicable while ensuring continuity of supply. Excluding the AbbVie Studies, we are responsible for all costs to develop and manufacture Duvelisib Products up to a maximum amount of $667 million, after which we will share Duvelisib Product development and manufacturing costs equally with AbbVie. The development and manufacturing costs of the AbbVie Studies will be shared equally. We and AbbVie will share the cost of manufacturing and supply for commercialization of Duvelisib Products in the United States, and AbbVie will bear the cost of manufacturing and supply for commercialization of Duvelisib Products outside the United States. 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

Under the AbbVie Agreement, we and AbbVie share operational responsibility and decision making authority for commercialization of Duvelisib Products in the United States, while AbbVie has, with limited exceptions, operational responsibility and decision making authority to

commercialize Duvelisib Products outside of the United States. We are currently developing the infrastructure and personnel we believe to be necessary to successfully market, sell, and distribute Duvelisib Products in the United States, and we intend for

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such infrastructure to serve as the foundation for the launch of future drug products, subject to receiving marketing approval for those products. Further, we expect AbbVie s established marketing and sales infrastructure, global marketing presence, and history of successful product launches positions duvelisib to best be delivered to patients, subject to receipt of marketing approval by the requisite regulatory bodies.

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, extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting, and import and export of pharmaceutical products. The processes for obtaining marketing approvals in the United States and in foreign countries and jurisdictions, along with subsequent compliance with applicable statutes and regulations and other regulatory authorities, require the expenditure of substantial time and financial resources. We are currently developing the infrastructure and personnel we believe to be necessary to support an effective compliance program.

Review and Approval of Drugs in the United States

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

A product candidate must be approved by the FDA through the new drug application, or NDA. An applicant seeking approval to market and distribute a new drug product in the United States must typically undertake the following:

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

satisfactory completion of FDA audits of clinical trial sites to assure compliance with GCPs and the integrity of the clinical data;

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payment of user fees and securing FDA approval of the NDA; and

compliance with any post-approval requirements, including the potential requirement to implement a Risk Evaluation and Mitigation Strategy, or REMS, and the potential requirement to conduct post-approval studies.

Preclinical Studies

Before an applicant begins testing a compound with potential therapeutic value in humans, the drug candidate enters the preclinical testing stage. Preclinical studies include laboratory evaluation of product chemistry, toxicity and formulation, and the purity and stability of the drug substance, as well as *in vitro* and animal studies to assess the potential safety and activity of the drug for initial testing in humans and to establish a rationale for therapeutic use. The conduct of preclinical studies is subject to federal regulations and requirements, including GLP regulations. Applicants usually must complete some long-term nonclinical testing, such as animal tests of reproductive adverse events and carcinogenicity, and must also develop additional information about the chemistry and physical characteristics of the drug and finalize a process for manufacturing the drug 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, the manufacturer must develop methods for testing the identity, strength, quality and purity of the final drug product. 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. Preclinical tests and studies can take several years to complete.

The IND Process

An IND is an exemption from the FDCA that allows an unapproved drug to be shipped in interstate commerce for use in an investigational clinical trial and a request for FDA authorization to administer an investigational drug to humans. Such authorization must be secured prior to interstate shipment and administration of any new drug that is not the subject of an approved NDA. In support of a request for an IND, applicants must submit a protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical trials, among other things, are submitted to the FDA as part of an IND. The FDA requires a 30-day waiting period after the filing of each IND before clinical trials may begin. This waiting period is designed to allow the FDA to review the IND to determine whether human research subjects will be exposed to unreasonable health risks. At any time during this 30-day period, the FDA may raise concerns or questions about the conduct of the trials as outlined in the IND and impose a clinical hold. In this case, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can begin.

Following commencement of a clinical trial under an IND, the FDA may also place a clinical hold or partial clinical hold on that trial. A clinical hold is an order issued by the FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. A partial clinical hold is a delay or suspension of only part of the clinical work requested under the IND. For example, a specific protocol or part of a protocol is not allowed to proceed, while other protocols may do so. No more than 30 days after imposition of a clinical hold or partial clinical hold, the FDA will provide the sponsor a written explanation of the basis for the hold. Following issuance of a clinical hold or partial clinical hold, an investigation may only resume after the FDA has notified the sponsor that the investigation may proceed. The FDA will base that determination on information provided by the sponsor correcting the deficiencies previously cited or otherwise satisfying the FDA that the investigation can proceed.

A sponsor may choose, but is not required, to conduct a foreign clinical study under an IND. When a foreign clinical study is conducted under an IND, all FDA IND requirements must be met unless waived. When the foreign clinical study is not conducted under an IND, the sponsor must ensure that the study complies with FDA

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certain regulatory requirements in order to use the study as support for an IND or application for marketing approval. Specifically, on April 28, 2008, the FDA amended its regulations governing the acceptance of foreign clinical studies not conducted under an investigational new drug application as support for an IND or a new drug application. The final rule provides that such studies must be conducted in accordance with good clinical practice, or 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. Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health, or NIH, for public dissemination on its ClinicalTrials.gov website.

Human Clinical Trials in Support of an NDA

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

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

Phase 1. The drug is initially introduced into a small number of healthy human subjects or, in certain indications such as cancer, patients with the target disease or condition (e.g., cancer) and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an early indication of its effectiveness and to determine optimal dosage.

Phase 2. The drug is administered to a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage.

Phase 3. These clinical trials are commonly referred to as pivotal studies, which denotes a study that presents the data that the FDA or other relevant regulatory agency will use to determine whether or not to approve a drug. The drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well-controlled clinical trials to generate enough data to statistically evaluate the efficacy and safety of the product for approval, identify adverse effects, establish the overall risk-benefit profile of the product and to provide adequate information for the labeling of the product.

Phase 4. Post-approval studies may be conducted after initial marketing approval. These studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. In addition, IND safety reports must be submitted to the FDA for any of the following: serious and unexpected suspected adverse reactions; findings from other studies or animal or *in vitro* testing that suggest a significant risk in humans exposed to the drug; and any clinically important increase in the case of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The FDA or the sponsor or the data monitoring committee may suspend or terminate a clinical trial at

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any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB s requirements or if the drug has been associated with unexpected serious harm to patients. The FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the clinical data submitted.

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

If clinical trials are successful, the next step in the drug development process is the preparation and submission to the FDA of a NDA. The NDA is the vehicle through which drug applicants formally propose that the FDA approve a new drug for marketing and sale in the United States for one or more indications. The NDA must contain a description of the manufacturing process and quality control methods, as well as results of preclinical tests, toxicology studies, clinical trials and proposed labeling, among other things. Every new drug 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, currently exceeding $2.3 million, and the sponsor of an approved NDA is also subject to annual product and establishment user fees, currently exceeding $114,000 per product and $585,000 per establishment. These fees are typically increased annually. Certain exceptions and waivers are available for some of these fees, such as an exception from the application fee for drugs with orphan designation and a waiver for certain small businesses, an exception from the establishment fee when the establishment does not engage in manufacturing the drug during a particular fiscal year, and an exception from the product fee for a drug that is the same as another drug approved under an abbreviated pathway.

Following submission of an NDA, the FDA conducts a preliminary review of an NDA generally within 60 calendar days of its receipt and strives to inform the sponsor by the 74th day after the FDA s receipt of the submission to determine whether the application is sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA has agreed to specified performance goals in the review process of NDAs. Under that agreement, 90% of applications seeking approval of New Molecular Entities, or NMEs, are meant to be reviewed within ten months from the date on which FDA accepts the NDA for filing, and 90% of applications for NMEs that have been designated for priority review are meant to be reviewed within six months of the filing date. For applications seeking approval of drugs that are not NMEs, the ten-month and six-month review periods run from the date that FDA receives the application. The review process and the Prescription Drug User Fee Act goal date may be extended by the FDA for three additional months to consider new information or clarification provided by the applicant to address an outstanding deficiency identified by the FDA following the original submission.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is or will be manufactured. These pre-approval inspections may cover all facilities associated with an NDA submission, including drug component manufacturing (e.g., active pharmaceutical ingredients), finished drug product manufacturing, and control testing laboratories. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP.

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In addition, as a condition of approval, the FDA may require an applicant to develop a REMS. REMS use risk minimization strategies beyond the professional labeling to ensure that the benefits of the product outweigh the potential risks. To determine whether a REMS is needed, the FDA will consider the size of the population likely to use the product, seriousness of the disease, expected benefit of the product, expected duration of treatment, seriousness of known or potential adverse events, and whether the product is a new molecular entity. REMS can include medication guides, physician communication plans for healthcare professionals, and elements to assure safe use, or ETASU. ETASU may include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patient registries. The FDA may require a REMS before approval or post-approval if it becomes aware of a serious risk associated with use of the product. The requirement for a REMS can materially affect the potential market and profitability of a product.

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

The FDA s Decision on an NDA

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

If the FDA approves a product, it may limit the approved indications for use for the product, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess the drug s safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms, including REMS, which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs. After approval, many types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Fast Track, Breakthrough Therapy and Priority Review Designations

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

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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, in 2012, Congress enacted the Food and Drug Administration Safety and Innovation Act, or FDASIA. This law established a new regulatory scheme allowing for expedited review of products designated as breakthrough therapies. A product may be designated as a breakthrough therapy if it is intended, either alone or in combination with one or more other products, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The FDA may take certain actions with respect to breakthrough therapies, including holding meetings with the sponsor throughout the development process; providing timely advice to the product sponsor regarding development and approval; involving more senior staff in the review process; assigning a cross-disciplinary project lead for the review team; and taking other steps to design the clinical trials in an efficient manner.

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

Accelerated Approval Pathway

The FDA may grant accelerated approval to a product for a serious or life-threatening condition that provides meaningful therapeutic advantage to patients over existing treatments based upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. The FDA may also grant accelerated approval for such a condition when the product has an effect on an intermediate clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality, or IMM, and that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. Products granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted regular 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 product, such as an effect on IMM. The FDA has limited experience with accelerated approvals based on intermediate clinical endpoints, but has indicated that such endpoints generally may support accelerated approval where the therapeutic effect measured by the endpoint is not itself a clinical benefit and basis for regular 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

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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.

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 withdraw the product from the market on an expedited basis. All promotional materials for product candidates approved under accelerated regulations are subject to prior review by the FDA.

Post-Approval Requirements

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. There also are continuing, annual user fee requirements for any marketed products and the establishments at which such products are manufactured, as well as new application fees for supplemental applications with clinical data.

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance.

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

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

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Drugs may be promoted only for the approved indications and in accordance with the provisions of the

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approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

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

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. This three-year exclusivity period often

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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.

505(b)(2) NDAs

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

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 or 505(b)(2) 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. Specifically, the applicant must certify with respect to each patent that:

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

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

If the ANDA or 505(b)(2) applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA or the 505(b)(2) application has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA or 505(b)(2) application until the earlier of 30 months after the receipt of the Paragraph IV notice, expiration of the patent, or a decision in the infringement case that is favorable to the applicant. The ANDA or 505(b)(2) application also will not be approved until any applicable non-patent exclusivity listed in the Orange Book for the branded reference drug has expired.

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Pediatric Studies and Exclusivity

Under the Pediatric Research Equity Act, an NDA or supplement thereto must contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. With enactment of the Food and Drug Safety and Innovation Act, or the FDASIA, in 2012, sponsors must also submit pediatric study plans prior to the assessment data. Those plans must contain an outline of the proposed pediatric study or studies the applicant plans to conduct, including study objectives and design, any deferral or waiver requests, and any other information required by regulation. The applicant, the FDA, and the FDA s internal review committee must then review the information submitted, consult with each other, and agree upon a final plan. The FDA or the applicant may request an amendment to the plan at any time.

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

Pediatric exclusivity is another type of non-patent marketing exclusivity in the United States and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity, including the non-patent and orphan exclusivity. This six-month exclusivity may be granted if an NDA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA s request, the additional protection is granted. If reports of requested pediatric studies are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patent protection cover the product are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot approve another application. With regard to patents, the six-month pediatric exclusivity period will not attach to any patents for which an ANDA or 505(b)(2) applicant submitted a paragraph IV patent certification, unless the NDA sponsor or patent owner first obtains a court determination that the patent if valid and infringed by the proposed product.

Orphan Drug Designation and Exclusivity

Under the Orphan Drug Act, the FDA may designate a drug product as an orphan drug if it is intended to treat a rare disease or condition, generally meaning that it affects fewer than 200,000 individuals in the United States, or more in cases in which there is no reasonable expectation that the cost of developing and making a drug product available in the United States for treatment of the disease or condition will be recovered from sales of the product. A company must request orphan drug designation before submitting an NDA for the drug and rare disease or condition. 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 indication for seven years, except in certain limited circumstances. Orphan exclusivity does not block the approval of a different drug for the same rare disease or condition, nor does it block the approval of the same drug for different indications. 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

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exclusivity will not bar approval of another product under certain circumstances, including if a subsequent product with the same drug for the same indication is shown to be clinically superior to the approved product on the basis of greater efficacy or safety, or providing a major contribution to patient care, or if the company with orphan drug exclusivity is not able to meet market demand.

Patent Term Restoration and Extension

A patent claiming a new drug product or its method of use may be eligible for a limited patent term extension, also known as patent term restoration, 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. Patent term extension is generally available only for drug products whose active ingredient has not previously been approved by the FDA. The restoration period granted is typically one-half the time between the effective date of an IND and the submission date of an NDA, plus the time between the submission date of an NDA and the ultimate approval date. Patent term extension cannot be used to extend the remaining term of a patent past a total of 14 years from the product s approval date. Only one patent applicable to an approved drug product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent in question. A patent that covers multiple drugs for which approval is sought can only be extended in connection with one of the approvals. The United States PTO reviews and approves the application for any patent term extension in consultation with the FDA.

Review and Approval of Drugs in Europe and other Foreign Jurisdictions

In addition to regulations in the United States, a manufacturer is subject to a variety of regulations in foreign jurisdictions to the extent it chooses to sell any drug products in those foreign countries. Even if a manufacturer obtains FDA approval of a product, it must still obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical trials or marketing of the product in those countries. To obtain regulatory approval of an investigational drug in the European Union (EU), a manufacturer must submit a marketing authorization application, or MAA, to the European Medicines Agency, or EMA. For other countries outside of the European Union, such as countries in Eastern Europe, Latin America or Asia, the requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, clinical trials are to be conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

Clinical Trial Approval in the EU

Pursuant to the currently applicable Clinical Trials Directive 2001/20/EC and the Directive 2005/28/EC on Good Clinical Practice, or GCP, an applicant must obtain approval from the competent national authority of the EU Member State in which the clinical trial is to be conducted. If the clinical trial is conducted in different EU Member States, the competent authorities in each of these EU Member States must provide their approval for the conduct of the clinical trial. Furthermore, the applicant may only start a clinical trial at a specific study site after the competent ethics committee has issued a favorable opinion.

In April 2014, the EU adopted a new Clinical Trials Regulation (EU) No 536/2014, which is set to replace the current Clinical Trials Directive 2001/20/EC. The new Clinical Trials Regulation will be directly applicable to and binding in all 28 EU Member States without the need for any national implementing legislation. The new Clinical Trials Regulation (EU) No 536/2014 will become applicable no earlier than 28 May 2016. It will overhaul the current system of approvals for clinical trials in the EU. Specifically, the new legislation aims at simplifying and streamlining the approval of clinical trials in the EU. Under the new coordinated procedure for the approval of clinical trials, the sponsor of a clinical trial will be required to submit a single application for approval of a clinical trial to a reporting EU Member State (RMS) through an EU Portal. The submission procedure will be the same irrespective of whether the clinical trial is to be conducted in a single EU Member State or in more than one EU Member State. The Clinical Trials Regulation also aims to streamline and simplify the rules on safety reporting for clinical trials.

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Marketing Authorization

In the EU, marketing authorizations for medicinal products may be obtained through several different procedures founded on the same basic regulatory process.

The centralized procedure provides for the grant of a single marketing authorization that is valid for all EU Member States. The centralized procedure is compulsory for medicinal products produced by certain biotechnological processes, products designated as orphan medicinal products, and products with a new active substance indicated for the treatment of certain diseases,. It is optional for those products that are highly innovative or for which a centralized process is in the interest of patients. Under the centralized procedure in the EU, the maximum timeframe for the evaluation of a MAA is 210 days, excluding clock stops, when additional written or oral information is to be provided by the applicant in response to questions asked by the Committee for Medicinal Products for Human use or CHMP. Accelerated evaluation may be granted by the CHMP in exceptional cases. These are defined as circumstances in which a medicinal product is expected to be of a major public health interest. Three cumulative criteria must be fulfilled in such circumstances: the seriousness of the disease, such as severely disabling or life-threatening diseases, to be treated; the absence or insufficiency of an appropriate alternative therapeutic approach; and anticipation of high therapeutic benefit. In these circumstances, the EMA ensures that the opinion of the CHMP is given within 150 days.

The decentralized procedure provides for approval by one or more other concerned EU Member States of an assessment of an application for marketing authorization conducted by one EU Member State, known as the reference EU Member State. In accordance with this procedure, an applicant submits an application for marketing authorization to the reference EU Member State and the concerned EU Member States. This application is identical to the application that would be submitted to the EMA for authorization through the centralized procedure. The reference EU Member State prepares a draft assessment and drafts of the related materials within 120 days after receipt of a valid application. The resulting assessment report is submitted to the concerned EU Member States which, within 90 days of receipt, must decide whether to approve the assessment report and related materials. If a concerned EU Member State cannot approve the assessment report and related materials due to concerns relating to a potential serious risk to public health, disputed elements may be referred to the European Commission, whose decision is binding on all EU Member States. In accordance with the mutual recognition procedure, the sponsor applies for national marketing authorization in one EU Member State. Upon receipt of this authorization the sponsor can then seek the recognition of this authorization by other EU Member States. Authorization in accordance with either of these procedures will result in authorization of the medicinal product only in the reference EU Member State and in the other concerned EU Member States..

A marketing authorization may be granted only to an applicant established in the EU. Regulation No. 1901/2006 provides that, prior to obtaining a marketing authorization in the EU, an applicant must demonstrate compliance with all measures included in a Pediatric Investigation Plan, or PIP, approved by the Pediatric Committee of the EMA, covering all subsets of the pediatric population, unless the EMA has granted a product-specific waiver, class waiver, or a deferral for one or more of the measures included in the PIP.

Regulatory Data Exclusivity in the European Union

Innovative medicinal products authorized in the EU on the basis of a full MAA (as opposed to an application for marketing authorization that relies on data available in the marketing authorization dossier for another, previously approved, medicinal product) are entitled to eight years of data exclusivity. During this period, applicants for authorization of generic versions of these innovative products cannot rely on data contained in the marketing authorization dossier submitted for the innovative medicinal product. Innovative medicinal products are also entitled to ten years of market exclusivity. During this ten year period no generic version of the medicinal product can be placed on the EU market. The overall ten-year period will be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to

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authorization, is held to bring a significant clinical benefit in comparison with existing therapies. Even if a compound is considered to be a new chemical entity so that the innovator gains the prescribed period of data exclusivity, another company may market another version of the product if such company obtained marketing authorization based on an MAA with a complete independent data package of pharmaceutical tests, preclinical tests and clinical trials.

Periods of Authorization and Renewals in the EU

A marketing authorization is valid for five years, in principle, and it may be renewed after five years on the basis of a reevaluation of the risk-benefit balance by the EMA or by the competent authority of the relevant EU Member State. To that end, the marketing authorization holder must provide the EMA or the relevant competent authority of the EU Member State with a consolidated version of the file in respect of quality, safety and efficacy, including all variations introduced since the marketing authorization was granted, at least six months before the marketing authorization ceases to be valid. Once renewed, the marketing authorization is valid for an unlimited period, unless the European Commission or the relevant competent authority of the EU Member State decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal period. Any marketing authorization that is not followed by the marketing of the medicinal product on the EU market (in the case of the centralized procedure) or on the market of the EU Member State which delivered the marketing authorization within three years after authorization ceases to be valid.

Regulatory Requirements after Marketing Authorization

As in the United States, marketing authorization holders and manufacturers of medicinal products are subject to comprehensive regulatory oversight by the EMA and the competent authorities of the individual EU Member States both before and after grant of the manufacturing and marketing authorizations.

The holder of an EU marketing authorization for a medicinal product must also comply with EU pharmacovigilance legislation and its related regulations and guidelines, which detail requirements for conducting pharmacovigilance or the assessment and monitoring of the safety of medicinal products. These rules can impose on central marketing authorization holders for medicinal products the obligation to conduct a labor intensive collection of data regarding the risks and benefits of marketed products and to engage in ongoing assessments of those risks and benefits, including the possible requirement to conduct additional clinical studies.

The manufacturing process for medicinal products in the EU is highly regulated and regulators may shut down manufacturing facilities that they believe do not comply with regulations. Manufacturing requires a manufacturing authorization, and the manufacturing authorization holder must comply with various requirements set out in 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. Similarly, the distribution of medicinal products into and within the EU is subject to compliance with the applicable EU laws, regulations and guidelines, including the requirement to hold appropriate authorizations for distribution granted by the competent authorities of the EU Member States.

In the EU, the advertising and promotion of products are subject to EU Member States laws governing promotion of medicinal products, interactions with physicians, misleading and comparative advertising and unfair commercial practices. In addition, other legislation adopted by individual EU Member States may apply to the advertising and promotion of medicinal products. These laws require that promotional materials and advertising in relation to medicinal products comply with the product s Summary of Product Characteristics, or SmPC, as approved by the competent authorities. Promotion of a medicinal product that does not comply with the SmPC is considered to constitute off-label promotion. The off-label promotion of medicinal products is

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prohibited in the EU. The applicable laws at EU level and in the individual EU Member States also prohibit the direct-to-consumer advertising of prescription-only medicinal products. These laws may further limit or restrict the advertising and promotion of products to the general public and may also impose limitations on promotional activities with health care professionals.

Orphan Drug Designation and Exclusivity in the EU

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

Once authorized, orphan medicinal products are entitled to ten years of market exclusivity in all EU Member States and, in addition, a range of other benefits during the development and regulatory review process, including scientific assistance for 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 ten year period with the consent of the marketing authorization holder for the original orphan medicinal product or if the manufacturer of the original orphan medicinal product is unable to supply sufficient quantities. Marketing authorization may also be granted to a similar medicinal product with the same orphan indication if the product is safer, more effective or otherwise clinically superior to the original orphan medicinal product. The period of market exclusivity may, in addition, be reduced to six years if it can be demonstrated on the basis of available evidence that the original orphan medicinal product is sufficiently profitable not to justify maintenance of market exclusivity.

Pharmaceutical Coverage, Pricing and Reimbursement

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

In order to secure coverage and reimbursement for any product that might be approved for sale, a company may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA or other comparable marketing approvals. Nonetheless, product candidates may not be considered medically necessary or cost effective. A decision by a third-party payor not to cover a product candidate could reduce physician utilization once the product is approved and have a material adverse effect on sales, results of operations and financial condition.

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Additionally, a payor s decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Further, one payor s determination to provide coverage for a drug product does not assure that other payors will also provide coverage and reimbursement for the product, and the level of coverage and reimbursement can differ significantly from payor to payor.

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

Outside the United States, ensuring adequate coverage and payment for a product also involves challenges. Pricing of prescription pharmaceuticals is subject to governmental control in many countries. Pricing negotiations with governmental authorities can extend well beyond the receipt of regulatory marketing approval for a product and may require a clinical trial that compares the cost effectiveness of a product to other available therapies. The conduct of such a clinical trial could be expensive and result in delays in commercialization.

In the European Union, pricing and reimbursement schemes vary widely from country to country. Some countries provide that products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular drug candidate to currently available therapies or so called health technology assessments, in order to obtain reimbursement or pricing approval. For example, the European Union 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. European Union 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 European Union 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 European Union. The downward pressure on health care costs in general, particularly prescription drugs, has become intense. As a result, increasingly high barriers are being erected to the entry of new products. Political, economic and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various European Union member states, and parallel trade, i.e., arbitrage between low-priced and high-priced member states, can further reduce prices. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any products, if approved in those countries.

Healthcare Law and Regulation

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

- the federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, paying, receiving or providing remuneration, directly or

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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 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 Affordable Care Act, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report annually to the Centers for Medicare & Medicaid Services, or CMS, within the United States Department of Health and Human Services, information related to payments and other transfers of value made by that entity to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members; and

analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, which may apply to healthcare items or services that are reimbursed by 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 in addition to requiring drug manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Healthcare Reform

A primary trend in the United States healthcare industry and elsewhere is cost containment. There have been a number of federal and state proposals during the last few years regarding the pricing of pharmaceutical and biopharmaceutical products, limiting coverage and reimbursement for drugs and other medical products, government control and other changes to the healthcare system in the United States.

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By way of example, the United States and state governments continue to propose and pass legislation designed to reduce the cost of healthcare. In March 2010, the United States Congress enacted the Affordable Care Act, which, among other things, includes changes to the coverage and payment for products under government health care programs. Among the provisions of the Affordable Care Act of importance to potential drug candidates are:

- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs, although this fee would not apply to sales of certain products approved exclusively for orphan indications;

- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing a manufacturer s Medicaid rebate liability;

- expanded manufacturers rebate liability under the Medicaid Drug Rebate Program by increasing the minimum rebate for both branded and generic drugs and revising the definition of average manufacturer price, or AMP, for calculating and reporting Medicaid drug rebates on outpatient prescription drug prices and extending rebate liability to prescriptions for individuals enrolled in Medicare Advantage plans;

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

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

- established the Medicare Part D coverage gap discount program by requiring manufacturers to provide a 50% point-of-sale-discount off the negotiated price of applicable brand drugs to eligible beneficiaries during their coverage gap period as a condition for the manufacturers outpatient drugs to be covered under Medicare Part D;

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

- the Independent Payment Advisory Board, or IPAB, which has authority to recommend certain changes to the Medicare program to reduce expenditures by the program that could result in reduced payments for prescription drugs. However, the IPAB implementation has been not been clearly defined. PPACA provided that under certain circumstances, IPAB recommendations will become law unless Congress enacts legislation that will achieve the same or greater Medicare cost savings; and

- established the Center for Medicare and Medicaid Innovation within CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending. Funding has been allocated to support the mission of the Center for Medicare and Medicaid Innovation from 2011 to 2019.

Other legislative changes have been proposed and adopted in the United States since the Affordable Care Act was enacted. For example, in August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2012 through 2021, was unable to reach required goals, thereby triggering the legislation s automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of up to 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2024 unless additional Congressional action is taken. In January 2013, President Obama signed into law the American Taxpayer

Relief Act of 2012, which, among other things, further reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

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There have been, and likely will continue to be, legislative and regulatory proposals at the foreign, federal and state levels directed at broadening the availability of healthcare and containing or lowering the cost of healthcare. Such reforms could have an adverse effect on anticipated revenues from product candidates that we may successfully develop and for which we may obtain marketing approval and may affect overall financial condition and ability to develop product candidates.

Employees

As of February 1, 2016, we had 222 full-time employees, 164 of whom were engaged in research and development and 58 of whom were engaged in general business management, administration and finance. Approximately 46% 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 subsidiary 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 February 1, 2016:

Name	Age	Position
Adelene Q. Perkins	56	President and Chief Executive Officer
Julian Adams, Ph.D.	61	President of Research & Development
William C. Bertrand, Jr., J.D.	51	Executive Vice President, General Counsel
Lawrence E. Bloch, M.D., J.D.	50	Executive Vice President, Chief Financial Officer and Chief Business Officer
Sujay Kango	52	Executive Vice President, Chief Commercial Officer

Adelene Q. Perkins has served as our President and Chief Executive Officer since January 2010, President and Chief Business Officer from October 2008 through December 2009 and as 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

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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 as a director of the Biotechnology Industry Organization since 2012, a director of Project Hope, a not-for-profit social services company since 2013, a director of the Massachusetts Life Sciences Center, a quasi-public agency of the Commonwealth of Massachusetts, since 2014, a director of the Massachusetts Biotechnology Council, a not-for-profit organization, since 2014, and a director of Padlock Therapeutics, a privately held biopharmaceutical company since 2015. 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.

Julian Adams, Ph.D., has served as our President of Research & Development since October 2007, our Chief Scientific Officer between September 2006 and May 2010, as Chief Scientific Officer of IPI from October 2003 until the merger with DPI in September 2006, as our President between September 2006 and October 2007 and as President of IPI from February 2006 until September 2006. Prior to joining Infinity, Dr. Adams served as Senior Vice President, Drug Discovery and Development at Millennium Pharmaceuticals, Inc. from 1999 to 2001, where he led the development of bortezomib, also known as Velcade®. Dr. Adams served as Senior Vice President, Research and Development at LeukoSite Inc., a private biopharmaceutical company, from July 1999 until its acquisition by Millennium in December 1999. Dr. Adams served as a director and Executive Vice President of Research and Development at ProScript, Inc., a private biopharmaceutical company, from 1994 until its acquisition by LeukoSite in 1999. Prior to joining ProScript, Dr. Adams held a variety of positions with Boehringer Ingelheim, a private pharmaceutical company, and Merck & Co., Inc., a publicly traded pharmaceutical company. Dr. Adams has served as a director of Aileron Therapeutics, Inc., a privately held biopharmaceutical company, between 2011 and 2013, a director of Warp Drive Bio, LLC, since 2013, and a director of the Princess Margaret Cancer Foundation since November 2014. Dr. Adams received a B.S. from McGill University and a Ph.D. from the Massachusetts Institute of Technology in the field of synthetic organic chemistry.

William C. Bertrand, Jr., J.D., has served as Executive Vice President and General Counsel since October 2015. Prior to Infinity, Mr. Bertrand held various roles of increasingly responsibility at Salix Pharmaceuticals, Inc., a subsidiary of Valeant Pharmaceuticals, Inc., a pharmaceutical company, and most recently served as senior vice president, general manager at Salix where he was responsible for its commercial business as well as the transition and integration of Salix into Valeant. From 2001 to 2013, Mr. Bertrand held positions of increasing responsibility at MedImmune, Inc., a pharmaceutical company, serving as its first and only general counsel from 2003 to 2013, prior to and following its sale to AstraZeneca PLC in 2008. Prior to MedImmune, Mr. Bertrand served as associate general counsel at Pharmacia Corporation, a pharmaceutical company. Mr. Bertrand currently serves as a director of Ardelyx, a publicly traded biotechnology company, from October 2015 and has served as a director of Trustwave Holdings, Inc., a privately held information security corporation, from 2011 to August 2015, Inotek Pharmaceuticals, a publicly traded biotechnology company, from 2011 to 2013, BrainCells, Inc., a privately held biotechnology company, from 2008 to 2011, Tech Council of Maryland, a technology and biotechnology trade association, from 2010 to 2013, and Montgomery County Roundtable for Education from 2010 to 2013. He earned a B.S. in Biology from Wayne State University and a J.D. from the University of Wisconsin-Madison.

Lawrence E. Bloch, M.D., J.D., has served as Executive Vice President, Chief Financial Officer and Chief Business Officer since July 2012. 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

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Hospital and Brigham & Woman s Hospital. Dr. Bloch has served as director of NeurAxon, Inc., a privately held biopharmaceutical company, from 2007 to 2011. 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.

Sujay Kango has served as Executive Vice President and Chief Commercial Officer since April 2015. Prior to joining Infinity, Mr. Kango most recently served from April 2011 to March 2015 as vice president, global marketing, sales operations, and business analytics, at Onyx Pharmaceuticals, an Amgen subsidiary and a pharmaceutical company, where he led the global Onyx proteasome inhibitor franchise, including Kyprolis® and oprozomib and co-chaired the Onyx-Bayer executive committee responsible for oversight of the companies global kinase inhibitor franchise. Prior to Onyx, from January 2006 to March 2011, he held several leadership positions at Merck & Co., a pharmaceutical company, including vice president, hepatitis franchise and vice president, oncology integrated business unit. Prior to Merck, from November 1990 to May 2005, Mr. Kango held various commercial and marketing roles of increasing responsibility at Johnson & Johnson and Schering-Plough, each of which is a pharmaceutical company. Mr. Kango serves as a director of Cancer Care of New Jersey. Mr. Kango earned a B.S. in Microbiology and an M.B.A. from McNeese State University.

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.

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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 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, may never become profitable, or if we become profitable, we may not remain profitable.

We have a limited operating history for you to evaluate our business. We have no approved products and have generated no product revenue from sales. We have primarily incurred operating losses. As of December 31, 2015, we had an accumulated deficit of $595.6 million. We expect to continue to spend significant resources to fund the research and development of duvelisib and our other product candidates. While we may have net income in some periods as the result of non-recurring collaboration revenue, we expect to incur substantial operating losses over the next several years as our clinical trial and drug manufacturing activities increase. In addition, in connection with seeking and possibly obtaining regulatory approval of any of our product candidates, 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.

Our product candidates are in varying stages of preclinical and 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 one of our product candidates successfully completes clinical trials and receives regulatory approval. We do not expect to generate any revenue from product sales until at least 2017, assuming we are able to file for regulatory approval for duvelisib in 2016 and receive approval in 2017. 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, maintain our research and development efforts, diversify our pipeline of product candidates or continue our operations and cause a decline in the value of our common stock.

We have no history of commercializing pharmaceutical products, which may make it difficult to evaluate the prospects for our future viability.

To date, our operations have focused on financing and staffing our company, developing our product pipeline and conducting preclinical and clinical research. We have not yet demonstrated an ability to obtain marketing approvals, manufacture a commercial scale product or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful product commercialization. Accordingly, you should consider our prospects in light of the costs, uncertainties, delays and difficulties frequently encountered by companies in the early stages of development, especially clinical stage biopharmaceutical companies such as ours. Any predictions you make about our future success or viability may not be as accurate as they could be if we had a history of successfully developing and commercializing pharmaceutical products.

We may encounter unforeseen expenses, difficulties, complications, delays and other known or unknown factors in achieving our business objectives. We are transitioning from a company with a development focus to a company capable of supporting commercial activities. We may not be successful in such a transition.

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

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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 our product development programs or commercialization efforts.

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, and we expect our expenses to increase in connection with seeking and possibly obtaining regulatory approval of any of our product candidates and building our product sales, marketing, manufacturing and distribution capabilities. If we are unable to raise capital when needed or on attractive terms, we would be forced to delay, reduce or eliminate our research and development programs or commercialization efforts.

In the absence of additional funding or business development activities and based on our current operating plans, we believe that our existing cash, cash equivalents and available-for-sale securities at December 31, 2015 will be adequate to satisfy our capital needs through the first quarter of 2017. Until we can generate sufficient levels of cash from operations, which we do not expect to achieve for at least the next two years, if at all, 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, and/or through licensing select programs or partial economic rights that could include payments to us of up-front, royalty and/or milestone payments. Our need to raise additional funds may be accelerated if our research and development or commercialization expenses exceed our current expectation, 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:

- our product candidates require more extensive clinical or preclinical testing than we currently expect;
- we advance our product candidates into clinical trials for more indications than we currently expect;
- we advance more of our product candidates than expected into costly later stage clinical trials;
- we advance more preclinical product candidates than expected into early stage clinical trials;
- we acquire additional business, technologies, products or product candidates;
- the cost of acquiring raw materials for, and of manufacturing, our product candidates is higher than anticipated;
- the cost or quantity required of comparator drugs used in clinical studies increases;
- the costs of commercialization activities for any of our product candidates that receive marketing approval, including the costs and timing of establishing product sales, marketing, distribution and manufacturing capabilities, increases, to the extent such costs are not the responsibility of any collaborators;
- the costs of preparing, filing and prosecuting patent applications, maintaining and protecting our intellectual property rights and defending against intellectual property related claims increases;
- the receipt of any potential milestone payments from our strategic collaborator AbbVie Inc., or AbbVie, is delayed beyond our original assumptions;

we are required, or consider it advisable, to acquire or license intellectual property rights from one or more third parties; or

we experience 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

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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. If we incur indebtedness, we could become subject to covenants that would restrict our operations and potentially impair our competitiveness, such as limitations on 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. Any of these events could significantly harm our business, financial condition and prospects. 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 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.

Risks Related to the Discovery, Development and Commercialization of Product Candidates

In the near term, we are dependent on the success of our PI3K inhibitor programs including duvelisib and IPI-549. If we are unable to complete the clinical development of, obtain marketing approval for or successfully commercialize these product candidates, either alone or with collaborators, or if we experience significant delays in doing so, our business could be substantially harmed.

We currently have no products approved for sale and are investing a significant portion of our efforts and financial resources in the development of our phosphoinositide-3-kinase, or PI3K, inhibitor programs including duvelisib and IPI-549. Our prospects are substantially dependent on our ability, or that of AbbVie or any future collaborator, to develop, obtain marketing approval for and successfully commercialize product candidates in one or more disease indications.

The success of our PI3K inhibitor programs will depend on several factors, including the following:

- initiation and successful enrollment and completion of clinical trials;
- 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 performance of AbbVie;
- 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;

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- 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.

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 duvelisib, IPI-549, or any other product candidates under our PI3K inhibitor programs, on our own or with any collaborator, or experience delays as a result of any of these factors or otherwise, our business could be substantially harmed.

We may fail to discover and develop additional potential product candidates.

A significant portion of the research that we are conducting involves our PI3K inhibitor programs including duvelisib and IPI-549. We may not be successful in identifying additional compounds that have commercial value or therapeutic utility. Our drug discovery process may fail to yield viable product candidates for clinical development or commercialization for a number of reasons, including:

- potential product candidates may, on further study, be shown to have harmful side effects or other characteristics that indicate that they are unlikely to receive marketing approval and achieve market acceptance;
- competitors may develop alternative therapies that render our potential product candidates non-competitive or less attractive; or
- a potential product candidate may not be capable of being produced at an acceptable cost.

Our research programs to identify new product candidates will require substantial technical, financial and human resources, and we may be unsuccessful in our efforts to identify new product candidates. If we are unable to identify suitable additional compounds for preclinical and clinical development, our ability to develop product candidates and obtain product revenues in future periods could be compromised, which could result in significant harm to our financial position and adversely impact our stock price.

All of our product candidates remain subject to clinical testing and regulatory approval. This process is highly uncertain, and we may never be able to obtain marketing approval for any of our product candidates.

To date, we have not obtained approval from the FDA or any foreign regulatory authority to market or sell any of our product candidates. Our product candidates are subject to extensive governmental regulations relating to development, clinical trials, manufacturing and commercialization. Rigorous preclinical testing and 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 like our product candidates.

For example, we are evaluating duvelisib, our most advanced product candidate, in all phases of clinical development, and we anticipate initiating additional trials of duvelisib in 2016 (see Item 1 - Business above). If any of these trials or other trials of our product candidates are successful, we may need to conduct further clinical trials and will need to apply for regulatory approval before we may market or sell any of our future products. Satisfaction of these and other regulatory requirements is costly, time consuming, uncertain and subject to unanticipated delays. It is possible that none of the product candidates we are developing, or may in the future develop, either alone or with collaborators, will obtain marketing approval. Even if one or more of our product candidates 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

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clinical trials. Conversely, as a result of the same factors, our clinical trials may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any. Similarly, in our clinical trials we may fail to detect toxicity of or intolerability caused by our product candidates, or mistakenly believe that our product candidates are toxic or not well tolerated when that is not in fact the case.

Our product candidates must undergo rigorous clinical trials prior to receipt of regulatory approval. Any problems in these clinical trials could delay or prevent commercialization of our product candidates.

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 our product candidates:

- 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, Infinity, or an Infinity vendor, 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 a product candidate 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 our product candidates, for any of the foregoing reasons, could adversely affect our efforts 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.

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Adverse events or undesirable side effects caused by, or other unexpected properties of, product candidates that we develop may be identified during development and could delay or prevent their marketing approval or limit their use.

Adverse events or undesirable side effects caused by, or other unexpected properties of, any current or future product candidates that we may develop could cause us, any collaborators, an institutional review board or regulatory authorities to interrupt, delay or halt clinical trials of one or more of our product candidates and could result in a more restrictive label or the delay or denial of marketing approval by the FDA or comparable foreign regulatory authorities. If any of our product candidates is associated with adverse events or undesirable side effects or has properties that are unexpected, we, or any collaborators, may need to abandon development or limit development of that product candidate to certain uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective. Many compounds that initially showed promise in clinical or earlier stage testing have later been found to cause undesirable or unexpected side effects that prevented further development of the compound.

If we, or any current or future collaborators, experience any of a number of possible unforeseen events in connection with clinical trials of our current or future product candidates that we, or any collaborators, may develop, potential clinical development, marketing approval or commercialization of our product candidates could be delayed or prevented.

We, or any 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 our current or future product candidates that we, or any collaborators, may develop, 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 our product candidates 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 product development programs;
- the number of patients required for clinical trials of our product candidates 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 our product candidates may be greater than we anticipate;
- our third-party contractors or those of any collaborators, including those manufacturing our product candidates 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 our product candidates for various reasons, including a finding that the participants are being exposed to unacceptable health risks, undesirable side effects or other unexpected characteristics of the product candidate;

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

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to unacceptable health risks, undesirable side effects or other unexpected characteristics of the product candidate or findings of undesirable effects caused by a chemically or mechanistically similar product or product candidate;

the FDA or comparable foreign regulatory authorities may disagree with our, or 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 or other materials necessary to conduct clinical trials of our product candidates may be insufficient, inadequate or not available at an acceptable cost, or we may experience interruptions in supply; and

the approval policies or regulations of the FDA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient to obtain marketing approval.

Product development costs for us, 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 our product candidates. We do not know whether any preclinical tests or 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 our product candidates 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 our product candidates and may harm our business and results of operations. We have designed our DYNAMO study with the potential to support accelerated approval of duvelisib for the treatment of follicular lymphoma and SLL, indications for which Gilead has received accelerated approval to manufacture and market idelalisib. If we experience delays in the conduct of our DYNAMO study, or Gilead is able to complete its confirmatory study and receive full approval to market idelalisib for the treatment of follicular lymphoma or SLL faster than anticipated, our efforts to seek accelerated approval for duvelisib for the treatment of follicular lymphoma or SLL may be materially adversely affected. In addition, many of the factors that lead to clinical trial delays may ultimately lead to the denial of marketing approval of any of our product candidates.

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

We have completed a small number of clinical trials for our lead product candidate duvelisib, and we are currently conducting several additional trials for duvelisib and 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 our product candidates warrant marketing approval, the FDA or comparable foreign regulatory authorities may disagree and may not grant marketing approval of our product candidates.

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

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protocols, differences in the size and type of the patient populations, changes in and adherence to the dosing regimen and other clinical trial protocols and the rate of dropout among clinical trial participants. If we fail to receive positive results in clinical trials of our product candidates, the development timeline and regulatory approval and commercialization prospects for our most advanced product candidates, and, correspondingly, our business and financial prospects would be negatively impacted.

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.

Additionally, the availability of safe and effective treatments for the relevant disease being studied may impact patient enrollment in our clinical trials. For example, AbbVie has received approval to manufacture and market ibrutinib, a BTK inhibitor for the treatment of chronic lymphocytic leukemia, or CLL, an indication for which we are currently evaluating duvelisib in our DUO and SYNCHRONY clinical trials, and Gilead has received accelerated approval to manufacture and market idelalisib for the treatment of follicular lymphoma and SLL, indications for which we are currently evaluating duvelisib.

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 any of our product candidates. 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 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 efforts 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.

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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 our current or future product candidates that we, or any collaborators, may develop.

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 submit for our product candidates or may conclude after review of our data that our application is insufficient to obtain marketing approval of our product candidates. If the FDA does not accept or approve our NDAs for any of our product candidates, 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 NDA or 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 our product candidates 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 our product candidates, which could significantly harm our business.

Even if any product candidates that we, or any collaborators, may develop receive marketing approval, we or others may later discover that the product is less effective than previously believed or causes undesirable side effects that were not previously identified, which could compromise our ability, or that of any collaborator, to market the product, and we could become subject to costly and damaging product liability claims.

Even if we receive regulatory approval for any of our product candidates, we will have tested them in only a small number of patients in carefully defined subsets and over a limited period of time during our clinical trials. If our applications for marketing are approved and more patients begin to use our products, or patients use our products for a longer period of time, the product candidate might be less effective than indicated by our clinical trials. Furthermore, new risks and side effects associated with our 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 our product (including a black box warning or a contraindication) or the manner in which it is administered, reformulate our product or make changes and obtain new approvals for our and our suppliers manufacturing facilities. We also might have to withdraw or recall our products from the marketplace, and regulators might seize our products. We might be subject to fines, injunctions, or the imposition of civil or criminal penalties. Any safety concerns with respect to a product may also result in a significant drop in the potential sales of that 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 any product candidates that we, or any collaborators, may develop receive 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 any of our product candidates obtains regulatory approval, that product 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;

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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 the product is designated under physician treatment guidelines as a first, second or third line therapy;

changes in the standard of care for the targeted indications for the product;

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 of our approved drugs fails to achieve market acceptance, we would not be able to generate significant revenue from those drugs, which may adversely impact our ability to become profitable.

Even if we receive regulatory approvals for marketing our product candidates, 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 of our product candidates, the manufacturing, marketing and sale of these drugs will be subject to continuing regulation, including compliance with quality systems regulations, 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 our 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. We plan to build focused capabilities to commercialize development programs for certain indications where we believe that the medical specialists for the indications are sufficiently concentrated to allow us to effectively promote the product with a targeted sales team. The development of sales, marketing and distribution capabilities will require substantial resources, will 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

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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 plan to target. If we are unable to establish or retain a sales force and marketing and distribution capabilities, our operating results may be adversely affected. If 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.

In certain indications, we plan to seek to enter into collaborations that we believe may contribute to our ability to advance development and ultimately commercialize our product candidates. We also intend to seek to enter into collaborations where we believe that realizing the full commercial value of our development programs will require access to broader geographic markets or the pursuit of broader patient populations or indications. Under our collaboration and license agreement with AbbVie, which we refer to as the AbbVie Agreement, for example, we and AbbVie are obligated to each provide half of the sales representative effort to promote products containing duvelisib, which we refer to as Duvelisib Products, in the United States. Outside the United States, AbbVie has, with limited exceptions, operational responsibility and decision making authority to commercialize Duvelisib Products. We and AbbVie will share the cost of manufacturing and supply for commercialization of Duvelisib Products in the United States, and AbbVie will bear the cost of manufacturing and supply for commercialization of Duvelisib Products outside the United States.

As a result of entering into arrangements such as the AbbVie Agreement 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 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 any of our product candidates that receive marketing approval.

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

In building our product development pipeline, we have intentionally pursued targets with applicability across multiple therapeutic areas and indications. This approach gives us several product opportunities in oncology diseases, which 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. Moreover, there are a number of large pharmaceutical companies currently marketing and selling products in this segment including Bristol-Myers Squibb Company; the Roche Group and its subsidiary Genentech; Novartis AG; Pfizer, Inc.; and Johnson & Johnson. In addition to currently approved drugs, there are a significant number of drugs that are currently under development and may become available in the future for the treatment of various forms of cancer.

Duvelisib is a dual inhibitor of the delta and gamma isoforms of PI3K. We are aware of a number of companies developing product candidates or selling products directed to isoforms of PI3K. Specifically, we believe that Gilead Sciences, Inc., or Gilead; Incyte Corporation; Acerta Pharma BV; and TG Therapeutics, Inc. are conducting clinical trials of drugs that target the delta isoform of PI3K. We also believe that Rhizen Pharmaceuticals S.A. is conducting clinical trials of a drug that targets both the delta and gamma isoforms of

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PI3K. We also believe that SignalRx Pharmaceuticals is conducting a clinical trial of a drug that targets the delta, gamma, and alpha isoforms of PI3K, and that Novartis AG, Bayer, and Genentech are each conducting clinical trials of drugs that target the delta, gamma, alpha, and beta isoforms of PI3K.

Additionally, many companies are developing product candidates or selling products directed to disease targets such as Bruton s tyrosine kinase (or BTK), B-cell lymphoma 2 (or BCL-2), Janus Kinase (or JAK), B-lymphocyte antigen CD-19, and programmed death 1/ligand 1 (or PD-1/PD-L1), Cluster of Differentiation 79B antibody-drug conjugate (or CD79B ADC), and pleiotropic pathways in the fields of hematology-oncology, including in the specific diseases for which we are currently developing duvelisib, or for which we may develop duvelisib in the future, including: AbbVie; Pharmacyclics LLC, a wholly-owned subsidiary of AbbVie; BeiGene Co., Ltd; Janssen Biotech through its collaboration with AbbVie; Celgene Corporation; a joint collaboration between Gilead and Ono Pharmaceutical Group under their exclusive license agreement; Acerta Pharma BV; Incyte Corporation; MorphoSys AG; Novartis AG; Roche Group and its subsidiary Genentech; Bristol-Myers Squibb Company; and AstraZeneca PLC.

Many of our competitors have:

- significantly greater financial, technical and human resources than we have, and may be better equipped to discover, develop, manufacture and commercialize product candidates than we are;
- more experience in preclinical testing and clinical trials, obtaining regulatory approvals and manufacturing and marketing products than we do; and/or
- product candidates that are in later-stage clinical development than our own product candidates, or have been approved by the FDA, such as ibrutinib, a BTK inhibitor being developed and commercialized by AbbVie for the treatment of people with mantle cell lymphoma or CLL, and idelalisib, a compound targeting the delta isoform of PI3K, being developed and commercialized by Gilead for the treatment of people with CLL, follicular B-cell non-Hodgkin lymphoma, or small lymphocytic lymphoma.

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 our own product candidates. These competitive products may have superior safety or efficacy, have more attractive pharmacologic properties, or may be manufactured less expensively than our future products. 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 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 future products 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 any product candidate that we, or they, develop, the product may become subject to unfavorable pricing regulations, third-party payor reimbursement practices or healthcare reform initiatives, any of which could harm our business.

The commercial success of our product candidates will depend substantially, both domestically and abroad, on the extent to which the costs of our product candidates will be paid by third-party payors, including government health care programs and private health insurers. If coverage is not available, or reimbursement is limited, we, or any future collaborators, may not be able to successfully commercialize our product candidates. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us, or any

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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.

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, 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 one or more product candidates, even if our product candidates obtain marketing approval.

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

There may also be delays in obtaining coverage and reimbursement for newly approved drugs, and coverage may be more limited than the indications for which the drug is approved by the FDA or comparable foreign regulatory authorities. Moreover, eligibility for reimbursement does not imply that any drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Reimbursement rates may vary, 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 any of our product candidates for which we, or any future collaborator, obtain marketing approval could significantly harm our operating results, our ability to raise capital needed to commercialize products and our overall financial condition.

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If the FDA or comparable foreign regulatory authorities approve generic versions of any of our products that receive marketing approval, or such authorities do not grant our products appropriate periods of data exclusivity before approving generic versions of our products, the sales of our products 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 typically 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.

We may have significant product liability exposure that may harm our business and our reputation.

We face exposure to significant product liability or other claims if any of our product candidates is alleged to have caused harm. These risks are inherent in the testing, manufacturing and marketing of human medicinal products. Although we do not currently commercialize any products, claims could be made against us based on the use of our product candidates in clinical trials. We currently have clinical trial insurance and will seek to obtain product liability insurance prior to the commercial launch of any of our product candidates. Our insurance may not, however, provide adequate coverage against potential liabilities. Furthermore, clinical trial and product liability insurance is becoming increasingly expensive. As a result, we may be unable to maintain current amounts of insurance coverage or obtain additional or sufficient insurance at a reasonable cost. If we are sued for any injury caused by our product candidates or future products, our liability could exceed our insurance coverage and our total assets, and we would need to divert management attention to our defense. Claims against us, regardless of their merit or potential outcome, may also generate negative publicity or hurt our ability to recruit investigators and patients to our clinical trials, obtain physician acceptance of our future products, or expand our business.

Risks Related to Our Dependence on Third Parties

If our strategic alliance with AbbVie, or any future alliance we may enter into, is unsuccessful, our operations may be negatively impacted.

We have a strategic collaboration with AbbVie to research, develop and jointly commercialize products containing or comprised of duvelisib, which we refer to as Duvelisib Products, in oncology indications. We refer to this agreement as the AbbVie Agreement. Pursuant to the AbbVie Agreement, AbbVie has committed to

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providing substantial funding, as well as significant capabilities in development, manufacturing, marketing and sales. However, we may not be able to maintain our alliance with AbbVie or any future collaborator if, for example, development or approval of duvelisib or other product candidates is delayed or sales of Duvelisib Products or other products are disappointing. Further, AbbVie may be the only alliance we are able to successfully execute, making us overly dependent on the success of duvelisib in oncology indications and therefore particularly vulnerable if duvelisib or the alliance with AbbVie fails, as discussed in the next risk factor.

If a collaborator terminates or fails to perform its obligations under agreements with us, the development and commercialization of our product candidates could be delayed or terminated.

The success of a strategic alliance, whether with AbbVie or any future 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:

- decides not to devote the necessary resources because of internal constraints, such as limited personnel with the requisite scientific or commercial expertise, limited cash resources or specialized equipment limitations;
- decides not to pursue development and commercialization of our product candidates 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 product candidate through clinical development, regulatory approval and commercialization; or