IDERA PHARMACEUTICALS, INC.
Form 10-K
March 13, 2014
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

þ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the Fiscal Year Ended December 31, 2013

OR

¨ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the Transition Period from to

Commission File Number: 001-31918

IDERA PHARMACEUTICALS, INC.

(Exact name of Registrant as specified in its charter)

Delaware	**04-3072298**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
167 Sidney Street Cambridge, Massachusetts	**02139**
(Address of principal executive offices)	**(Zip Code)**

(617) 679-5500

(Registrant s telephone number, including area code)

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

Title of Class:	Name of Each Exchange on Which Registered
Common Stock, $.001 par value	**Nasdaq Capital Market**

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

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

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

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 the filing requirements for the past 90 days. Yes þ 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 þ No ¨

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405) is not contained herein, and will not be contained, to the best of the registrant s knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ¨

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

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

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant was $25,882,078 based on the last sale price of the registrant s common stock as reported on the Nasdaq Capital Market on June 28, 2013. As of February 15, 2014, the registrant had 82,360,165 shares of common stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant s Proxy Statement with respect to the Annual Meeting of Stockholders to be held on June 10, 2014 are incorporated by reference into Items 10, 11, 12, 13 and 14 of Part III of this Form 10-K.

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FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K and the documents we incorporate by reference contain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. All statements, other than statements of historical fact, included or incorporated in this report regarding our strategy, future operations, collaborations, intellectual property, cash resources, financial position, future revenues, projected costs, prospects, plans, and objectives of management are forward-looking statements. The words believes, anticipates, estimates, plans, expects, intends, may, could, should, potentia continue, will, would and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. We cannot guarantee that we actually will achieve the plans, intentions or expectations disclosed in our forward-looking statements and you should not place undue reliance on our forward-looking statements. There are a number of important factors that could cause our actual results to differ materially from those indicated or implied by forward-looking statements. These important factors include those set forth below under Part II, Item 1A Risk Factors. These factors and the other cautionary statements made in this Annual Report on Form 10-K and the documents we incorporate by reference should be read as being applicable to all related forward-looking statements whenever they appear in this Annual Report on Form 10-K and the documents we incorporate by reference. In addition, any forward-looking statements represent our estimates only as of the date that this Annual Report on Form 10-K is filed with the Securities and Exchange Commission and should not be relied upon as representing our estimates as of any subsequent date. We do not assume any obligation to update any forward-looking statements. We disclaim any intention or obligation to update or revise any forward-looking statement, whether as a result of new information, future events or otherwise.

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PART I.

Item 1. *Business.*

Overview

We are a clinical stage biotechnology company advancing drug candidates for the treatment of autoimmune diseases and for certain genetically defined forms of B-cell lymphoma. These drug candidates are designed to inhibit over-activation of specific Toll-like receptors, or TLRs. In addition to our TLR program, we have initiated a research program employing our gene silencing oligonucleotides, or GSOs, to inhibit the production of disease-associated proteins by targeting RNA.

Programs for the Inhibition of Specific Toll-like Receptors

Our lead drug candidate in our TLR program is IMO-8400, an antagonist of TLR7, TLR8, and TLR9. IMO-8400 is in clinical development for the treatment of autoimmune diseases and certain genetically defined forms of B-cell lymphoma. We also are conducting preclinical studies of IMO-9200, a second antagonist of TLR7, TLR8, and TLR9, to support the submission of an Investigational New Drug application, or IND, to the United States Food and Drug Administration, or FDA. A TLR antagonist is a compound that blocks activation of an immune response through the targeted TLR.

Our business strategy is to develop IMO-8400, IMO-9200, and other TLR antagonist candidates for the treatment of autoimmune diseases with orphan indications and for the treatment of certain genetically defined forms of B-cell lymphomas. In addition, we may seek to enter into collaborative alliances with pharmaceutical companies to advance our TLR antagonist candidates in broader autoimmune disease indications, such as psoriasis, lupus, and arthritis.

Program in Autoimmune Diseases. We believe that we have achieved clinical proof-of-concept for our approach of inhibition of over-activation of specific TLRs for the treatment of psoriasis and potentially other autoimmune diseases based on the results of our Phase 2 clinical trial of IMO-3100, a TLR7 and TLR9 antagonist, in patients with moderate to severe psoriasis, which we completed in 2012. We currently are focusing clinical development in our autoimmune disease program on IMO-8400, as it targets TLR8 in addition to TLR7 and TLR9. We have completed a Phase 1 clinical trial of IMO-8400 in 42 healthy subjects, in which IMO-8400 was well tolerated and showed inhibition of TLR7, TLR8, and TLR9. In September 2013, we completed enrollment in a randomized, double-blind, placebo-controlled Phase 2 clinical trial that we are conducting to evaluate the safety, tolerability and clinical activity of IMO-8400 over a 12-week treatment period in patients with moderate to severe plaque psoriasis. In this trial, 32 patients were randomized for treatment at three dose levels of IMO-8400: 0.075 mg/kg, 0.15 mg/kg and 0.3 mg/kg; or placebo. To date, IMO-8400 treatment in this Phase 2 clinical trial has been well tolerated, with no treatment-related discontinuations. In October 2013, we expanded the trial to evaluate a higher dose cohort of 0.6 mg/kg and placebo in up to 12 patients. We expect to report top-line data from the trial, including the expansion cohort, in the first half of 2014.

We have selected IMO-9200, a second novel antagonist of TLR7, TLR8, and TLR9, for development as a drug candidate for potential use in selected autoimmune disease indications. We have initiated preclinical studies of IMO-9200 to support submission of an IND to the FDA. Pending the results of these studies, we expect to submit an IND for IMO-9200 and to initiate a Phase 1 clinical trial in the second half of 2014.

Program in Autoimmune Diseases with Orphan Indications. We are planning to initiate clinical development of IMO-8400 and IMO-9200 for the treatment of autoimmune diseases with orphan indications. We have selected polymyositis and dermatomyositis as the first two orphan indications for which we plan to develop IMO-8400. We selected these indications for development based on the reported involvement of altered TLR expression in these disease states, expression of cytokines indicative of key TLR-mediated pathways, the presence of auto-antibodies that can induce TLR-mediated immune responses, and the identification of

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prospective clinical biomarkers for evaluation in early clinical trials. We anticipate initiating clinical development in these two indications by submitting a protocol for a Phase 1/2 clinical trial to the FDA in the first half of 2014 and initiating patient treatment in this trial in the second half of 2014.

Program in Genetically Defined Forms of B-cell Lymphoma. Independent research has suggested that the inhibition of specific TLRs may be a useful approach to the treatment of certain B-cell lymphomas characterized by the presence of the oncogenic mutation referred to scientifically as MYD88 L265P. Oncogenic mutations are changes in the DNA of tumor cells that promote the survival and proliferation of the tumor cells. In this research, the inhibition of TLR7 and TLR9 suppressed MYD88 L265P induced signaling and promoted tumor cell death. Our internal studies using IMO-8400, which inhibits TLR7-, TLR8- and TLR9-mediated activity, have shown similar results of inducing cell death in tumor cells harboring the MYD88 L265P oncogenic mutation.

Based on this independent research, we determined to evaluate IMO-8400 with respect to two forms of non-Hodgkin lymphoma where the MYD88 L265P oncogenic mutation is present. One is Waldenström s macroglobulinemia, a lymphoma that commonly involves the blood and bone marrow and may spread to almost any organ in the body. Based on published independent reports, we believe that approximately 90% of patients with Waldenström s macroglobulinemia have the MYD88 L265P oncogenic mutation. The second is diffuse large B-cell lymphoma, or DLBCL. Based on published independent reports, we believe that approximately 30% of patients with the activated B-cell-like, or ABC, sub-type of DLBCL are reported to carry the MYD88 L265P oncogenic mutation. We believe that Waldenström s macroglobulinemia and DLBCL in patients with the MYD88 L265P mutation are each orphan indications with unmet medical need, based on prevalence of the indications.

In December 2013, we were cleared to open enrollment for a Phase 1/2 clinical trial of IMO-8400 in patients with Waldenström s macroglobulinemia, following acceptance of our IND by the FDA. We anticipate that patient treatment in this trial will begin in the first half of 2014. We initiated clinical development of IMO-8400 in patients with DLBCL by submitting a protocol for a Phase 1/2 clinical trial to the FDA in March 2014. We expect to initiate patient treatment in this trial in the second half of 2014.

Gene Silencing Oligonucleotide Technology to Target RNA

We have created our GSOs to inhibit the expression of disease-associated proteins by targeting RNA. Based on evaluations of GSOs targeted to disease-associated RNA in preclinical models, we believe our GSO technology has the potential to overcome several of the hurdles of antisense and RNA interference, or RNAi, technologies. We are currently undertaking an analysis of priority disease indications for development of drug candidates from our GSO technology. Our key considerations in identifying disease indications in our GSO program are: strong evidence that the disease is caused by a specific protein; clear criteria to identify a target patient population; biomarkers for early assessment of clinical proof-of-concept; a targeted therapeutic mechanism for action; and unmet medical need to allow for a rapid development path to approval. We expect to identify the first two disease indications to be targeted in our GSO program in the second half of 2014, with the goal of initiating disease model studies and an IND-enabling development program in the first half of 2015. Based on this timeline, we could initiate proof-of-concept clinical trials for the first two disease indications as early as the second half of 2015.

Our business strategy for our GSO program is focused on the further development of our GSO technology. We may seek to enter into collaborative alliances with pharmaceutical companies with respect to applications of our GSO technology program.

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Research and Development Programs

We are advancing development of TLR antagonist candidates for the treatment of autoimmune diseases and for certain genetically defined forms of B-cell lymphoma. In addition, we are identifying drug candidates based on our GSO program. The following table summarizes the development status of our programs.

RESEARCH AND DEVELOPMENT PROGRAMS

Drug Candidate(s)	Indication / Application	Development Status
Programs for the Inhibition of Specific Toll-like Receptors		
Autoimmune Diseases		
IMO-8400	Moderate to Severe Plaque Psoriasis	Ongoing Phase 2 Clinical Trial Top-Line Data Anticipated During the First Half of 2014*
IMO-8400	Polymyositis	Phase 1/2 Clinical Trial Protocol Submission to FDA Anticipated in the First Half of 2014*
IMO-8400	Dermatomyositis	Phase 1/2 Clinical Trial Protocol Submission to FDA Anticipated in the First Half of 2014
IMO-9200	Autoimmune Diseases	IND-enabling Studies Ongoing; Planned IND Submission in the Second Half of 2014
B-cell Lymphomas		
IMO-8400	Waldenström s Macroglobulinemia	Phase 1/2 Clinical Trial Anticipated to Begin in the First Half of 2014
IMO-8400	Diffuse Large B-Cell Lymphoma with MYD88 L265P Oncogenic Mutation	Phase 1/2 Clinical Trial Protocol Submission to FDA Anticipated in the First Quarter of 2014
Gene Silencing Oligonucleotides		
Discovery Candidates	Inhibition of Gene Expression by Targeting RNA	Research

*We may conduct a single Phase 1/2 clinical trial in patients with polymyositis or dermatomyositis.

Programs for the Inhibition of Specific Toll-like Receptors

We have designed drug candidates to inhibit over-activation of TLRs and are developing these therapeutics for the treatment of autoimmune diseases and for certain genetically defined forms of B-cell lymphoma. Using a chemistry-based approach, we have created synthetic DNA- and RNA-based compounds that are targeted to TLR3, TLR7, TLR8 and TLR9. Our lead drug candidate in our TLR program is IMO-8400, an antagonist for TLR7, TLR8 and TLR9, which we are developing for the treatment of autoimmune diseases and certain genetically defined forms of B-cell lymphoma. IMO-9200, a second antagonist of TLR 7, TLR8, and TLR9, is in preclinical development.

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About Toll-like Receptors

TLRs comprise a family of receptors of the immune system. Of the ten human TLRs identified to date, TLR3, TLR7, TLR8, and TLR9 are receptors which are present inside specific immune cells. These TLRs are activated upon recognition of pathogen-associated molecular patterns associated with RNA and DNA from pathogens. TLR9 is a receptor that specifically recognizes DNA of the pathogen. TLR3, TLR7, and TLR8 are receptors that recognize RNA of the pathogen. TLRs provide a scientific basis to modulate immune responses for the treatment of a broad range of diseases.

We have created synthetic DNA- and RNA-based compounds to target specific TLRs with the goal of modulating immune responses for therapeutic applications. Our TLR-targeted compounds are of two unique classes. One class is referred to as TLR antagonists, which inhibit over-activation of TLR-mediated responses. The second class is referred to as TLR agonists, which induce immune responses mediated by the targeted TLRs.

Our TLR antagonist lead candidates include IMO-8400 and IMO-9200, which both are antagonists of TLR7, TLR8, and TLR9. We also have created compounds that are agonists of TLR3, TLR7, TLR8, and TLR9.

Program in Autoimmune Disease. In autoimmune diseases such as lupus, psoriasis, rheumatoid arthritis, polymyositis, dermatomyositis, graft-versus-host disease, Sjögren s syndrome, and Behçet s disease, the immune system forms autoantibodies, and damage-associated molecular patterns, or DAMPs, which may include self-DNA or self-RNA. Independent published reports have provided evidence that these autoantibodies and DAMPs are recognized by TLR7, TLR8, or TLR9 and exacerbate the autoimmune disease. Engagement of TLRs leads to activation of immune responses and induction of multiple cytokines and signaling cascades such as the Th1, Th17 and inflammasome pathways. These pathways are associated with inflammatory processes that can exacerbate disease. In preclinical models of psoriasis, lupus and rheumatoid arthritis, treatment with TLR antagonist candidates, such as IMO-3100 and IMO-8400, has blocked activation of immune response through TLRs and improved several disease associated parameters. In preclinical disease models, these candidates have been shown to inhibit the Th1, Th17, and inflammasome pathways, leading to the suppression of cytokines such as tumor necrosis factor-alpha, or TNF-a, and interleukins IL-12, IL-6, IL-17, and IL-1ß. In a recent publication, we and our collaborators at The Rockefeller University presented results showing that treatment with IMO-8400, which targets TLR8 in addition to TLR7 and TLR9, had a broader therapeutic effect than did IMO-3100, an antagonist of TLR7 and TLR9, in a preclinical model of skin inflammation. TLR antagonism provides a novel approach to the treatment of a broad range of autoimmune diseases by blocking TLR-mediated signaling and induction of multiple cytokines. Current therapeutic approaches include blocking the activity of one specific cytokine with an antibody.

Clinical Proof-of-Concept Clinical Trial with an Antagonist of TLR7 and TLR9.

IMO-3100 is an antagonist of TLR7 and TLR9. In November 2009, we submitted an IND to the FDA for the clinical evaluation of IMO-3100 in autoimmune diseases. IMO-3100 has been well tolerated in both single-dose and multiple-dose Phase 1 clinical trials. In 2012, we conducted a randomized, double-blind, placebo-controlled Phase 2 trial of IMO-3100 in patients with moderate to severe plaque psoriasis. We selected psoriasis as the initial indication to evaluate clinical proof-of-concept of TLR antagonism. In this trial, 44 patients received subcutaneous doses of IMO-3100 once weekly for four weeks at two dose levels or placebo. Treatment with IMO-3100 was well tolerated and a treatment effect was demonstrated in measures of clinical efficacy, including reductions in Psoriasis Area Severity Index, or PASI, scores, which correlated with down-regulation of the IL-17 pathway compared to placebo-treated patients. We presented data from this trial at medical meetings in May and October 2013. We believe that the results of this trial provide clinical proof-of-concept of TLR antagonism for the treatment of psoriasis and potentially other autoimmune diseases.

IMO-8400.

IMO-8400 is a first-in-class synthetic oligonucleotide-based antagonist of TLR7, TLR8, and TLR9. In the first quarter of 2012, we began development of IMO-8400 as a drug candidate.

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We submitted an IND to the FDA in the third quarter of 2012. In the fourth quarter of 2012, we initiated a Phase 1 clinical trial in the United States to assess the safety and the pharmacodynamic activity of IMO-8400 in healthy subjects. A total of 42 subjects were enrolled in the trial and received single or multiple ascending doses of IMO-8400 or placebo. IMO-8400 was well tolerated at all dosages in both single- and multiple-dose regimens. In addition, IMO-8400-treated subjects showed inhibition of immune responses mediated through TLR7, TLR8, and TLR9, compared to placebo-treated subjects. Results from this Phase 1 clinical trial were presented at a medical meeting in June 2013. We are focusing clinical development in our autoimmune disease program on IMO-8400, as it targets TLR8 in addition to TLR7 and TLR9.

We are conducting a randomized, double-blinded, placebo-controlled Phase 2 clinical trial of IMO-8400 in patients with moderate to severe plaque psoriasis. The purpose of this study is to evaluate the safety, tolerability, and clinical activity of IMO-8400 with a treatment period of up to 12 weeks. Under the protocol for this Phase 2 trial, we enrolled 32 adult patients with moderate to severe plaque psoriasis as indicated by a score of 12 or greater on the PASI. These patients were randomized 1:1:1:1 into one of four cohorts and assigned to receive either placebo or weekly subcutaneous injections of IMO-8400 at a dose level of 0.075, 0.15, or 0.3 mg/kg/week for 12 weeks, with a six-week follow-up period. Safety, tolerability, and changes in PASI score will be monitored throughout the trial. Enrollment of 32 patients in this trial was completed in September 2013. To date, all treatments had been well tolerated in the trial, and based on this demonstrated safety profile, we expanded the trial to include evaluation of a higher dose cohort of 0.6 mg/kg or placebo in up to 12 patients. The data remain blinded, as the follow-up period of the trial continues. We expect to report top-line data from this Phase 2 trial, including from the expansion cohort, during the first half of 2014. We may consider additional dosing regimens based on the safety and tolerability observed in this expansion cohort.

IMO-9200.

We also have selected IMO-9200 as a second antagonist of TLR7, TLR8, and TLR9 for development as a drug candidate with potential use in selected autoimmune disease indications. In the fourth quarter of 2013, we initiated IND-enabling studies of IMO-9200 and, pending the results from these studies, anticipate filing an IND and initiating a Phase 1 clinical trial of IMO-9200 in the second half of 2014. Based on this timeline, we anticipate receiving top-line data from this Phase 1 trial as early as the first half of 2015.

We may seek to enter into collaborative alliances with pharmaceutical companies to advance our TLR antagonist candidates in broader autoimmune disease indications, such as psoriasis, lupus, and arthritis.

Program in Autoimmune Diseases with Orphan Indications

As part of our business strategy for our autoimmune disease program, we have selected polymyositis and dermatomyositis as the first two orphan indications for which we plan to develop IMO-8400. Polymyositis and dermatomyositis are automimmune diseases characterized by chronic inflammatory damage of skeletal muscle and frequently involving other organ systems including the lung, joints, and gastrointestinal tract. Dermatomyositis, unlike polymyositis, is associated with a variety of characteristic skin manifestations, and differences in the microscopic changes that are associated with muscle damage distinguish polymyositis and dermatomyositis as two distinct diseases. We selected these two indications following a strategic review based on the following criteria, which are applicable to both indications:

High unmet medical need serious consequence of the disease with absence of effective therapy;

Established clinical diagnosis;

Evidence that TLR7, TLR8, or TLR9 expression is altered in the disease state;

Presence of key inflammatory cells in the disease state, such as dendritic cells, especially with infiltration into diseased tissue;

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Cytokine profile indicative of key pathways, such as type 1 interferon, Th17, IL-12/23, that can be induced by TLR-mediated immune responses;

Auto-antibody profile indicative of self-derived nucleic acids that can induce TLR-mediated immune responses; and

Prospective clinical biomarker or endpoint for evaluation in early clinical trials.

We anticipate initiating clinical development in these two indications by submitting a protocol for a Phase 1/2 clinical trial to the FDA in the first half of 2014. If we determine to conduct separate Phase 1/2 clinical trials in patients with polymyositis and dermatomyositis, we would anticipate submitting protocols for each trial in the first half of 2014. We expect to initiate patient treatment in this trial in the second half of 2014. Based on this timeline, we anticipate top-line data from this trial to be available during the second half of 2015. If we observe a therapeutic effect in either or both of these indications, we plan to meet with regulatory authorities to discuss the possibility of an accelerated clinical development and regulatory path for the applicable program. We cannot predict whether or when any of our product candidates will prove effective or safe in humans, if we will be able to participate in FDA expedited review and approval programs, including breakthrough and fast track designation, or if they will receive regulatory approval. We are continuing to use the above criteria to prioritize additional autoimmune diseases with orphan indications for which we may develop our TLR antagonist candidates, such as graft-versus-host disease and Sjögren s syndrome.

Program in Genetically Defined Forms of B-cell Lymphoma. Independent research suggests that the inhibition of specific TLRs may be a useful approach to the treatment of B-cell lymphomas characterized by the presence of the oncogenic mutation MYD88 L265P. In this research, MYD88 L265P has been shown to engage TLR7 and TLR9 and also to confer a survival benefit to the tumor cells. Further, in this research inhibiting the expression of TLR7 and TLR9 suppressed MYD88 L265P induced signaling and promoted cell death in tumor cells harboring this mutation.

The MYD88 L265P oncogenic mutation has been reported in several types of B-cell lymphomas, including Waldenström s macroglobulinemia and DLBCL. Waldenström s macroglobulinemia is classified as a non-Hodgkin lymphoma of malignant lymphoplasmacytic B-cells that commonly involves the blood and bone marrow and may spread to almost any organ in the body. The cells typically produce immunoglobulin M, or IgM, resulting in high serum levels of the protein and, potentially, hyperviscosity syndrome, with thickening of the blood, decrease in circulation and oxygen delivery, and ultimately impaired function of almost any organ in the body. Approximately 90% of Waldenström s macroglobulinemia patients are reported to have the MYD88 L265P oncogenic mutation. DLBCL is a fast-growing lymphoma that can arise in lymph nodes or outside of the lymphatic system. Approximately 30% of the patients with the ABC sub-type are reported to have the MYD88 L265P oncogenic mutation. Waldenström s macroglobulinemia and DLBCL with the MYD88 L265P mutation are each orphan indications, based on prevalence of the indications.

Based on the Surveillance, Epidemiology, and End-Results, or SEER, Cancer Statistics Review, 1975-2001, from the National Cancer Institute s SEER database and published independent reports of the frequency of the specific oncogenic mutation among patients with B-cell lymphoma, and allowing for population growth, we estimate that there will be approximately 1,200 patients with Waldenström s macroglobulinemia with the mutation and approximately 2,000 patients with DLBCL with the mutation newly diagnosed in the United States per year. Based on this information, we also believe that at least 7,500 patients in the United States currently have B-cell lymphoma with the MYD88 L265P oncogenic mutation. We believe Waldenström s macroglobulinemia and DLBCL with the MYD88 L265P oncogenic mutation are orphan indications with unmet medical need. There are currently no drugs specifically approved for the treatment of Waldenström s macroglobulinemia or DLBCL with the MYD88 L265P oncogenic mutation. Currently, patients with non-Hodgkin lymphoma are often treated with the monoclonal antibody rituximab and/or with one or more chemotherapeutic agents.

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We have conducted preclinical studies of IMO-8400 in human lymphoma cells that carry the MYD88 L265P oncogenic mutation and in human lymphoma cell lines lacking the mutation. In these studies, IMO-8400 increased rates of cell death, inhibited cytokine production, and inhibited key components of signaling pathways in the human lymphoma cell lines that carry the MYD88 L265P oncogenic mutation. IMO-8400 did not have any significant effects in human lymphoma cell lines that did not carry the mutation. In addition, in a study that we conducted in a mouse tumor model, IMO-8400 monotherapy showed anti-tumor activity using a human lymphoma cell line that carries the MYD88 L265P mutation. Our preclinical research related to the effects of IMO-8400 on human lymphoma cells with the MYD88 L265P oncogenic mutation has been accepted for presentation at a medical meeting in the second quarter of 2014. We believe that these observations provide the scientific rationale for clinical evaluation of IMO-8400 for the treatment of B-cell lymphomas with the MYD88 L265P mutation.

In December 2013, we were cleared to open enrollment for a Phase 1/2 clinical trial of IMO-8400 in patients with Waldenström s macroglobulinemia, following acceptance of our IND by the FDA. We anticipate that patient treatment in this Phase 1/2 clinical trial will begin in the first half of 2014.

We initiated clinical development of IMO-8400 in patients with DLBCL by submitting a protocol for a Phase 1/2 clinical trial to the FDA in March 2014. Patient enrollment in this trial will be based on screening for the presence of the MYD88 L265P oncogenic mutation. We expect to initiate patient treatment in this trial in the second half of 2014.

We expect that the Phase 1/2 clinical trials in patients with Waldenström s macroglobulinemia and DLBCL will provide us with the opportunity to assess the clinical activity of IMO-8400 in patients with the MYD88 L265P oncogenic mutation. The planned Phase 1/2 clinical trials are designed to evaluate safety and tolerability of IMO-8400 in dose-escalation cohorts in the Phase 1 portion of these trials, and to evaluate the potential for clinical activity in expansion cohorts at one or more dose levels in the Phase 2 portions of these trials. The Phase 1 portion of each trial is designed to include approximately 12 to 18 patients. In the Phase 2 portion of each trial, an additional 12 patients will be evaluated for safety and for signals of potential clinical activity. Each trial therefore is expected to enroll approximately 30 patients.

If we observe a therapeutic effect in either or both of these trials, we plan to meet with regulatory authorities to discuss the possibility of an accelerated clinical development and regulatory path for the applicable program. We cannot predict whether or when any of our product candidates will prove effective or safe in humans, if we will be able to participate in FDA expedited review and approval programs, including breakthrough and fast track designation, or if they will receive regulatory approval.

In parallel with our anticipated Phase 1/2 clinical trials in patients with genetically defined forms of B-cell lymphoma, we are seeking to collaborate with an experienced medical device company to develop and commercialize a companion diagnostic device. We currently anticipate entering into a companion diagnostic device collaboration during the first half of 2014.

Collaboration Program in Vaccine Adjuvants. Vaccines are composed of one or more antigens and one or more adjuvants in an appropriate formulation. The function of the adjuvants is to enhance immune recognition of the antigens and increase the ability of the immune system to make antigen-specific antibodies.

In preclinical animal models, our TLR7, TLR8, and TLR9 agonists have shown adjuvant activity when combined with various types of antigens. Preclinical studies that we conducted with our TLR7, TLR8, and TLR9 agonists and various antigens have shown improvements in several measures of antigen recognition, such as achievement of higher antibody levels, higher ratios of specific to nonspecific antibodies, and a reduction in the number of doses required to achieve effective antibody levels. Based in part on these results, we believe that agonists of TLR7, TLR8, and TLR9 have the potential to be used as adjuvants in vaccines.

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In December 2006, we entered into a research collaboration with Merck Sharp & Dohme Corp. (formerly Merck & Co., Inc.), or Merck & Co., and granted Merck & Co. an exclusive license to develop and commercialize our TLR7, TLR8, and TLR9 agonists by incorporating them in therapeutic and prophylactic vaccines being developed by Merck & Co. for cancer, infectious diseases, and Alzheimer s disease. The original term of the research collaboration was two years, and Merck & Co. extended the research collaboration for two additional years to December 2010. During the four-year research collaboration period, multiple TLR agonists were created by us and evaluated by Merck & Co. against the criteria established in the license agreement. In January 2012, in accordance with the research collaboration, Merck & Co. selected multiple novel TLR7, TLR8, and TLR9 agonists for Merck & Co. s exclusive evaluation and use as vaccine adjuvants under the current license agreement.

Gene Silencing Oligonucleotide Technology to Target RNA

We have created our GSOs to inhibit the production of disease-associated proteins by targeting RNA. We are currently undertaking an analysis of priority disease indications for development of drug candidates from our GSO technology.

Although currently used technologies to silence RNA have demonstrated the ability to inhibit the expression of disease-associated proteins, we believe that to reach their full therapeutic potential, gene silencing technologies need to achieve an improved therapeutic index with efficient systemic delivery without using a delivery technology, reduced immunotoxicity and increased potency. We have designed our GSOs to provide these attributes. For example, in preclinical studies, our GSOs have exerted gene-silencing activity in animals following systemic administration. Preclinical data also have shown that systemic delivery of GSOs targeted to the messenger RNA, or mRNA, of apolipoprotein B and proprotein convertase subtilisin/kexin type 9, which are proteins associated with cardiovascular diseases, resulted in reduced serum total cholesterol and low-density-lipoprotein cholesterol, in addition to reduced levels of the targeted mRNA and associated proteins. Additionally, in mouse models, systemic administration of GSOs showed significant specific gene-silencing activity with minimized induction of immune responses. We have published and presented at several scientific meetings preclinical data from our research on the structure and gene silencing activity of our GSOs.

We believe our GSO technology provides us with a platform from which drug candidates for multiple disease indications can be developed. We are currently undertaking an analysis of priority indications and development strategies to determine next steps in developing our GSO technology. We expect to identify the first two disease indications to be targeted in the second half of 2014, with the goal of initiating an IND-enabling development program in the first half of 2015. Based on this timeline, we anticipate that we could initiate proof-of-concept clinical trials for the first two disease indications as early as the second half of 2015. Key considerations in identifying disease indications in our GSO program are: strong evidence that the disease is caused by a specific protein; unmet medical need; clear criteria to identify a target patient population; biomarkers for early assessment of clinical proof-of-concept; a targeted therapeutic mechanism for action; and a potential for a rapid development path to approval. We also may seek to enter into collaborative alliances with pharmaceutical companies with respect to applications of our GSO technology program.

Collaborative Alliances

An element of our business strategy includes entering into collaborative alliances with corporate collaborators, primarily large pharmaceutical companies, for the development, commercialization, marketing, and distribution of our TLR antagonist candidates in broader autoimmune disease indications, such as psoriasis, lupus and arthritis. We may also seek to enter into collaborative alliances with pharmaceutical companies with respect to applications of our GSO technology program. We are currently party to a collaboration with Merck & Co.

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Merck & Co.

In December 2006, we entered into an exclusive license and research collaboration agreement with Merck & Co. to research, develop and commercialize vaccine products containing our TLR7, TLR8, and TLR9 agonists in the fields of cancer, infectious diseases and Alzheimer s disease. Under the terms of the agreement, we granted Merck & Co. worldwide exclusive rights to a number of our TLR7, TLR8, and TLR9 agonists for use in combination with Merck & Co. s therapeutic and prophylactic vaccines under development in the fields of cancer, infectious diseases, and Alzheimer s disease. There is no limit under the agreement to the number of vaccines to which Merck & Co. can apply our agonists within these fields. We also agreed with Merck & Co. to engage in a two-year research collaboration to generate novel agonists targeting TLR7 and TLR8 and incorporating both Merck & Co. s and our chemistry for use in vaccines in the defined fields. Under the terms of the agreement, Merck & Co. extended the research collaboration for two additional years to December 2010. Under the terms of the agreement:

Merck & Co. paid us a $20.0 million upfront license fee;

Merck & Co. purchased $10.0 million of our common stock at $5.50 per share;

Merck & Co. agreed to fund the research and development collaboration through its term;

Merck & Co. agreed to pay us milestone payments as follows:

up to $165.0 million if vaccines containing our TLR9 agonist compounds are successfully developed and marketed in each of the oncology, infectious disease and Alzheimer s disease fields;

up to $260.0 million if vaccines containing our TLR9 agonist compounds are successfully developed and marketed for follow-on indications in the oncology field and if vaccines containing our TLR7 or TLR8 agonists are successfully developed and marketed in each of the oncology, infectious disease, and Alzheimer s disease fields; and

if Merck & Co. develops and commercializes additional vaccines using our agonists, we would be entitled to receive additional milestone payments; and

Merck & Co. agreed to pay us mid to upper single-digit royalties on net product sales of vaccines using our TLR agonist technology that are developed and marketed, with the royalty rates being dependent on disease indication and the TLR agonist employed.

Under the agreement, Merck & Co. is obligated to pay us royalties, on a product-by-product and country-by-country basis, until the later of the expiration of the patent rights licensed to Merck & Co. and the expiration of regulatory-based exclusivity for the vaccine product. If the patent rights and regulatory-based exclusivity expire in a particular country before the 10th anniversary of the product s first commercial sale in such country, Merck & Co. s obligation to pay us royalties will continue at a reduced royalty rate until such anniversary, except that Merck & Co. s royalty obligation will terminate upon the achievement of a specified market share in such country by a competing vaccine containing an agonist targeting the same toll-like receptor as that targeted by the agonist in the Merck & Co. vaccine. In addition, the applicable royalties may be reduced if Merck & Co. is required to pay royalties to third parties for licenses to intellectual property rights, which royalties exceed a specified threshold. Merck & Co. s royalty and milestone obligations may also be reduced if Merck & Co. terminates the agreement based on specified uncured material breaches by us.

Merck & Co. may terminate the collaborative alliance without cause upon 90 days written notice to us. Either party may terminate the collaborative alliance upon the other party s filing or institution of bankruptcy, reorganization, liquidation or receivership proceedings, or for a material breach if such breach is not cured within 60 days after delivery of written notice.

In January 2012, in accordance with the agreement, Merck & Co. selected multiple novel TLR7, TLR8, and TLR9 agonists for Merck & Co. s exclusive evaluation and use as vaccine adjuvants.

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Licensing Agreements

We have not licensed any rights to our TLR technology to any third party other than in connection with the strategic alliance which we have entered into with Merck & Co., and have not in-licensed any technology for our TLR program. Similarly, we have not licensed any rights to our GSO technology to any third party. We have licensed specified rights related to antisense technology to certain parties. We also have in-licensed certain rights related to antisense technology.

Licensing Agreement with Isis. In 2001 we entered into an agreement with Isis Pharmaceuticals, Inc., or Isis, under which we granted Isis a license (with the right to sublicense) to our antisense chemistry and delivery patents and patent applications, but we retained the right to use these patents and applications in our own drug discovery and development efforts and in collaborations with third parties. Isis paid us $15.0 million in cash and issued 857,143 shares of its common stock having an aggregate fair market value on the dates on which title to the shares was received of $17.3 million and agreed to pay us a mid double-digit percentage of specified sublicense income it receives from some types of sublicenses of our patents and patent applications. As of December 31, 2013, we have received $0.3 million in sublicense income from Isis. Also under the agreement, we licensed from Isis specified antisense patents and patent applications, principally Isis suite of RNase H patents and patent applications. We paid to Isis $0.7 million and issued 1,005,499 shares of our common stock having a fair market value of approximately $1.2 million on the date of issuance for this license and are obligated to pay Isis an annual patent maintenance fee and low single-digit royalties on net sales of antisense products sold that are covered by Isis s patent rights. We have the right to use these patents and patent applications in our drug discovery and development efforts and in some types of third-party collaborations. As of December 31, 2013, we have only paid Isis annual maintenance fees and have not paid any royalties. The agreement may be terminated for an uncured material breach by either party. The licenses granted under the Isis agreement terminate upon the last to expire of the patents and patent applications licensed under the agreement. We may terminate at any time the sublicense by Isis to us of the patents and patent applications.

In addition, we are party to two other license agreements involving the license of our antisense patents and patent applications for antisense chemistry and delivery and for specific gene targets, under which we generally are entitled to receive license fees, sublicensing income, research payments, payments upon achievement of developmental milestones, and royalties on product sales. As of December 31, 2013, we had received a total of $1.5 million under these agreements.

In-licenses. Our principal in-license related to antisense technology is with University of Massachusetts Medical Center for antisense chemistry and for certain gene targets. Under the terms of our license agreement with University of Massachusetts Medical Center, we are the worldwide, exclusive licensee under a number of U.S. issued patents and various patent applications owned by University of Massachusetts Medical Center relating to the chemistry of antisense oligonucleotides and their use. Many of these patents and patent applications have corresponding applications on file or corresponding patents in other major industrial countries. The patents licensed to us by University of Massachusetts Medical Center, none of which are material to our current development programs, expire in 2014. This license expires upon the expiration of the last to expire of the patents covered by the license. Under the agreement, we have agreed to pay a low single-digit royalty on net product sales, a low double-digit percentage of any sublicense license income we receive, and a small annual license maintenance fee through 2014. Since 1999, we have paid approximately $1.8 million to University of Massachusetts Medical Center under this license agreement.

Additionally, we have entered into five other royalty-bearing license agreements under which we have acquired rights to antisense related patents, patent applications, and technology. Under all of these in-licenses, we are obligated to pay low to mid single-digit royalties on our net sales of products or processes covered by a valid claim of a licensed patent or patent application. Under some of these in-licenses, we are required to pay a low double-digit percentage of any sublicense income. All of our in-licenses impose various commercialization, sublicensing, insurance, and other obligations on us, and our failure to comply with these requirements could result in termination of the in-licenses.

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Academic and Research Collaborations

We have entered into research collaborations with scientists at leading academic research institutions. These research collaborations allow us to augment our internal research capabilities and obtain access to specialized knowledge and expertise. In general, our research collaborations may require us to supply compounds and pay various amounts to support the research. Under these research agreements, if a collaborator, solely or jointly with us, creates any invention, we may own exclusively such invention, have an automatic paid-up, royalty-free non-exclusive license or have an option to negotiate an exclusive, worldwide, royalty-bearing license to such invention. Inventions developed solely by our scientists in connection with research collaborations are owned exclusively by us. These collaborative agreements are non-exclusive and may be terminated with limited notice.

Research and Development Expenses

For the years ended December 31, 2013, 2012 and 2011, we spent approximately $10.5 million, $13.7 million, and $18.0 million on research and development activities.

Patents, Proprietary Rights and Trade Secrets

Our success depends in part on our ability to obtain and maintain proprietary protection for our drug candidates, technology and know-how, to operate without infringing the proprietary rights of others and to prevent others from infringing our proprietary rights. We use a variety of methods to seek to protect our proprietary position, including filing U.S. and foreign patent applications related to our proprietary technology, inventions and improvements that are important to the development of our business. We also rely on trade secrets, know-how, continuing technological innovation, and in-licensing opportunities to develop and maintain our proprietary position.

We have devoted and continue to devote a substantial amount of our resources into establishing intellectual property protection for:

Novel chemical entities that function as agonists of TLR3, TLR7, TLR8 or TLR9;

Novel chemical entities that function as antagonists of TLR7, TLR8 or TLR9;

Use of our novel chemical entities and chemical modifications to treat and prevent a variety of diseases; and

Composition and use of our GSO compounds to treat and prevent a variety of diseases.

As of February 15, 2014, we owned more than 45 U.S. patents and patent applications and more than 80 patents and patent applications throughout the rest of the world for our TLR-targeted immune modulation technologies. These patents and patent applications include novel chemical compositions of matter and methods of use of our IMO compounds, including IMO-3100, IMO-8400, IMO-9200, and IMO-2055. As of February 15, 2014, all of our intellectual property covering immune modulatory compositions and methods of their use is based on discoveries made solely by us. These patents expire at various dates ranging from 2017 to 2031. With respect to IMO-3100, we have issued U.S. patents that cover the chemical composition of matter of IMO-3100 and methods of its use that will expire at the earliest in 2026. With respect to IMO-8400, we have an issued U.S. patent that covers the chemical composition of matter of IMO-8400 and methods of its use that will expire at the earliest in 2031. With respect to IMO-9200, we have a U.S. patent application that covers the chemical composition for IMO-9200 and methods of its use, which, if issued, would expire at the earliest in 2034.

As of February 15, 2014, we owned one issued U.S. patent, two U.S. patent applications and six foreign patent applications for our GSO compounds and methods of their use. The issued patent covering our GSO technologies would expire at the earliest in 2030.

In addition to our TLR-targeted and GSO patent portfolios, we are the owner or hold licenses of patents and patent applications related to antisense technology. As of February 15, 2014, our antisense patent portfolio

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included more than 60 U.S. patents, one U.S. patent application and more than 60 patents throughout the rest of the world. These antisense patents and patent applications include novel compositions of matter, the use of these compositions for various genes, sequences and therapeutic targets, and oral and other routes of administration. Some of the patents and patent applications in our antisense portfolio were in-licensed. These in-licensed patents expire at various dates ranging from 2014 to 2021.

Because patent applications in the United States and many foreign jurisdictions are typically not published until 18 months after filing, or in some cases not at all, and because publications of discoveries in the scientific literature often lag behind actual discoveries, neither we nor our licensors can be certain that we or they were the first to make the inventions claimed in issued patents or pending patent applications, or that we or they were the first to file for protection of the inventions set forth in these patent applications.

Litigation may be necessary to defend against or assert claims of infringement, to enforce patents issued to us, to protect trade secrets or know-how owned by us, or to determine the scope and validity of the proprietary rights of others or to determine the appropriate term for an issued patent. In addition, the United States Patent and Trademark Office, or USPTO, may declare interference proceedings to determine the priority of inventions with respect to our patent applications or reexamination or reissue proceedings to determine if the scope of a patent should be narrowed. Litigation or any of these other proceedings could result in substantial costs to and diversion of effort by us, and could have a material adverse effect on our business, financial condition and results of operations. These efforts by us may not be successful.

We may rely, in some circumstances, on trade secrets and confidentiality agreements to protect our technology. Although trade secrets are difficult to protect, wherever possible, we use confidential disclosure agreements to protect the proprietary nature of our technology. We regularly implement confidentiality agreements with our employees, consultants, scientific advisors, and other contractors and collaborators. However, there can be no assurance that these agreements will not be breached, that we will have adequate remedies for any breach, or that our trade secrets and/or proprietary information will not otherwise become known or be independently discovered by competitors. To the extent that our employees, consultants or contractors use intellectual property owned by others in their work for us, disputes may also arise as to the rights in related or resulting know-how and inventions.

Government Regulation

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 regulatory approvals in the United States and in foreign countries and jurisdictions, along with subsequent compliance with applicable statutes and regulations and other regulatory authorities, require the expenditure of substantial time and financial resources.

Review and Approval of Drugs in the United States

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and associated implementing regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations requires the expenditure of substantial time and financial resources. Failure to comply with the applicable U.S. requirements 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 DOJ, or other governmental entities.

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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 in the United States;
- 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;
- review of the product 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;
- payment of user fees and securing FDA approval of the NDA; and
- compliance with any post-approval requirements, including Risk Evaluation and Mitigation Strategies, or REMS, where applicable or appropriate, and post-approval studies required by the FDA.

Preclinical Studies

Preclinical studies include laboratory evaluation of the purity and stability of the manufactured drug substance or active pharmaceutical ingredient and the formulated drug or drug product, as well as *in vitro* and animal studies to assess the safety and activity of the drug for initial testing in humans and to establish a rationale for therapeutic use. The conduct of preclinical studies is subject to federal regulations and requirements, including GLP regulations. The results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical studies, among other things, are submitted to the FDA as part of an IND. Additional preclinical testing, such as animal tests of reproductive adverse events and carcinogenicity, may continue after the IND is submitted.

Human Clinical Studies 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 objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to a proposed clinical trial and places the trial on clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin.

In addition, 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 for public dissemination on their ClinicalTrials.gov website.

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

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

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

Phase 3: The drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well-controlled clinical trials to generate enough data to statistically evaluate the efficacy and safety of the product for approval, to establish the overall risk-benefit profile of the product, and to provide adequate information for the labeling of the product.

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. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB s requirements or if the drug has been associated with unexpected serious harm to patients. The FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the clinical data submitted.

Section 505(b)(2) NDAs

NDAs for most new drug products are based on two full clinical studies which must contain substantial evidence of the safety and efficacy of the proposed new product. These applications are submitted under Section 505(b)(1) of the FDCA. The FDA is, however, authorized to approve an alternative type of NDA under Section 505(b)(2) of the FDCA. This type of application allows the applicant to rely, in part, on the FDA s previous findings of safety and efficacy for a similar product, or published literature. Specifically, Section 505(b)(2) applies to NDAs for a drug for which the investigations made to show whether or not the drug is safe for use and effective in use and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

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

Submission of an NDA to the FDA

Assuming successful completion of required clinical testing and other requirements, the results of the preclinical and clinical studies, together with detailed information relating to the product s chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the drug product for one or more indications. Under federal law, the submission of

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most NDAs is additionally subject to an application user fee, currently exceeding $2.1 million, and the sponsor of an approved NDA is also subject to annual product and establishment user fees, currently exceeding $104,000 per product and $554,000 per establishment. These fees are typically increased annually.

The FDA conducts a preliminary review of an NDA within 60 days of its receipt and informs 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. Most such applications are meant to be reviewed within ten months from the date of filing, and most applications for priority review products are meant to be reviewed within six months of filing. The review process 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 cover all facilities associated with an NDA submission, including drug component manufacturing (such as 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.

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

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

Fast Track, Breakthrough Therapy and Priority Review Designations

The FDA is authorized to designate certain products for expedited review if they are intended to address an unmet medical need in the treatment of a serious or life-threatening disease or condition. These programs are 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 drugs, 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 NDA before the application is complete. This rolling review may be available if the FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a fast track product may

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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 NDA 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 drugs, 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 drug 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 drug 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 drug 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 to six months.

Accelerated Approval Pathway

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

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

The accelerated approval pathway is most often used in settings in which the course of a disease is long and an extended period of time is required to measure the intended clinical benefit of a drug, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly. Thus, accelerated approval has been used extensively

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in the development and approval of drugs for treatment of a variety of cancers in which the goal of therapy is generally to improve survival or decrease morbidity and the duration of the typical disease course requires lengthy and sometimes large trials to demonstrate a clinical or survival benefit.

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

The FDA s Decision on an NDA

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

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

Post-Approval Requirements

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

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

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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, 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 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, which regulates the distribution of drugs and drug samples at the federal level, and sets minimum standards for the registration and regulation of drug distributors by the states. Both the PDMA and state laws limit the distribution of prescription pharmaceutical product samples and impose requirements to ensure accountability in distribution.

Abbreviated New Drug Applications for Generic Drugs

With passage of the Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Amendments, which amended the FDCA, Congress authorized the FDA to approve generic drugs that are the same as drugs previously approved by the FDA under the NDA provisions of the statute. To obtain approval of a generic drug, an applicant must submit an abbreviated new drug application, or ANDA, to the agency. In support of such applications, a generic manufacturer may rely on the preclinical and clinical testing previously conducted for a drug product previously approved under an NDA, known as the reference listed drug, or RLD.

Specifically, in order for an ANDA to be approved, the FDA must find that the generic version is identical to the RLD with respect to the active ingredients, the route of administration, the dosage form, and the strength of the drug. 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

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exclusivity for a new drug containing a new chemical entity. 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, in which case the applicant may submit its application four years following the original product approval. The FDCA also provides for a period of three years of exclusivity if the NDA includes reports of one or more new clinical investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the applicant and are essential to the approval of the application. This three-year exclusivity period often protects changes to a previously approved drug product, such as a new dosage form, route of administration, combination or indication.

Hatch-Waxman Patent Certification and the 30-Month Stay

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

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

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

A certification that the new product will not infringe the already approved product s listed patents or that such patents are invalid or unenforceable is called a Paragraph IV certification. If the applicant does not challenge the listed patents or indicates that it is not seeking approval of a patented method of use, the ANDA 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 ANDA applicant is not seeking approval).

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

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

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Pediatric Studies and Exclusivity

Under the Pediatric Research Equity Act of 2003, an NDA or supplement thereto must contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. With enactment of the 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 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 the FDASIA. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation.

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

Orphan Designation and Exclusivity

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

If a product with orphan status receives the first FDA approval for the disease or condition for which it has such designation, the product generally will receive orphan product exclusivity. Orphan product exclusivity means that the FDA may not approve any other applications for the same product for the same indication for seven years, except in certain limited circumstances. Competitors may receive approval of different products for the indication for which the orphan product has exclusivity and may obtain approval for the same product but for a different indication. If a drug or drug product designated as an orphan product ultimately receives marketing approval for an indication broader than what was designated in its orphan product application, it may not be entitled to exclusivity.

Patent Term Restoration and Extension

A patent claiming a new drug product may be eligible for a limited patent term extension under the Hatch-Waxman Amendments, which permits a patent restoration of up to five years for patent term lost during product development and the FDA regulatory review. The restoration period granted is typically one-half the time

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

Review and Approval of Drug Products in the European Union

In order to market any product outside of the United States, a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of drug products. Whether or not it obtains FDA approval for a product, the company would need to obtain the necessary approvals by the comparable foreign regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions. The approval process ultimately varies between countries and jurisdictions and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries and jurisdictions might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country or jurisdiction does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country or jurisdiction may negatively impact the regulatory process in others.

Pursuant to the European Clinical Trials Directive, a system for the approval of clinical trials in the European Union has been implemented through national legislation of the member states. Under this system, an applicant must obtain approval from the competent national authority of a European Union member state in which the clinical trial is to be conducted. Furthermore, the applicant may only start a clinical trial after a competent ethics committee has issued a favorable opinion. Clinical trial application must be accompanied by an investigational medicinal product dossier with supporting information prescribed by the European Clinical Trials Directive and corresponding national laws of the member states and further detailed in applicable guidance documents.

To obtain marketing approval of a drug under European Union regulatory systems, an applicant must submit a marketing authorization application, or MAA, either under a centralized or decentralized procedure.

The centralized procedure provides for the grant of a single marketing authorization by the European Commission that is valid for all European Union member states. The centralized procedure is compulsory for specific products, including for medicines produced by certain biotechnological processes, products designated as orphan medicinal products, advanced therapy products and products with a new active substance indicated for the treatment of certain diseases. For products with a new active substance indicated for the treatment of other diseases and products that are highly innovative or for which a centralized process is in the interest of patients, the centralized procedure may be optional.

Under the centralized procedure, the Committee for Medicinal Products for Human Use, or the CHMP, established at the European Medicines Agency, or EMA, is responsible for conducting the initial assessment of a drug. The CHMP is also responsible for several post-authorization and maintenance activities, such as the assessment of modifications or extensions to an existing marketing authorization. Under the centralized procedure in the European Union, the maximum timeframe for the evaluation of an MAA is 210 days, excluding clock stops, when additional information or written or oral explanation is to be provided by the applicant in response to questions of the CHMP. Accelerated evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation. In this circumstance, the EMA ensures that the opinion of the CHMP is given within 150 days.

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The decentralized procedure is available to applicants who wish to market a product in various European Union member states where such product has not received marketing approval in any European Union member states before. The decentralized procedure provides for approval by one or more other, or concerned, member states of an assessment of an application performed by one member state designated by the applicant, known as the reference member state. Under this procedure, an applicant submits an application based on identical dossiers and related materials, including a draft summary of product characteristics, and draft labeling and package leaflet, to the reference member state and concerned member states. The reference member state prepares a draft assessment report and drafts of the related materials within 210 days after receipt of a valid application. Within 90 days of receiving the reference member state s assessment report and related materials, each concerned member state must decide whether to approve the assessment report and related materials.

If a member state cannot approve the assessment report and related materials on the grounds of potential serious risk to public health, the disputed points are subject to a dispute resolution mechanism and may eventually be referred to the European Commission, whose decision is binding on all member states.

Pharmaceutical Coverage, Pricing and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of products approved by the FDA and other government authorities. Sales of products will depend, in part, on the extent to which the costs of the products will be covered by third-party payors, including government health programs in the United States such as Medicare and Medicaid, commercial health insurers and managed care organizations. 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 may limit coverage to specific products on an approved list, or 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 regulatory approvals. A payor s decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Third-party reimbursement may not be sufficient to maintain price levels high enough to realize an appropriate return on investment in product development.

In the European Union, pricing and reimbursement schemes vary widely from country to country. Some countries provide that drug 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. For example, the European Union provides options for its member states to restrict the range of drug 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 drug product or may instead adopt a system of direct or indirect controls on the profitability of the company placing the drug product on the market. Other member states allow companies to fix their own prices for drug products, but monitor and control company profits. 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. In addition, in some countries, cross-border imports from low-priced markets exert competitive pressure that may reduce pricing within a country. Any country that has price controls or reimbursement limitations for drug products may not allow favorable reimbursement and pricing arrangements.

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Healthcare Law and Regulation

Healthcare providers, physicians and third-party payors play a primary role in the recommendation and prescription of drug products that are granted marketing approval. Arrangements with third-party payors and customers are subject to broadly applicable fraud and abuse and other healthcare laws and regulations. Such restrictions under applicable federal and state healthcare laws and regulations, include the following:

- the federal healthcare Anti-Kickback Statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward 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 False Claims Act imposes civil penalties, and provides for civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent or making a false 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, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;

- the federal false statements statute 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 under the Health Care Reform Law will require manufacturers of drugs, devices, drugs and medical supplies to report to the Department of Health and Human Services information related to payments and other transfers of value to physicians and teaching hospitals and physician ownership and investment interests; and

- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, may apply to sales or marketing arrangements and claims involving healthcare items or services 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.

Manufacturing

We do not currently own or operate manufacturing facilities for the production of clinical or commercial quantities of any of our drug candidates. We currently rely and expect to continue to rely on other companies for the manufacture of our drug candidates for preclinical and clinical development. We currently source our bulk drug manufacturing requirements from a limited number of contract manufacturers through the issuance of work orders on an as-needed basis. We depend and will continue to depend on our contract manufacturers to manufacture our drug candidates in accordance with cGMP regulations for use in clinical trials. We will ultimately depend on contract manufacturers for the manufacture of our products for commercial sale. Contract manufacturers are subject to extensive governmental regulation.

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Under our collaborative agreement with Merck & Co., Merck & Co. is responsible for manufacturing the drug candidates.

Competition

We are developing our TLR-targeted drug candidates for use in the treatment of autoimmune diseases and certain genetically defined forms of B-cell lymphomas and for use as vaccine adjuvants. We have one drug candidate, IMO-8400, in clinical development in our autoimmune disease program and for the treatment of patients with certain genetically defined forms of B-cell lymphomas, including Waldenström s macroglobulinemia and DLBCL with the MYD88 L265P oncogenic mutation. We are also collaborating with Merck & Co. for the use of agonists of TLR7, TLR8 and TLR9 as vaccine adjuvants for cancer, infectious diseases and Alzheimer s disease. Finally, we may seek to enter into collaborative alliances with pharmaceutical companies to advance our TLR antagonist candidates in broader autoimmune disease indications, such as psoriasis, lupus and arthritis. For all of these disease areas, there are many other companies, public and private, that are actively engaged in discovery, development, and commercializing products and technologies that may compete with our drug candidates and programs, including TLR-targeted compounds as well as non-TLR-targeted therapeutics.

Our principal competitor developing TLR-targeted compounds for autoimmune diseases is Dynavax Technologies Corporation, or Dynavax, with its collaborator, GlaxoSmithKline plc., or GlaxoSmithKline. Merck & Co. s vaccines using our TLR7, TLR8 or TLR9 agonists as adjuvants may compete with vaccines using TLR agonists as adjuvants being developed or marketed by GlaxoSmithKline, Novartis Pharmaceuticals, Ltd., or Novartis, Dynavax, VaxInnate, Inc., Intercell AG, and Cytos Biotechnology AG.

We are developing drug candidates for the treatment of moderate to severe plaque psoriasis. There are a number of well-known immune suppressors and biologics that are currently being widely used for the treatment of moderate to severe plaque psoriasis, including methotrexate and cyclosporine, which are both immune suppressors, and biologics like Enbrel, which is marketed by Amgen Inc., or Amgen, Pfizer, Inc., or Pfizer, and Takeda Pharmaceutical Company Limited; Remicade, which is marketed by Janssen Biotech, Merck & Co., and Mitsubishi Tanabe Pharma; Humira, which is marketed by Abbott Laboratories; and Stelara, which is marketed by Janssen Biotech. In addition to existing treatments, we are also aware of additional compounds for the treatment of moderate to severe plaque psoriasis that are currently in late stage development, including apremilast, which is being developed by Celgene Corporation; to facitinib, which is being developed by Pfizer; secukinumab, which is being developed by Novartis; ixekizumab, which is being developed by Eli Lilly and Company; and brodalumab, which is being developed by Amgen, AstraZeneca PLC, and Kyowa Hakko Kirin Co., Ltd.

We are also developing IMO-8400 for the treatment of certain genetically defined forms of B-cell lymphoma. There are currently no drugs specifically approved for the treatment of Waldenström s macroglobulinemia or DLBCL with the MYD88 L265P oncogenic mutation. Currently, patients with any form of non-Hodgkin lymphoma are most often treated with monoclonal antibody rituximab and/or with one or more chemotherapeutic agents. Rituximab is co-marketed in the United States by Biogen Idec and Genentech and Hoffmann-La Roche and Chugai Pharmaceuticals in territories outside the United States. We are aware of additional compounds in development for the treatment of genetically defined forms of B-cell lymphoma, including ibrutinib, which is being developed by Pharmacyclics, Inc. and Janssen Research & Development, LLC, and an inhibitor of interleukin-1 receptor-associated kinase 4, which is being developed by Nimbus Discovery, Inc.

In addition, we are developing GSOs that we have created using our proprietary technology, to inhibit the production of disease-associated proteins by targeting RNA. We also face competition from other companies working to develop novel drugs using technologies that may compete with our GSO technology. We are aware of multiple companies that are developing technologies that use oligonucleotide-based compounds to inhibit the production of disease associated proteins. These technologies include, but are not limited to, antisense

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technology as well as RNAi. In the field of antisense technologies, we compete with multiple companies, including Isis and its partners. Isis is currently marketing an antisense drug, Kynamro®, and has several antisense product candidates in clinical trials. In the field of RNAi, our primary competition is with Alnylam Pharmaceuticals, Inc., or Alnylam, and its partners. Alnylam is currently developing multiple RNAi-based technologies and has several product candidates in clinical trials. Any of the competing companies may develop gene-silencing technologies more rapidly and more effectively than us, and antisense technology and RNAi may become the preferred technology for drugs that target RNA in order to inhibit the production of disease-associated proteins.

Some of these potentially competitive products have been in development or commercialized for years, in some cases by large, well established pharmaceutical companies. Many of the marketed products have been accepted by the medical community, patients, and third-party payors. Our ability to compete may be affected by the previous adoption of such products by the medical community, patients, and third-party payors. Additionally, in some instances, insurers and other third-party payors seek to encourage the use of generic products, which makes branded products, such as our drug candidates, potentially less attractive, from a cost perspective, to buyers.

We recognize that other companies, including large pharmaceutical companies, may be developing or have plans to develop products and technologies that may compete with ours. Many of our competitors have substantially greater financial, technical, and human resources than we have. In addition, many of our competitors have significantly greater experience than we have in undertaking preclinical studies and human clinical trials of new pharmaceutical products, obtaining FDA and other regulatory approvals of products for use in health care and manufacturing, and marketing and selling approved products. Our competitors may discover, develop or commercialize products or other novel technologies that are more effective, safer or less costly than any that we are developing. Our competitors may also obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours.

We anticipate that the competition with our products and technologies will be based on a number of factors including product efficacy, safety, availability, and price. The timing of market introduction of our products and competitive products will also affect competition among products. We expect the relative speed with which we can develop products, complete the clinical trials and approval processes, and supply commercial quantities of the products to the market to be important competitive factors. Our competitive position will also depend upon our ability to attract and retain qualified personnel, to obtain patent protection or otherwise develop proprietary products or processes, protect our intellectual property, and to secure sufficient capital resources for the period between technological conception and commercial sales.

Employees

As of February 15, 2014, we employed 18 individuals, nine of whom are engaged in research and development and 10 of whom hold a Ph.D., M.D., or equivalent degree. None of our employees are covered by a collective bargaining agreement, and we consider relations with our employees to be good.

Corporate Information

We were incorporated in Delaware in 1989 and have our corporate headquarters at 167 Sidney Street, Cambridge, Massachusetts.

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Information Available on the Internet

Our internet address is www.iderapharma.com. The contents of our website are not part of this Annual Report on Form 10-K and our internet address is included in this document as an inactive textual reference. We make available free of charge through our web site our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and amendments to these reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act, as soon as reasonably practicable after we electronically file or furnish such materials to the Securities and Exchange Commission, or the SEC.

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Item 1A. ***RISK FACTORS.***

RISK FACTORS

Investing in our securities involves a high degree of risk. You should carefully consider the risks and uncertainties described below in addition to the other information included or incorporated by reference in this Annual Report on Form 10-K before purchasing our common stock. Our business, financial condition and results of operations could be materially and adversely affected by any of these risks or uncertainties. In that case, the market price of our common stock could decline, and you may lose all or part of your investment in our securities.

Risks Relating to Our Financial Results and Need for Financing

We will need additional financing, which may be difficult to obtain. Our failure to obtain necessary financing or doing so on unattractive terms could result in the termination of our operations and the sale and license of our assets or otherwise adversely affect our research and development programs and other operations.

We had cash, cash equivalents and investments of approximately $35.6 million at December 31, 2013.We believe that our existing cash, cash equivalents and investments, including the estimated net proceeds of $37.2 million from the follow-on public offering that we closed in February 2014, will be sufficient to fund our operations into the second half of 2016. Specifically, we believe that our available funds will be sufficient to enable us to:

- complete our ongoing Phase 2 clinical trial of IMO-8400 in patients with psoriasis, our planned Phase 1/2 clinical trial in patients with Waldenström s macroglobulinemia and our planned Phase 1/2 clinical trial in patients with DLBCL and the MYD88 L265P oncogenic mutation;
- submit an IND to the FDA for IMO-9200 and conduct a Phase 1 clinical trial of IMO-9200 in healthy subjects;
- conduct a Phase 1/2 clinical trial of IMO-8400 in patients with polymyositis or dermatomyositis as the first two orphan indications that we have selected for further development in our autoimmune disease program;
- conduct disease model studies and an IND-enabling development program in our GSO program; and
- conduct a Phase 1 proof-of-concept clinical trial in each of the first two disease indications selected for further development in our GSO program.

We will need additional funds in order to conduct further clinical development of IMO-8400 or IMO-9200, or to conduct any further development of our GSO technology and our other drug candidates or technologies.

We expect that we will require substantial additional funds to conduct additional research and development, including preclinical testing and clinical trials of our drug candidates, and to fund our operations. We may seek additional funding through collaborations, the sale or license of assets or financings of equity or debt securities. We believe that the key factors that will affect our ability to obtain funding are:

- the results of our clinical and preclinical development in our autoimmune disease and genetically defined forms of B-cell lymphoma programs and our GSO program and our ability to advance our product candidates and GSO technology on the timelines anticipated;
- the cost, timing, and outcome of regulatory reviews;

competitive and potentially competitive products and technologies and investors receptivity to our drug candidates and the technology underlying them in light of competitive products and technologies;

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the receptivity of the capital markets to financings by biotechnology companies generally and companies with drug candidates and technologies such as ours specifically; and

our ability to enter into additional collaborations with biotechnology and pharmaceutical companies and the success of such collaborations.

In addition, increases in expenses or delays in clinical development may adversely impact our cash position and require additional funds or further cost reductions.

Additional financing may not be available to us when we need it or may not be available to us on favorable or acceptable terms or at all. We could be required to seek funds through collaborative alliances or through other means that may require us to relinquish rights to some of our technologies, drug candidates or drugs that we would otherwise pursue on our own. In addition, if we raise additional funds by issuing equity securities, our then existing stockholders will experience dilution. The terms of any financing may adversely affect the holdings or the rights of existing stockholders. An equity financing that involves existing stockholders may cause a concentration of ownership. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends, and are likely to include rights that are senior to the holders of our common stock. Any additional debt financing or equity that we raise may contain terms, such as liquidation and other preferences, or liens or other restrictions on our assets, which are not favorable to us or our stockholders.

If we are unable to obtain adequate funding on a timely basis or at all, we will be required to terminate, modify or delay preclinical or clinical trials of one or more of our drug candidates, significantly curtail or terminate discovery or development programs for new drug candidates or relinquish rights to portions of our technology, drug candidates and/or products.

We have incurred substantial losses and expect to continue to incur losses. We will not be successful unless we reverse this trend.

We have incurred losses in every year since our inception, except for 2002, 2008, and 2009 when our recognition of revenues under license and collaboration agreements resulted in our reporting net income for those years. As of December 31, 2013, we had an accumulated deficit of $412.9 million. Since January 1, 2001, we have primarily been involved in the development of our TLR pipeline. From January 1, 2001 to December 31, 2013, we incurred losses of $152.7 million. We incurred losses of $260.2 million prior to December 31, 2000, during which time we were primarily involved in the development of non-TLR-targeted antisense technology. These losses, among other things, have had and will continue to have an adverse effect on our stockholders equity, total assets, and working capital.

We have never had any products of our own available for commercial sale and have received no revenues from the sale of drugs. As of December 31, 2013, almost all of our revenues have been from collaborative and license agreements. We have devoted substantially all of our efforts to research and development, including clinical trials, and have not completed development of any drug candidates. Because of the numerous risks and uncertainties associated with developing drugs, we are unable to predict the extent of any future losses, whether or when any of our drug candidates will become commercially available, or when we will become profitable, if at all. We expect to incur substantial operating losses in future periods.

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Risks Relating to Our Business, Strategy and Industry

We are depending heavily on the development of TLR-targeted drug candidates for the treatment of autoimmune diseases and certain genetically defined forms of B-cell lymphomas and on the development of our GSO technology. If we terminate the development of any of our programs or any of our drug candidates in such programs, are unable to successfully develop and commercialize any of our drug candidates, or experience significant delays in doing so, our business may be materially harmed.

We have invested a significant portion of our time and financial resources in the development of TLR-targeted clinical stage lead drug candidates as part of our autoimmune disease program. In the future, we intend to invest a significant portion of our time and financial resources in the development of our TLR- targeted candidates, including IMO-8400 and IMO-9200 for the treatment of certain genetically defined forms of B-cell lymphoma and for orphan autoimmune diseases. We also plan to invest substantial time and resources to further advance the development of our GSOs under our GSO program. For instance:

- we are planning to initiate patient treatment in a Phase 1/2 clinical trial of IMO-8400 in patients with Waldenström s macroglobulinemia in the first half of 2014 and in a Phase 1/2 clinical trial of IMO-8400 in patients with DLBCL and the MYD88 L265P oncogenic mutation in the second half of 2014;

- we initiated IND-enabling studies of IMO-9200 and, pending the results from these studies, expect to submit an IND for IMO-9200 and initiate a Phase 1 clinical trial of IMO-9200 in healthy subjects in the second half of 2014;

- we are planning to initiate patient treatment in a Phase 1/2 clinical trial of IMO-8400 in patients with polymyositis or dermatomyositis in the second half of 2014; and

- we are planning to initiate a Phase 1 proof-of-concept clinical trial in each of the first two disease indications selected for further development in our GSO program in the second half of 2015.

We anticipate that our ability to generate product revenues will depend heavily on the successful development and commercialization of our drug candidates in our autoimmune disease and our genetically defined forms of B-cell lymphoma programs, and the successful identification, development and commercialization of drug candidates in our GSO program.

Our ability to generate product revenues under our collaboration with Merck & Co., and under any other collaboration that we enter into with respect to our other programs, will depend on the development and commercialization of the drug candidates being developed.

Our efforts, and the efforts of Merck & Co., to develop and commercialize these compounds are at an early stage and are subject to many challenges. We have experienced setbacks with respect to our programs for IMO-3100, IMO-2125, and IMO-2055, including:

- During the fourth quarter of 2010, we commenced additional nonclinical studies of IMO-3100 in light of some reversible immune responses that were observed in the 13-week nonclinical toxicology studies and that were inconsistent with observations made in our other nonclinical studies of IMO-3100. In June 2011, we submitted a Phase 2 protocol to the FDA to conduct a 12-week clinical trial of IMO-3100 in patients with psoriasis. In July 2011, the FDA placed a clinical hold on the protocol that we had submitted. In October 2011, we submitted to FDA a new Phase 2 protocol to evaluate IMO-3100 in adult patients with moderate to severe plaque psoriasis, over a four-week treatment period. In December 2011, the FDA removed the clinical hold. We subsequently initiated in the second quarter of 2012 the four-week Phase 2 clinical trial that we completed in the fourth quarter of 2012. We cannot be certain that the FDA will allow us to conduct further clinical trials of IMO-3100 in patients with psoriasis for treatment periods of more than four weeks or at all without additional clinical or preclinical data.

In April 2011, we chose to delay initiation of our planned 12-week Phase 2 randomized clinical trial of IMO-2125 plus ribavirin in treatment-naïve, genotype 1 hepatitis C virus, or HCV, patients based on

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preliminary observations in an ongoing 26-week chronic nonclinical toxicology study of IMO-2125 in rodents. We subsequently completed a 39-week chronic nonclinical toxicology study of IMO-2125 in non-human primates in which there were no similar observations. During the third quarter of 2011, we re-assessed and prioritized our drug development programs, and determined to discontinue further investment of internal resources on the development of IMO-2125 for the treatment of HCV.

In July 2011, Merck KGaA, Darmstadt, Germany, or Merck KGaA, informed us that, based on increased incidence of neutropenia and electrolyte imbalances reported in its Phase 1 trial of IMO-2055 in combination with cisplatin/5-FU and cetuximab in patients with first-line squamous cell carcinoma of the head and neck, or SCCHN, and subsequent re-evaluation of its clinical development program, Merck KGaA had determined that it would not conduct further clinical development of IMO-2055. In November 2011, as part of an agreed-upon termination of our collaboration with Merck KGaA, we regained global rights to IMO-2055 and our other TLR9 agonists, including preclinical lead drug candidates selected for further evaluation under the collaboration, for the treatment of cancer. In May 2012, we announced that in the Phase 2 trial of IMO-2055 in combination with cetuximab in patients with second-line SCCHN, the combination of IMO-2055 and cetuximab did not meet the primary endpoint of the trial.

We may seek to enter into collaborative alliances with pharmaceutical companies to advance our TLR antagonist candidates in broader autoimmune disease indications, such as psoriasis, lupus and arthritis. We may seek to enter into collaborative alliances with pharmaceutical companies with respect to applications of our GSO technology program. Our setbacks with respect to our programs for IMO-3100, IMO-2125, and IMO-2055 could negatively impact our ability to license any of such compounds to a third party.

Our ability to successfully develop and commercialize these drug candidates, or other potential candidates, will depend on our ability to overcome these recent challenges and on several factors, including the following:

- the drug candidates demonstrating activity in clinical trials;
- the drug candidates demonstrating an acceptable safety profile in nonclinical toxicology studies and during clinical trials;
- timely enrollment in clinical trials of IMO-8400 and other drug candidates, which may be slower than anticipated, potentially resulting in significant delays;
- satisfying conditions imposed on us and/or our collaborators by the FDA or equivalent foreign regulatory authorities regarding the scope or design of clinical trials;
- the ability to demonstrate to the satisfaction of the FDA, or equivalent foreign regulatory authorities, the safety and efficacy of the drug candidates through current and future clinical trials;
- timely receipt of necessary marketing approvals from the FDA and equivalent foreign regulatory authorities;
- the ability to combine our drug candidates and the drug candidates being developed by Merck & Co. and any other collaborators safely and successfully with other therapeutic agents;
- achieving and maintaining compliance with all regulatory requirements applicable to the products;
- establishment of commercial manufacturing arrangements with third-party manufacturers;

the successful commercial launch of the drug candidates, assuming FDA approval is obtained, whether alone or in combination with other products;

acceptance of the products as safe and effective by patients, the medical community, and third-party payors;

competition from other companies and their therapies;

changes in treatment regimens;

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successful protection of our intellectual property rights from competing products in the United States and abroad; and

a continued acceptable safety and efficacy profile of the drug candidates following marketing approval.

We have recently begun to focus our efforts on the research and development of product candidates for use in the treatment of certain genetically defined forms of B-cell lymphomas, and our approach for the treatment of these genetically defined B-cell lymphomas is novel and may not result in any approved and marketable products.

We are in the early stages of developing our program in genetically defined forms of B-cell lymphoma, an area in which we have little experience. In connection with this program, we are focusing our efforts on the research and development of TLR antagonist product candidates for use in the treatment of certain genetically defined forms of B-cell lymphomas. The scientific evidence to support the feasibility of developing product candidates for this use is both preliminary and limited. We have conducted preclinical studies in human lymphoma cell lines that carry the MYD88 L265P oncogenic mutation and have also entered into an M-CRADA with NCI to evaluate our TLR antagonists as a potential approach to the treatment of certain genetically defined forms of B-cell lymphomas. Although the preliminary results of our preclinical studies have been promising, it is unknown whether these results are indicative of results that may be obtained in our planned clinical trials. Therefore, we do not know if our approach of inhibiting TLRs to treat patients with genetically defined forms of B-cell lymphomas will be successful or if we will ever succeed in obtaining regulatory approval to market any product for this purpose. In addition, in the event that our development efforts for such a product candidate progress towards commercialization, we will need to develop companion diagnostics for such product candidate. We have no experience in developing companion diagnostics and will be dependent on the efforts of third-party collaborators to successfully develop and commercialize these companion diagnostics on our behalf.

We are in the early stages of developing our GSO program, which is a novel technology, and our efforts may not be successful or result in any approved and marketable products.

We are in the early stages of developing our GSO technology program, and the scientific evidence to support the feasibility of developing drugs based on this technology is preliminary. Further, neither we nor any other company has received regulatory approval to market therapeutics utilizing GSOs.

The future success of our GSO technology program depends on our success in identifying and developing marketable products based on such technology. Although the results of our preclinical studies to date have been supportive of the viability of this technology, it is unknown whether these results are indicative of results that may be obtained in any future clinical trials that we may conduct. We are currently undertaking an analysis of priority disease indications and development strategies to determine next steps in developing our GSO technology. However, we do not expect to identify the first two disease indications in our GSO program until the second half of 2014 at the earliest and, if and when a disease indication is identified, do not anticipate initiating our Phase 1 proof-of-concept clinical trials prior to the second half of 2015. Many steps must be successfully achieved prior to any initiation of clinical development with respect to a GSO-based product candidate. Given the level of uncertainty of our ability to successfully achieve these many steps and the uncertainty of the clinical development process in general, there can be no assurance that we will succeed in developing any marketable product as a result of our efforts with respect to our GSO technology program.

If we experience delays or difficulties in the enrollment of patients in clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented.

We may not be able to initiate or continue clinical trials for our product candidates if we are unable to locate and enroll a sufficient number of eligible patients to participate in these trials as required by the FDA or similar regulatory authorities outside the United States. In particular, because there are a limited number of patients with

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Waldenström s macroglobulinemia or DLBCL and the MYD88 L265P oncogenic mutation, and a limited number of patients with polymyositis, dermatomyositis, or other autoimmune diseases having orphan indications for which we may determine to develop our TLR antagonists, our ability to enroll eligible patients in any clinical trials for these indications may be limited or may result in slower enrollment than we anticipate. In addition, some of our competitors have ongoing clinical trials for product candidates that treat the same indications as our product candidates, and patients who would otherwise be eligible for our clinical trials may instead enroll in clinical trials of our competitors product candidates.

Patient enrollment is affected by other factors including:

- the severity of the disease under investigation;
- the eligibility criteria for the study in question;
- the perceived risks and benefits of the TLR antagonist product candidates under study;
- the efforts to facilitate timely enrollment in clinical trials;
- the patient referral practices of physicians;
- the ability to monitor patients adequately during and after treatment; and
- the proximity and availability of clinical trial sites for prospective patients.

Our inability to enroll a sufficient number of patients for our clinical trials would result in significant delays and could require us to abandon one or more clinical trials altogether. Enrollment delays in our clinical trials may result in increased development costs for our product candidates, which would cause the value of our company to decline and limit our ability to obtain additional financing.

With respect to our genetically defined forms of B-cell lymphoma program, we plan to include in our planned Phase 1/2 clinical trial patients with the MYD88 L265P oncogenic mutation that contributes to the disease with a view to assessing possible early evidence of potential therapeutic effect. If we are unable to include patients with the MYD88 L265P oncogenic mutation, we may be unable to seek participation in FDA expedited review and approval programs, including breakthrough therapy and fast track designation, or otherwise seek to accelerate clinical development and regulatory timelines.

If our clinical trials are unsuccessful, or if they are delayed or terminated, we may not be able to develop and commercialize our products.

In order to obtain regulatory approvals for the commercial sale of our products, we are required to complete extensive clinical trials in humans to demonstrate the safety and efficacy of our drug candidates. Clinical trials are lengthy, complex, and expensive processes with uncertain results. We may not be able to complete any clinical trial of a potential product within any specified time period. Moreover, clinical trials may not show our potential products to be both safe and efficacious. The FDA or other equivalent foreign regulatory agencies may not allow us to complete these trials or commence and complete any other clinical trials. For example, in July 2011, the FDA placed a clinical hold on a protocol we had submitted for a proposed Phase 2 clinical trial of IMO-3100 in patients with psoriasis.

The results from preclinical testing of a drug candidate that is under development may not be predictive of results that will be obtained in human clinical trials. In addition, the results of early human clinical trials may not be predictive of results that will be obtained in larger scale, advanced stage clinical trials. Furthermore, interim results of a clinical trial do not necessarily predict final results, and failure of any of our clinical trials can occur at any stage of testing. Companies in the biotechnology and pharmaceutical industries, including companies with greater experience in preclinical testing and clinical trials than we have, have suffered significant setbacks in clinical trials, even after demonstrating promising results in earlier trials. Moreover, effects seen in nonclinical

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studies, even if not observed in clinical trials, may result in limitations or restrictions on clinical trials. Numerous unforeseen events may occur during, or as a result of, preclinical testing, nonclinical testing or the clinical trial process that could delay or inhibit the ability to receive regulatory approval or to commercialize drug products.

Other companies developing drugs targeted to TLRs have experienced setbacks in clinical trials. For example in 2007, Coley Pharmaceutical Group, which since has been acquired by Pfizer, discontinued four clinical trials for PF-3512676, its investigational TLR9 agonist compound, in combination with cytotoxic chemotherapy in cancer, and suspended its development of Actilon®, a TLR9 agonist, for HCV infection. In July 2007, Anadys Pharmaceuticals, Inc. and its partner Novartis, discontinued the development of ANA975, the investigational TLR7 agonist compound for HCV infection. Dynavax announced in May 2008 discontinuation of the clinical development program for TOLAMBA®, an investigational vaccine which contained a TLR9 agonist adjuvant, and in February 2013 Dynavax announced receipt of a Complete Response Letter from FDA regarding its Biological License Application for HEPLISAV®, which is an investigational hepatitis B vaccine that contains a TLR9 agonist adjuvant. These may result in enhanced scrutiny by regulators or IRBs of clinical trials of our drug candidates and GSOs, including our TLR-targeted drug candidates, which could result in regulators or IRBs prohibiting the commencement of clinical trials, requiring additional nonclinical studies as a precondition to commencing clinical trials or imposing restrictions on the design or scope of clinical trials that could slow enrollment of trials, increase the costs of trials or limit the significance of the results of trials. Such setbacks could also adversely impact the desire of investigators to enroll patients in, and the desire of patients to enroll in, clinical trials of our drug candidates and GSOs.

Other events that could delay or inhibit conduct of our clinical trials include:

- regulators or IRBs may not authorize us to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- nonclinical or clinical data may not be readily interpreted, which may lead to delays and/or misinterpretation;
- our nonclinical tests, including toxicology studies, or clinical trials may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional nonclinical testing or clinical trials or we may abandon projects that we expect may not be promising;
- the rate of enrollment or retention of patients in our clinical trials may be lower than we expect;
- we might have to suspend or terminate our clinical trials if the participating subjects experience serious adverse events or undesirable side effects or are exposed to unacceptable health risks;
- regulators or IRBs may hold, suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements, issues identified through inspections of manufacturing or clinical trial operations or clinical trial sites, or if, in their opinion, the participating subjects are being exposed to unacceptable health risks;
- regulators may hold or suspend our clinical trials while collecting supplemental information on, or clarification of, our clinical trials or other clinical trials, including trials conducted in other countries or trials conducted by other companies;
- we, along with our collaborators and subcontractors, may not employ, in any capacity, persons who have been debarred under the FDA s Application Integrity Policy, or similar policy under foreign regulatory authorities. Employment of such debarred persons, even if inadvertent, may result in delays in the FDA s or foreign equivalent s review or approval of our products, or the rejection of data developed with the involvement of such person(s);

the cost of our clinical trials may be greater than we currently anticipate; and

our products may not cause the desired effects or may cause undesirable side effects or our products may have other unexpected characteristics.

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We do not know whether clinical trials will begin as planned, will need to be restructured or will be completed on schedule, if at all. Significant clinical trial delays also could allow our competitors to bring products to market before we do and impair our ability to commercialize our products.

Delays in commencing clinical trials of potential products could increase our costs, delay any potential revenues, and reduce the probability that a potential product will receive regulatory approval.

Our drug candidates and our collaborators drug candidates will require preclinical and other nonclinical testing and extensive clinical trials prior to submission of any regulatory application for commercial sales. In conducting clinical trials, we cannot be certain that any planned clinical trial will begin on time, if at all. Delays in commencing clinical trials of potential products could increase our product development costs, delay any potential revenues, and reduce the probability that a potential product will receive regulatory approval.

Commencing clinical trials may be delayed for a number of reasons, including delays in:

- manufacturing sufficient quantities of drug candidate that satisfy the required quality standards for use in clinical trials;
- demonstrating sufficient safety to obtain regulatory approval for conducting a clinical trial;
- reaching an agreement with any collaborators on all aspects of the clinical trial;
- reaching agreement with contract research organizations, if any, and clinical trial sites on all aspects of the clinical trial;
- resolving any objections from the FDA or any regulatory authority on an IND or proposed clinical trial design;
- obtaining IRB approval for conducting a clinical trial at a prospective site; and
- enrolling patients in order to commence the clinical trial.

The technologies on which we rely are unproven and may not result in any approved and marketable products.

Our technologies or therapeutic approaches are relatively new and unproven. We have focused our efforts on the research and development of RNA- and DNA-based compounds targeted to TLRs and on GSOs. Neither we nor any other company have obtained regulatory approval to market such compounds as therapeutic drugs, and no such products currently are being marketed. It is unknown whether the results of preclinical studies with TLR-targeted compounds will be indicative of results that may be obtained in clinical trials, and results we have obtained in the clinical trials we have conducted to date may not be predictive of results in subsequent large-scale clinical trials. Further, the chemical and pharmacological properties of RNA- and DNA-based compounds targeted to TLRs or of GSOs may not be fully recognized in preclinical studies and small-scale clinical trials, and such compounds may interact with human biological systems in unforeseen, ineffective or harmful ways that we have not yet identified.

As a result of these factors, we may never succeed in obtaining regulatory approval to market any product. Furthermore, the commercial success of any of our products for which we may obtain marketing approval from the FDA or other regulatory authorities will depend upon their acceptance by patients, the medical community, and third-party payors as clinically useful, safe, and cost-effective. In addition, if products being developed by our competitors have negative clinical trial results or otherwise are viewed negatively, the perception of our technologies and market acceptance of our products could be impacted negatively.

Our setbacks with respect to our TLR-targeted compounds, together with the setbacks experienced by other companies developing TLR-targeted compounds, may result in a negative perception of our technology and our TLR-targeted compounds, impact our ability to obtain marketing

approval of these drug candidates and adversely

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affect acceptance of our technology and our TLR-targeted compounds by patients, the medical community and third-party payors.

Our efforts to educate the medical community on our potentially unique approaches may require greater resources than would be typically required for products based on conventional technologies or therapeutic approaches. The safety, efficacy, convenience, and cost-effectiveness of our products as compared to competitive products will also affect market acceptance.

We face substantial competition, which may result in others discovering, developing or commercializing drugs before or more successfully than us.

We are developing our TLR-targeted drug candidates for use in the treatment of autoimmune diseases and certain genetically defined B-cell lymphomas and for use as vaccine adjuvants. We have one drug candidate, IMO-8400, in clinical development in our autoimmune disease program and for the treatment of certain genetically defined B-cell lymphomas, including Waldenström s macroglobulinemia and DLBCL with the MYD88 L265P oncogenic mutation. We are also collaborating with Merck & Co. for the use of agonists of TLR7, TLR8 and TLR9 as vaccine adjuvants for cancer, infectious diseases and Alzheimer s disease. Finally, we may seek to enter into collaborative alliances with pharmaceutical companies to advance our TLR antagonist candidates in broader autoimmune disease indications, such as psoriasis, lupus and arthritis. For all of these disease areas, there are many other companies, public and private, that are actively engaged in discovery, development, and commercializing products and technologies that may compete with our drug candidates and programs, including TLR-targeted compounds as well as non-TLR-targeted therapeutics.

Our principal competitor developing TLR-targeted compounds for autoimmune diseases is Dynavax, with its collaborator, GlaxoSmithKline. Merck & Co. s vaccines using our TLR7, TLR8 or TLR9 agonists as adjuvants may compete with vaccines using TLR agonists as adjuvants being developed or marketed by GlaxoSmithKline, Novartis, Dynavax, VaxInnate, Inc., Intercell AG, and Cytos Biotechnology AG.

We are developing drug candidates for the treatment of moderate to severe plaque psoriasis. There are a number of well-known immune suppressors and biologics that are currently being widely used for the treatment of moderate to severe plaque psoriasis, including methotrexate and cyclosporine, which are both immune suppressors, and biologics like Enbrel, which is marketed by Amgen, Pfizer, and Takeda Pharmaceutical Company Limited, Remicade, which is marketed by Janssen Biotech, Merck & Co., and Mitsubishi Tanabe Pharma, Humira, which is marketed by Abbott Laboratories, and Stelara, which is marketed by Janssen Biotech. In addition to existing treatments, we are also aware of additional compounds for the treatment of moderate to severe plaque psoriasis that are currently in late stage development, including apremilast, which is being developed by Celgene Corporation, tofacitinib, which is being developed by Pfizer, secukinumab, which is being developed by Novartis, ixekizumab, which is being developed by Eli Lilly and Company, and brodalumab, which is being developed by Amgen, AstraZeneca PLC, and Kyowa Hakko Kirin Co., Ltd.

We are developing IMO-8400 for the treatment of certain genetically defined forms of B-cell lymphoma. There are currently no drugs specifically approved for the treatment of Waldenström s macroglobulinemia or DLBCL with the MYD88 L265P oncogenic mutation. Currently, patients with any form of non-Hodgkin lymphoma are most often treated with monoclonal antibody rituximab and/or with one or more chemotherapeutic agents. Rituximab is co-marketed in the United States by Biogen Idec and Genentech and Hoffmann-La Roche and Chugai Pharmaceuticals in territories outside the United States. We are aware of additional compounds in development for the treatment of genetically defined forms of B-cell lymphoma, including Ibrutinib, which is being developed by Pharmacyclics, Inc., and an inhibitor of interleukin-1 receptor-associated kinase 4, which is being developed by Nimbus Discovery, Inc.

In addition, we are developing GSOs that we have created using our proprietary technology, to inhibit the production of disease-associated proteins by targeting RNA. We also face competition from other companies

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working to develop novel drugs using technologies that may compete with our GSO technology. We are aware of multiple companies that are developing technologies that use oligonucleotide-based compounds to inhibit the production of disease associated proteins. These technologies include, but are not limited to, antisense technology as well as RNAi. In the field of antisense technologies, we compete with multiple companies, including Isis and its partners. Isis is currently marketing an antisense drug, Kynamro®, and has several antisense product candidates in clinical trials. In the field of RNAi, our primary competition is with Alnylam Pharmaceuticals, Inc., or Alnylam, and its partners. Alnylam is currently developing multiple RNAi-based technologies and has several product candidates in clinical trials. Any of the competing companies may develop gene-silencing technologies more rapidly and more effectively than us, and antisense technology and RNAi may become the preferred technology for drugs that target RNA in order to inhibit the production of disease-associated proteins.

Some of these potentially competitive products have been in development or commercialized for years, in some cases by large, well established pharmaceutical companies. Many of the marketed products have been accepted by the medical community, patients, and third-party payors. Our ability to compete may be affected by the previous adoption of such products by the medical community, patients, and third-party payors. Additionally, in some instances, insurers and other third-party payors seek to encourage the use of generic products, which makes branded products, such as our drug candidates, potentially less attractive, from a cost perspective, to buyers.

We recognize that other companies, including large pharmaceutical companies, may be developing or have plans to develop products and technologies that may compete with ours. Many of our competitors have substantially greater financial, technical, and human resources than we have. In addition, many of our competitors have significantly greater experience than we have in undertaking preclinical studies and human clinical trials of new pharmaceutical products, obtaining FDA and other regulatory approvals of products for use in health care and manufacturing, and marketing and selling approved products. Our competitors may discover, develop or commercialize products or other novel technologies that are more effective, safer or less costly than any that we are developing. Our competitors may also obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours.

We anticipate that the competition with our products and technologies will be based on a number of factors including product efficacy, safety, availability, and price. The timing of market introduction of our products and competitive products will also affect competition among products. We expect the relative speed with which we can develop products, complete the clinical trials and approval processes, and supply commercial quantities of the products to the market to be important competitive factors. Our competitive position will also depend upon our ability to attract and retain qualified personnel, to obtain patent protection or otherwise develop proprietary products or processes, protect our intellectual property, and to secure sufficient capital resources for the period between technological conception and commercial sales.

Competition for technical and management personnel is intense in our industry, and we may not be able to sustain our operations or grow if we are unable to attract and retain key personnel.

Our success is highly dependent on the retention of principal members of our technical and management staff, including Dr. Sudhir Agrawal. Dr. Agrawal serves as our President and Chief Executive Officer. Dr. Agrawal has made significant contributions to the field of oligonucleotide-based drug candidates, and he has led the discovery and development of our compounds targeted to TLRs and our GSOs.

He is named as an inventor on over 400 patents and patent applications in countries around the world. Dr. Agrawal provides us with leadership for our management team and research and development activities. The loss of Dr. Agrawal s services would be detrimental to our ongoing scientific progress and the execution of our business plan.

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We are a party to an employment agreement with Dr. Agrawal that expires on October 19, 2016, but automatically extends annually for additional one-year periods. This agreement may be terminated by us or Dr. Agrawal for any reason or no reason at any time upon notice to the other party. We do not carry key man life insurance for Dr. Agrawal.

Furthermore, our future growth will require hiring a number of qualified technical and management personnel. Accordingly, recruiting and retaining such personnel in the future will be critical to our success. There is intense competition from other companies and research and academic institutions for qualified personnel in the areas of our activities. If we are not able to continue to attract and retain, on acceptable terms, the qualified personnel necessary for the continued development of our business, we may not be able to sustain our operations or growth.

Regulatory Risks

We are subject to comprehensive regulatory requirements, which are costly and time consuming to comply with; if we fail to comply with these requirements, we could be subject to adverse consequences and penalties.

The testing, manufacturing, labeling, advertising, promotion, export, and marketing of our products are subject to extensive regulation by governmental authorities in Europe, the United States, and elsewhere throughout the world.

In general, submission of materials requesting permission to conduct clinical trials may not result in authorization by the FDA or any equivalent foreign regulatory agency to commence clinical trials. Further, permission to continue ongoing trials may be withdrawn by the FDA or other regulatory agencies at any time after initiation, based on new information available after the initial authorization to commence clinical trials or for other reasons. In addition, submission of an application for marketing approval to the relevant regulatory agency following completion of clinical trials may not result in the regulatory agency approving the application if applicable regulatory criteria are not satisfied, and may result in the regulatory agency requiring additional testing or information.

Even if we obtain regulatory approval for any of our product candidates, we will be subject to continual requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, cGMP requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, requirements regarding the distribution of samples to physicians and recordkeeping. Even if marketing approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the product may be marketed or to the conditions of approval, including the requirement to implement a risk evaluation and mitigation strategy. If any of our product candidates receives marketing approval, the accompanying label may limit the approved use of our drug in this way, which could limit sales of the product. For example, new cancer drugs frequently are indicated only for patient populations that have not responded to an existing therapy or have relapsed.

Both before and after approval is obtained, failure to comply with regulatory requirements, or discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, may result in:

- the regulatory agency s delay in approving, or refusal to approve, an application for marketing of a product or a supplement to an approved application;
- restrictions on our products or the marketing or manufacturing of our products;
- withdrawal of our products from the market;
- warning letters;

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voluntary or mandatory product recalls;

fines;

suspension or withdrawal of regulatory approvals;

product seizure or detention;

refusal to permit the import or export of our products;

injunctions or the imposition of civil penalties; and

criminal penalties.

We may not be able to obtain marketing approval for products resulting from our development efforts.

All of the drug candidates that we are developing, or may develop in the future, will require additional research and development, extensive preclinical studies, nonclinical testing, clinical trials, and regulatory approval prior to any commercial sales. This process is lengthy, often taking a number of years, is uncertain, and is expensive. Since our inception, we have conducted clinical trials of a number of compounds and are planning to initiate clinical trials for a number of additional disease indications. Specifically, we are currently:

conducting a Phase 2 clinical trial of IMO-8400 in patients with moderate to severe plaque psoriasis;

planning to initiate patient treatment in a Phase 1/2 clinical trial of IMO-8400 in patients with Waldenström s macroglobulinemia in the first half of 2014 and in a Phase 1/2 clinical trial of IMO-8400 in patients with DLBCL and the MYD88 L265P oncogenic mutation in the second half of 2014;

planning to submit an IND to the FDA for IMO-9200 and to initiate a Phase 1 clinical trial of IMO-9200 in healthy subjects in the second half of 2014;

planning to initiate patient treatment in a Phase 1/2 clinical trial of IMO-8400 in patients with polymyositis or dermatomyositis in the second half of 2014; and

planning to initiate a Phase 1 proof-of-concept clinical trial in each of the first two disease indications selected for further development in our GSO program in the second half of 2015.

The FDA and other regulatory authorities may not approve any of our potential products for any indication.

We may need to address a number of technological challenges in order to complete development of our products. Moreover, these products may not be effective in treating any disease or may prove to have undesirable or unintended side effects, unintended alteration of the immune system over time, toxicities or other characteristics that may preclude our obtaining regulatory approval or prevent or limit commercial use. If we do not obtain necessary regulatory approvals, our business will be adversely affected.

We may not be able to obtain orphan drug exclusivity for applications of our TLR antagonist product candidates.

Regulatory authorities in some jurisdictions, including the United States and Europe, may designate drugs for relatively small patient populations as orphan drugs. Under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is a drug intended to treat a rare disease or condition, which is generally defined as a patient population of fewer than 200,000 individuals annually in the United States.

Generally, if a product with an orphan drug designation subsequently receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of marketing exclusivity, which precludes the European Medicines Agency, or EMA, or the FDA from approving another marketing application for the same drug for that time period. The applicable period is seven years in the United States and ten years in Europe. The European exclusivity period can be reduced to six years if a drug no longer meets the

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criteria for orphan drug designation or if the drug is sufficiently profitable so that market exclusivity is no longer justified. Orphan drug exclusivity may be lost if the FDA or EMA determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the drug to meet the needs of patients with the rare disease or condition.

Even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different drugs can be approved for the same condition. Even after an orphan drug is approved, the FDA can subsequently approve the same drug for the same condition if the FDA concludes that the later drug is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care.

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

We intend to seek fast track designation for some applications of our product candidates. If a drug is intended for the treatment of a serious or life-threatening condition and the drug demonstrates the potential to address unmet medical needs for this condition, the drug sponsor may apply for FDA fast track designation. The FDA has broad discretion whether or not to grant this designation, so even if we believe a particular product candidate is eligible for this designation, we cannot assure you that the FDA would decide to grant it. Even if we do receive fast track designation, we may not experience a faster development process, review or approval compared to conventional FDA procedures. The FDA may withdraw fast track designation if it believes that the designation is no longer supported by data from our clinical development program.

A breakthrough therapy designation by the FDA for any application of our product candidates may not lead to a faster development or regulatory review or approval process, and it does not increase the likelihood that those product candidates will receive marketing approval.

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

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

If we are unable to successfully develop companion diagnostics for our product candidates intended for the treatment of genetically defined forms of B-cell lymphoma, or experience significant delays in doing so, we may not achieve marketing approval or realize the full commercial potential of these product candidates.

We plan to develop companion diagnostics for our TLR antagonist product candidates in our genetically defined forms of B-cell lymphoma program. We expect that, at least in some cases, the FDA and similar

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regulatory authorities outside the United States may require the development and regulatory approval of a companion diagnostic as a condition to approving our TLR antagonist product candidates specifically for the treatment of patients with a genetically defined form of B-cell lymphoma. We do not have experience or capabilities in developing or commercializing diagnostics and plan to rely on third parties or collaborators to perform these functions. To date, we have not entered into any agreements for the development or commercialization of companion diagnostics for use with any of our product candidates. However, we expect to enter into our first such agreement in the first half of 2014 with respect to our identification of the MYD88 L265P oncogenic mutation in our genetically defined forms of B-cell lymphoma program with our TLR antagonist product candidates. Companion diagnostics are subject to regulation by the FDA and similar regulatory authorities outside the United States as medical devices and require separate regulatory approval prior to commercialization.

If we, any third parties that we engage to assist us or any of our collaborators are unable to successfully develop companion diagnostics for our TLR antagonist product candidates, or experience delays in doing so:

- the development of our TLR antagonist product candidates may be adversely affected if we are unable to appropriately select patients for enrollment in our clinical trials;
- our TLR antagonist product candidates may not receive marketing approval if their safe and effective use depends on a companion diagnostic; and
- we may not realize the full commercial potential of any TLR antagonist product candidates that receive marketing approval if, among other reasons, we are unable to appropriately identify patients with the specific oncogenic mutation targeted by our TLR antagonist product candidates.

If any of these events were to occur, our business would be harmed, possibly materially.

We have only limited experience in regulatory affairs and our products are based on new technologies; these factors may affect our ability or the time we require to obtain necessary regulatory approvals.

We have only limited experience in filing the applications necessary to obtain regulatory approvals. Moreover, the products that result from our research and development programs will likely be based on new technologies and new therapeutic approaches that have not been extensively tested in humans. The regulatory requirements governing these types of products may be more rigorous than for conventional drugs. As a result, we may experience a longer regulatory process in connection with obtaining regulatory approvals of any product that we develop.

Failure to obtain regulatory approval in jurisdictions outside the United States will prevent us from marketing our products abroad.

We intend to market our products, if approved, in markets outside the United States, which will require separate regulatory approvals and compliance with numerous and varying regulatory requirements. The approval procedures vary among such markets and may involve requirements for additional testing, and the time required to obtain approval may differ from that required to obtain FDA approval. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one foreign regulatory authority does not ensure approval by regulatory authorities in other foreign countries or by the FDA. The foreign regulatory approval process may include all of the risks associated with obtaining FDA approval. We may not obtain foreign regulatory approvals on a timely basis, if at all.

Risks Relating to Collaborators

If we are unable to establish additional collaborative alliances, our business may be materially harmed.

Collaborators provide the necessary resources and drug development experience to advance our compounds in their programs. We may seek to enter into collaborative alliances with pharmaceutical companies to advance

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our TLR antagonist candidates in broader autoimmune disease indications, such as psoriasis, lupus and arthritis. We may seek to enter into collaborative alliances with pharmaceutical companies with respect to applications of our GSO technology program.

Upfront payments and milestone payments received from collaborations help to provide us with the financial resources for our internal research and development programs. Our internal programs are focused on developing TLR-targeted drug candidates for the potential treatment of autoimmune diseases and certain genetically defined forms of B-cell lymphomas and on GSOs. We believe that additional resources will be required to advance compounds in all of these areas. If we do not reach agreements with additional collaborators in the future, we may not be able to obtain the expertise and resources necessary to achieve our business objectives, our ability to advance our compounds will be jeopardized and we may fail to meet our business objectives.

We may have difficulty establishing additional collaborative alliances, particularly with respect to our TLR-targeted drug candidates and technology and our GSO technology. For example, potential partners may note that our TLR collaborations with Novartis and with Merck KGaA have been terminated. Potential partners may also be reluctant to establish collaborations with respect to IMO-2125, IMO-3100, IMO-2055, and our other TLR-targeted drug candidates, given our recent setbacks with respect to these drug candidates. Additionally, in the event we seek collaborations for our GSO program, any potential collaborators may not be willing to enter into a collaboration with us due to the early stage of this technology. We also face, and expect to continue to face, significant competition in seeking appropriate collaborators.

Even if a potential partner were willing to enter into a collaborative alliance with respect to our TLR-targeted compounds or technology or our GSO technology, the terms of such a collaborative alliance may not be on terms that are favorable to us. Moreover, collaborations are complex and time consuming to negotiate, document, and implement. We may not be successful in our efforts to establish and implement collaborations on a timely basis.

Our existing collaboration and any collaborations we enter into in the future may not be successful.

An important element of our business strategy includes entering into collaborative alliances with corporate collaborators, primarily large pharmaceutical companies, for the development, commercialization, marketing, and distribution of some of our drug candidates. In December 2006, we entered into an exclusive license and research collaboration with Merck & Co. to research, develop, and commercialize vaccine products containing our TLR7, TLR8 and TLR9 agonists in the fields of cancer, infectious diseases, and Alzheimer s disease. In December 2007, we entered into an exclusive, worldwide license agreement with Merck KGaA to research, develop, and commercialize products containing our TLR9 agonists for treatment of cancer, excluding cancer vaccines.

Any collaboration that we enter into may not be successful. For instance, in July 2011, Merck KGaA informed us that it had determined not to conduct further clinical development of IMO-2055, and in November 2011, we entered into an agreement with Merck KGaA terminating our collaboration with them. The success of our collaborative alliances, if any, will depend heavily on the efforts and activities of our collaborators. Our existing collaboration and any potential future collaborations have risks, including the following:

- our collaborators may control the development of the drug candidates being developed with our technologies and compounds including the timing of development;
- our collaborators may control the development of the companion diagnostic to be developed for use in conjunction with our drug candidates including the timing of development;
- our collaborators may control the public release of information regarding the developments, and we may not be able to make announcements or data presentations on a schedule favorable to us;

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disputes may arise in the future with respect to the ownership of rights to technology developed with our collaborators;

disagreements with our collaborators could delay or terminate the research, development or commercialization of products, or result in litigation or arbitration;

we may have difficulty enforcing the contracts if any of our collaborators fail to perform;

our collaborators may terminate their collaborations with us, which could make it difficult for us to attract new collaborators or adversely affect the perception of us in the business or financial communities;

our collaboration agreements are likely to be for fixed terms and subject to termination by our collaborators in the event of a material breach or lack of scientific progress by us;

our collaborators may have the first right to maintain or defend our intellectual property rights and, although we would likely have the right to assume the maintenance and defense of our intellectual property rights if our collaborators do not, our ability to do so may be compromised by our collaborators acts or omissions;

our collaborators may challenge our intellectual property rights or utilize our intellectual property rights in such a way as to invite litigation that could jeopardize or invalidate our intellectual property rights or expose us to potential liability;

our collaborators may not comply with all applicable regulatory requirements, or may fail to report safety data in accordance with all applicable regulatory requirements;

our collaborators may change the focus of their development and commercialization efforts. Pharmaceutical and biotechnology companies historically have re-evaluated their priorities following mergers and consolidations, which have been common in recent years in these industries. For example, we have a strategic partnership with Merck & Co., which merged with Schering-Plough, which has been involved with certain TLR-targeted research and development programs. Although the merger has not affected our partnership with Merck & Co. to date, management of the combined company could determine to reduce the efforts and resources that the combined company will apply to its strategic partnership with us or terminate the strategic partnership. The ability of our products to reach their potential could be limited if our collaborators decrease or fail to increase spending relating to such products;

our collaborators may under fund or not commit sufficient resources to the testing, marketing, distribution or development of our products; and

our collaborators may develop alternative products either on their own or in collaboration with others, or encounter conflicts of interest or changes in business strategy or other business issues, which could adversely affect their willingness or ability to fulfill their obligations to us.

Given these risks, it is possible that any collaborative alliance into which we enter may not be successful. Collaborations with pharmaceutical companies and other third parties often are terminated or allowed to expire by the other party. For example, effective as of February 2010, Novartis terminated the research collaboration and option agreement that we entered into with it in May 2005, and in November 2011, we entered into an agreement with Merck KGaA terminating our collaboration with them. In addition, Merck & Co. may terminate its license and research collaboration agreement by giving us 90 days advance notice. The termination or expiration of our agreement with Merck & Co. or any other collaboration agreement that we enter into in the future may adversely affect us financially and could harm our business reputation.

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Risks Relating to Intellectual Property

If we are unable to obtain patent protection for our discoveries, the value of our technology and products will be adversely affected.

Our patent positions, and those of other drug discovery companies, are generally uncertain and involve complex legal, scientific, and factual questions. Our ability to develop and commercialize drugs depends in significant part on our ability to:

obtain patents;

obtain licenses to the proprietary rights of others on commercially reasonable terms;

operate without infringing upon the proprietary rights of others;

prevent others from infringing on our proprietary rights; and

protect our trade secrets.

We do not know whether any of our patent applications or those patent applications that we license will result in the issuance of any patents. Our issued patents and those that may be issued in the future, or those licensed to us, may be challenged, invalidated or circumvented, and the rights granted thereunder may not provide us proprietary protection or competitive advantages against competitors with similar technology. Moreover, intellectual property laws may change and negatively impact our ability to obtain issued patents covering our technologies or to enforce any patents that issue. Because of the extensive time required for development, testing, and regulatory review of a potential product, it is possible that, before any of our products can be commercialized, any related patent may expire or remain in force for only a short period following commercialization, thus reducing any advantage provided by the patent.

Because patent applications in the United States and many foreign jurisdictions are typically not published until 18 months after filing, or in some cases not at all, and because publications of discoveries in the scientific literature often lag behind actual discoveries, neither we nor our licensors can be certain that we or they were the first to make the inventions claimed in issued patents or pending patent applications, or that we or they were the first to file for protection of the inventions set forth in these patent applications.

As of February 15, 2014, we owned more than 45 U.S. patents and patent applications and more than 80 patents and patent applications throughout the rest of the world for our TLR-targeted immune modulation technologies. These patents and patent applications include novel chemical compositions of matter and methods of use of our IMO compounds, including IMO-3100, IMO-8400, IMO-9200, and IMO-2055. As of February 15, 2014, all of our intellectual property covering immune modulatory compositions and methods of their use is based on discoveries made solely by us. These patents expire at various dates ranging from 2017 to 2031. With respect to IMO-3100, we have issued U.S. patents that cover the chemical composition of matter of IMO-3100 and methods of its use that will expire at the earliest in 2026. With respect to IMO-8400, we have an issued U.S. patent that covers the chemical composition of matter of IMO-8400 and methods of its use that will expire at the earliest in 2031. With respect to IMO-9200, we have a U.S. patent application that covers the chemical composition for IMO-9200 and methods of its use, which, if issued, would expire at the earliest in 2034.

As of February 15, 2014, we owned one issued U.S. patent, two U.S. patent applications and six foreign patent applications for our GSO compounds and methods of their use. The issued patent covering our GSO technologies would expire at the earliest in 2030.

In addition to our TLR-targeted and GSO patent portfolios, we are the owner or hold licenses of patents and patent applications related to antisense technology. As of February 15, 2014, our antisense patent portfolio included more than 60 U.S. patents, one U.S. patent application and more than 60 patents throughout the rest of the world. These antisense patents and patent applications include novel compositions of matter, the use of these

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compositions for various genes, sequences and therapeutic targets, and oral and other routes of administration. Some of the patents and patent applications in our antisense portfolio were in-licensed. These in-licensed patents expire at various dates ranging from 2014 to 2021.

Third parties may own or control patents or patent applications and require us to seek licenses, which could increase our development and commercialization costs, or prevent us from developing or marketing products.

Although we have many issued patents and pending patent applications in the United States and other countries, we may not have rights under certain third-party patents or patent applications related to our products. Third parties may own or control these patents and patent applications in the United States and abroad. In particular, we are aware of third-party U.S. patents that contain broad claims related to the use of certain oligonucleotides for stimulating an immune response, although we do not believe that these claims are valid. In addition, there may be other patents and patent applications related to our products of which we are not aware. Therefore, in some cases, in order to develop, manufacture, sell or import some of our products, we or our collaborators may choose to seek, or be required to seek, licenses under third-party patents issued in the United States and abroad or under third-party patents that might issue from U.S. and foreign patent applications. In such an event, we would be required to pay license fees or royalties or both to the licensor. If licenses are not available to us on acceptable terms, we or our collaborators may not be able to develop, manufacture, sell or import these products.

We may lose our rights to patents, patent applications or technologies of third parties if our licenses from these third parties are terminated. In such an event, we might not be able to develop or commercialize products covered by the licenses.

Currently, we have not in-licensed any patents or patent applications related to our TLR-targeted drug candidate programs or our GSO compounds and methods of their use. However, we are party to six royalty-bearing license agreements under which we have acquired rights to patents, patent applications, and technology of third parties in the field of antisense technology, which may be applicable to our TLR-targeted antisense. Under these licenses we are obligated to pay royalties on net sales by us of products or processes covered by a valid claim of a patent or patent application licensed to us. We also are required in some cases to pay a specified percentage of any sublicense income that we may receive. These licenses impose various commercialization, sublicensing, insurance, and other obligations on us.

Our failure to comply with these requirements could result in termination of the licenses. These licenses generally will otherwise remain in effect until the expiration of all valid claims of the patents covered by such licenses or upon earlier termination by the parties. The issued patents covered by these licenses expire at various dates ranging from 2014 to 2021. If one or more of these licenses is terminated, we may be delayed in our efforts, or be unable, to develop and market the products that are covered by the applicable license or licenses.

We may become involved in expensive patent litigation or other proceedings, which could result in our incurring substantial costs and expenses or substantial liability for damages or require us to stop our development and commercialization efforts.

There has been substantial litigation and other proceedings regarding patent and other intellectual property rights in the biotechnology industry. We may become a party to various types of patent litigation or other proceedings regarding intellectual property rights from time to time even under circumstances where we are not practicing and do not intend to practice any of the intellectual property involved in the proceedings. For instance, in 2002, 2003, and 2005, we became involved in interference proceedings declared by the USPTO for some of our antisense and ribozyme patents. All of these interferences have since been resolved. We are neither practicing nor intending to practice the intellectual property that is associated with any of these interference proceedings.

The cost to us of any patent litigation or other proceeding, even if resolved in our favor, could be substantial. Some of our competitors may be able to sustain the cost of such litigation or proceedings more

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effectively than we can because of their substantially greater financial resources. If any patent litigation or other proceeding is resolved against us, we or our collaborators may be enjoined from developing, manufacturing, selling or importing our drugs without a license from the other party and we may be held liable for significant damages. We may not be able to obtain any required license on commercially acceptable terms or at all.

Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace. Patent litigation and other proceedings may also absorb significant management time.

Risks Relating to Product Manufacturing, Marketing and Sales, and Reliance on Third Parties

Because we have limited manufacturing experience, and no manufacturing facilities or infrastructure, we are dependent on third-party manufacturers to manufacture drug candidates for us. If we cannot rely on third-party manufacturers, we will be required to incur significant costs and devote significant efforts to establish our own manufacturing facilities and capabilities.

We have limited manufacturing experience and no manufacturing facilities, infrastructure or clinical or commercial scale manufacturing capabilities. In order to continue to develop our drug candidates, apply for regulatory approvals, and ultimately commercialize products, we need to develop, contract for or otherwise arrange for the necessary manufacturing capabilities.

We currently rely upon third parties to produce material for nonclinical and clinical testing purposes and expect to continue to do so in the future. We also expect to rely upon third parties to produce materials that may be required for the commercial production of our products. Our current and anticipated future dependence upon others for the manufacture of our drug candidates may adversely affect our future profit margins and our ability to develop drug candidates and commercialize any drug candidates on a timely and competitive basis. We currently do not have any long term supply contracts.

There are a limited number of manufacturers that operate under the FDA s cGMP regulations capable of manufacturing our drug candidates. As a result, we may have difficulty finding manufacturers for our products with adequate capacity for our needs. If we are unable to arrange for third-party manufacturing of our drug candidates on a timely basis, or to do so on commercially reasonable terms, we may not be able to complete development of our drug candidates or market them.

Reliance on third-party manufacturers entails risks to which we would not be subject if we manufactured drug candidates ourselves, including:

- reliance on the third party for regulatory compliance and quality assurance;
- the possibility of breach of the manufacturing agreement by the third party because of factors beyond our control;
- the possibility of termination or nonrenewal of the agreement by the third party, based on its own business priorities, at a time that is costly or inconvenient for us;
- the potential that third-party manufacturers will develop know-how owned by such third party in connection with the production of our drug candidates that becomes necessary for the manufacture of our drug candidates; and
- reliance upon third-party manufacturers to assist us in preventing inadvertent disclosure or theft of our proprietary knowledge.

Any contract manufacturers with which we enter into manufacturing arrangements will be subject to ongoing periodic, unannounced inspections by the FDA, or foreign equivalent, and corresponding state and

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foreign agencies or their designees to ensure compliance with cGMP requirements and other governmental regulations and corresponding foreign standards. For example, one of our contract manufacturers notified us that it had received a cGMP warning letter from the FDA in February 2011. This contract manufacturer no longer manufactures drug product for us. Any failure by our third-party manufacturers to comply with such requirements, regulations or standards could lead to a delay in the conduct of our clinical trials, or a delay in, or failure to obtain, regulatory approval of any of our drug candidates. Such failure could also result in sanctions being imposed, including fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, product seizures or recalls, imposition of operating restrictions, total or partial suspension of production or distribution, or criminal prosecution.

Additionally, contract manufacturers may not be able to manufacture our drug candidates at a cost or in quantities necessary to make them commercially viable. As of December 31, 2013, our third-party manufacturers have met our manufacturing requirements, but we cannot be assured that they will continue to do so. Furthermore, changes in the manufacturing process or procedure, including a change in the location where the drug substance or drug product is manufactured or a change of a third-party manufacturer, may require prior FDA review and approval in accordance with the FDA s cGMP and NDA/biologics license application regulations. Contract manufacturers may also be subject to comparable foreign requirements. This review may be costly and time-consuming and could delay or prevent the launch of a drug candidate. The FDA or similar foreign regulatory agencies at any time may also implement new standards, or change their interpretation and enforcement of existing standards for manufacture, packaging or testing of products. If we or our contract manufacturers are unable to comply, we or they may be subject to regulatory action, civil actions or penalties.

We have no experience selling, marketing or distributing products and no internal capability to do so.

If we receive regulatory approval to commence commercial sales of any of our drug candidates, we will face competition with respect to commercial sales, marketing, and distribution. These are areas in which we have no experience. To market any of our drug candidates directly, we would need to develop a marketing and sales force with technical expertise and with supporting distribution capability. In particular, we would need to recruit a large number of experienced marketing and sales personnel. Alternatively, we could engage a pharmaceutical or other healthcare company with an existing distribution system and direct sales force to assist us. However, to the extent we entered into such arrangements, we would be dependent on the efforts of third parties. If we are unable to establish sales and distribution capabilities, whether internally or in reliance on third parties, our business would suffer materially.

If third parties on whom we rely for clinical trials do not perform as contractually required or as we expect, we may not be able to obtain regulatory approval for or commercialize our products and our business may suffer.

We do not have the ability to independently conduct the clinical trials required to obtain regulatory approval for our drug candidates. We depend on independent clinical investigators, contract research organizations, and other third-party service providers in the conduct of the clinical trials of our drug candidates and expect to continue to do so. We contracted with contract research organizations to manage our Phase 1 and Phase 2 clinical trials of IMO-3100, our Phase 1 clinical trial of IMO-8400 and our ongoing Phase 2 clinical trial of IMO-8400 in patients with psoriasis and our planned Phase 1/2 clinical trial in patients with Waldenström s macroglobulinemia, and expect to contract with such organizations for future clinical trials. We rely heavily on these parties for successful execution of our clinical trials, but do not control many aspects of their activities. We are responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA and foreign regulatory agencies require us to comply with certain standards, commonly referred to as good clinical practices, and applicable regulatory requirements, for conducting, recording, and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity, and confidentiality of clinical trial participants are protected. Our reliance on third parties that we do not control does not relieve us of these responsibilities and requirements. Third parties may not complete activities on schedule, or at all, or may not conduct our clinical

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trials in accordance with regulatory requirements or our stated protocols. The failure of these third parties to carry out their obligations could delay or prevent the development, approval, and commercialization of our drug candidates. If we seek to conduct any of these activities ourselves in the future, we will need to recruit appropriately trained personnel and add to our infrastructure.

Failure of our third-party collaborators to successfully commercialize companion diagnostics developed for use with any TLR antagonist product candidates that we develop with respect to our genetically defined forms of B-cell lymphoma program could harm our ability to commercialize these TLR antagonist product candidates.

Some of the TLR antagonist product candidates that we develop with respect to our genetically defined forms of B-cell lymphoma program will necessitate the use of companion diagnostics. We do not plan to develop companion diagnostics internally and, as a result, we will be dependent on the efforts of our third-party collaborators to successfully commercialize these companion diagnostics. Our collaborators:

- may not perform their obligations as expected;
- may encounter production difficulties that could constrain the supply of the companion diagnostics;
- may have difficulties gaining acceptance of the use of the companion diagnostics in the clinical community;
- may not pursue commercialization of any TLR antagonist product candidates that achieve regulatory approval;
- may elect not to continue or renew commercialization programs based on changes in the collaborators strategic focus or available funding, or external factors, such as an acquisition, that divert resources or create competing priorities;
- may not commit sufficient resources to the marketing and distribution of such product or products; and
- may terminate their relationship with us.

If companion diagnostics for use with our genetically defined forms of B-cell lymphoma TLR antagonist product candidates fail to gain market acceptance, our ability to derive revenues from sales of these TLR antagonist product candidates could be harmed. If our collaborators fail to commercialize these companion diagnostics, we may not be able to enter into arrangements with another diagnostic company to obtain supplies of an alternative diagnostic test for use in connection with genetically defined forms of B-cell lymphoma TLR antagonist product candidates or do so on commercially reasonable terms, which could adversely affect and delay the development or commercialization of these TLR antagonist product candidates.

The commercial success of any drug candidates that we may develop will depend upon the degree of market acceptance by physicians, patients, third-party payors, and others in the medical community.

Any products that we ultimately bring to the market, if they receive marketing approval, may not gain market acceptance by physicians, patients, third-party payors or others in the medical community. For example, current cancer treatments like chemotherapy and radiation therapy are well established in the medical community, and doctors may continue to rely on these treatments. If our products do not achieve an adequate level of acceptance, we may not generate product revenue and we may not become profitable. The degree of market acceptance of our drug candidates, if approved for commercial sale, will depend on a number of factors, including:

- the prevalence and severity of any side effects, including any limitations or warnings contained in the product s approved labeling;

the efficacy and potential advantages over alternative treatments;

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the ability to offer our drug candidates for sale at competitive prices;

relative convenience and ease of administration;

the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;

the strength of marketing and distribution support and the timing of market introduction of competitive products; and

publicity concerning our products or competing products and treatments.

Even if a potential product displays a favorable efficacy and safety profile, market acceptance of the product will not be known until after it is launched. Our efforts to educate patients, the medical community, and third-party payors on the benefits of our drug candidates may require significant resources and may never be successful. Such efforts to educate the marketplace may require more resources than are required by conventional technologies marketed by our competitors.

If we are unable to obtain adequate reimbursement from third-party payors for any products that we may develop or acceptable prices for those products, our revenues and prospects for profitability will suffer.

Most patients rely on Medicare, Medicaid, private health insurers, and other third-party payors to pay for their medical needs, including any drugs we may market. If third-party payors do not provide adequate coverage or reimbursement for any products that we may develop, our revenues and prospects for profitability will suffer. Congress enacted a limited prescription drug benefit for Medicare recipients in the Medicare Prescription Drug, Improvement, and Modernization Act of 2003. While the program established by this statute may increase demand for our products if we were to participate in this program, our prices will be negotiated with drug procurement organizations for Medicare beneficiaries and are likely to be lower than we might otherwise obtain. Non-Medicare third-party drug procurement organizations may also base the price they are willing to pay on the rate paid by drug procurement organizations for Medicare beneficiaries or may otherwise negotiate the price they are willing to pay.

A primary trend in the United States healthcare industry is toward cost containment. In addition, in some foreign countries, particularly the countries of the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take six months or longer after the receipt of regulatory marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost effectiveness of our drug candidates or products to other available therapies. The conduct of such a clinical trial could be expensive and result in delays in commercialization of our products. These further clinical trials would require additional time, resources, and expenses. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our prospects for generating revenue, if any, could be adversely affected and our business may suffer.

In March 2010, the Patient Protection and Affordable Care Act and the Health Care and Education Reconciliation Act became law. These health care reform laws are intended to broaden access to health insurance; reduce or constrain the growth of health care spending, especially Medicare spending; enhance remedies against fraud and abuse; add new transparency requirements for health care and health insurance industries; impose new taxes and fees on certain sectors of the health industry; and impose additional health policy reforms. Among the new fees is an annual assessment on makers of branded pharmaceuticals and biologics, under which a company s assessment is based primarily on its share of branded drug sales to federal health care programs. Such fees could affect our future profitability. Although it is too early to determine the effect of the new health care legislation on our future profitability and financial condition, the new law appears likely to continue the pressure on pharmaceutical pricing, especially under the Medicare program, and may also increase our regulatory burdens and operating costs.

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Third-party payors are challenging the prices charged for medical products and services, and many third-party payors limit reimbursement for newly-approved health care products. These third-party payors may base their coverage and reimbursement on the coverage and reimbursement rate paid by carriers for Medicare beneficiaries. Furthermore, many such payors are investigating or implementing methods for reducing health care costs, such as the establishment of capitated or prospective payment systems. Cost containment pressures have led to an increased emphasis on the use of cost-effective products by health care providers. In particular, third-party payors may limit the indications for which they will reimburse patients who use any products that we may develop. Cost control initiatives could limit the price we might establish for products that we or our current or future collaborators may develop or sell, which would result in lower product revenues or royalties payable to us.

We face a risk of product liability claims and may not be able to obtain insurance.

Our