

GLYCOMIMETICS INC
Form 10-K
March 06, 2019
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, D.C. 20549

FORM 10-K

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d)

OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended December 31, 2018

Commission file number 001-36177

GlycoMimetics, Inc.

(Exact name of Registrant as specified in its charter)

Delaware
(State or other jurisdiction of
incorporation or organization)

06-1686563
(IRS Employer
Identification No.)

9708 Medical Center Drive

Rockville, Maryland
(Address of principal executive offices)

20850
(Zip Code)

Registrant's telephone number, including area code: (240) 243-1201

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

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Title of Each Class: Common Stock, \$0.001 par value
Name of Each Exchange on which Registered: The Nasdaq Stock Market

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

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

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

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

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

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

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

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

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

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

As of June 30, 2018, the last business day of the registrant's last completed second quarter, the aggregate market value of the Common Stock held by non-affiliates of the registrant was approximately \$538.3 million based on the closing price of the registrant's Common Stock, as reported by the Nasdaq Global Market, on such date.

At February 28, 2019, 43,168,969 shares of GlycoMimetics, Inc.'s Common Stock, \$0.001 par value per share, were outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

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Portions of GlycoMimetics, Inc.'s definitive proxy statement, to be filed pursuant to Regulation 14A under the Securities Exchange Act of 1934, for its 2019 Annual Meeting of Stockholders are incorporated by reference in Part III of this Form 10-K.

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SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K, or this Annual Report, contains 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, or the Exchange Act, that involve substantial risks and uncertainties. The forward-looking statements are contained principally in Part I, Item 1. “Business,” Part I, Item 1A. “Risk Factors,” and Part II, Item 7. “Management’s Discussion and Analysis of Financial Condition and Results of Operations,” but are also contained elsewhere in this Annual Report. In some cases, you can identify forward-looking statements by the words “may,” “might,” “will,” “could,” “would,” “should,” “expect,” “intend,” “plan,” “objective,” “anticipate,” “believe,” “estimate,” “predict,” “project,” “potential,” “ongoing,” or the negative of these terms, or other comparable terminology intended to identify statements about the future. These statements involve known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements. Although we believe that we have a reasonable basis for each forward-looking statement contained in this Annual Report, we caution you that these statements are based on a combination of facts and factors currently known by us and our expectations of the future, about which we cannot be certain. Forward-looking statements include statements about:

- our plans to develop and commercialize our glycomimetic drug candidates;
- our ongoing and planned clinical trials for our drug candidates uproleselan and GMI-1359, including the timing of initiation of and enrollment in the trials, the timing of availability of data from the trials and the anticipated results of the trials;
- our ability to achieve anticipated milestones and potential royalties under our license agreement with Pfizer for our drug candidate rivipansel and the timing and results of the ongoing Phase 3 clinical trial of rivipansel;
- the timing of and our ability to obtain and maintain regulatory approvals for our drug candidates;
- the clinical utility of our drug candidates;
- our commercialization, marketing and manufacturing capabilities and strategy;
- our intellectual property position;
- our ability to identify additional drug candidates with significant commercial potential that are consistent with our commercial objectives;
- our estimates regarding future revenues, expenses and needs for additional financing; and
- our beliefs about our capital expenditure requirements and that our capital resources will be sufficient to meet our anticipated cash requirements through our receipt of the top-line results from our Phase 3 clinical trial of uproleselan in individuals with relapsed/refractory AML.

You should refer to Item 1A. “Risk Factors” section of this Annual Report for a discussion of important factors that may cause our actual results to differ materially from those expressed or implied by our forward-looking statements. As a result of these factors, we cannot assure you that the forward-looking statements in this Annual Report will prove to be accurate. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified time frame, or at all. We undertake no obligation to publicly update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law. You should, therefore, not rely on these forward-looking statements as representing our views as of any date subsequent to the date of this Annual Report.

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PART I

ITEM 1. BUSINESS

Company Overview

We are a clinical stage biotechnology company focused on the discovery and development of novel glycomimetic drugs to address unmet medical needs resulting from diseases in which carbohydrate biology plays a key role. Glycomimetics are small molecules that mimic the structure of carbohydrates involved in important biological processes. Using our expertise in carbohydrate chemistry and knowledge of carbohydrate biology, we are developing a pipeline of proprietary glycomimetics designed to inhibit disease-related functions of carbohydrates, such as the roles they play in inflammation, cancer and infection. We believe this represents an innovative approach to drug discovery to treat a wide range of diseases.

Our proprietary glycomimetics platform is based on our expertise in carbohydrate chemistry and our understanding of the role carbohydrates play in key biological processes. Most human proteins are modified by the addition of complex carbohydrates to the surface of the proteins. The addition of these carbohydrate structures affects the functions of these proteins and their interactions with other molecules. Our initial research and development efforts have focused on drug candidates targeting selectins, which are proteins that serve as adhesion molecules and bind to carbohydrates that are involved in the inflammatory component and progression of a wide range of diseases, including hematologic disorders, cancer and cardiovascular disease. For example, we believe that members of the selectin family play a key role in the onset and progression of VOC and also in tumor metastasis and resistance to chemotherapy. Inhibiting specific carbohydrates from binding to selectins has long been viewed as a potentially attractive approach for therapeutic intervention. The ability to successfully develop drug-like compounds that inhibit binding with selectins, known as selectin antagonists, has been limited by the complexities of carbohydrate chemistry. We believe our expertise in carbohydrate chemistry and our understanding of carbohydrate-protein binding interactions enable us to design selectin antagonists and other glycomimetics that may inhibit the disease-related functions of certain carbohydrates in order to develop novel drug candidates to address orphan diseases with high unmet medical need.

Overview of our Drug Candidates

Rivipansel

Our first drug candidate, rivipansel, is being developed for the treatment of vaso-occlusive crisis, or VOC, a debilitating and painful condition that occurs periodically throughout the life of a person with sickle cell disease, or SCD. Rivipansel has received fast track designation from the U.S. Food and Drug Administration, or FDA, as well as orphan drug designation from the FDA in the United States and from the European Medicines Agency, or EMA, in the European Union, or EU.

Rivipansel is a glycomimetic drug candidate that acts as a pan-selectin antagonist, meaning it binds to all three members of the selectin family, E-, P- and L-selectin. We believe that rivipansel, by acting as a pan-selectin antagonist, inhibits the role that selectins play in VOC for people with SCD. VOC, one of the most severe complications of SCD, can result in acute ischemic tissue injury at one or more sites, with inflammation and pain of varying degrees of severity. The standard of care in the United States for people experiencing VOC is to manage its symptoms, which typically includes hospitalization, narcotic pain management and hydration. We believe that rivipansel, if approved, would be the first drug to interrupt the underlying cause of VOC, thereby potentially reducing the use of narcotics for pain management and enabling patients to leave the hospital more quickly.

We have completed four clinical trials of rivipansel involving a total of 163 subjects. In April 2013, we completed a Phase 2 clinical trial in which 76 patients hospitalized for VOC, ranging from 12 to 60 years old, were treated with the standard of care plus either rivipansel or placebo. In this trial, patients treated with rivipansel experienced reductions in the time to reach resolution of VOC, length of hospital stay and use of opioid analgesics for pain management, in each case as compared to patients receiving placebo. This improvement was seen in both adult and pediatric patients. Adverse event rates and severity were comparable between those treated with rivipansel and those receiving placebo.

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We have entered into a license agreement with Pfizer, Inc., or Pfizer, for the further development and potential commercialization of rivipansel worldwide. Since the completion of our Phase 2 clinical trial of rivipansel in 2013, Pfizer has been responsible for the further clinical development, regulatory approval and potential commercialization of rivipansel. Under a Special Protocol Assessment with the FDA, Pfizer enrolled the first patient in a pivotal Phase 3 clinical trial in June 2015, and we have been notified by Pfizer that it expects to complete enrollment in early 2019 and to have top-line data from the trial in the second quarter of 2019. Under our license agreement with Pfizer, we are eligible to receive payments of up to \$115.0 million upon the achievement of specified development milestones, up to \$70.0 million upon the achievement of specified regulatory milestones, and up to \$135.0 million upon the achievement of specified levels of annual net sales of licensed products. We are also eligible to receive tiered royalties, with percentages ranging from the low double digits to the low teens, based on net sales of rivipansel worldwide, subject to reductions in specified circumstances. Under a separate research agreement with the University of Basel, we have agreed to pay 10% of any milestone payments and royalties we may receive from Pfizer with respect to rivipansel.

Uproleselan

Building on our experience with rivipansel, we are developing uproleselan, a specific E-selectin inhibitor, to be used in combination with chemotherapy to treat patients with acute myeloid leukemia, or AML, and potentially other hematologic cancers. Uproleselan has been granted breakthrough therapy designation by the FDA for the treatment of adults with relapsed or refractory AML. In addition, uproleselan has received orphan drug designation by the FDA and European Commission for the treatment of AML.

E-selectin plays a critical role in binding cancer cells within vascular niches in the bone marrow, which prevents the cells from entering circulation where they can be more readily killed by chemotherapy. In animal studies, uproleselan mobilized AML cancer cells out of the bone marrow, making them more sensitive to chemotherapy. In these studies, tumor burden was significantly reduced in the animals treated with a combination of chemotherapy and uproleselan as compared to animals treated with chemotherapy alone. In addition, the combination of uproleselan with chemotherapy resulted in improved survival rates for the treated animals, compared to chemotherapy alone. In other animal studies, uproleselan appeared to also protect normal cells from some of the side effects of chemotherapy. Common side effects of chemotherapy include bone marrow toxicity resulting in neutropenia, which is an abnormally low number of neutrophils, the white blood cells that serve as the primary defense against infection, and mucositis, which is the inflammation and sloughing of the mucous membranes lining the digestive tract. Animals treated with uproleselan and chemotherapy had less severe neutropenia and mucositis and lower bone marrow toxicity as compared to animals treated with chemotherapy alone. We believe that treatment with uproleselan results in lower bone marrow toxicity due to its inhibition of E-selectin, which inhibition makes stem cells in the bone marrow divide less frequently, thereby protecting them from chemotherapy agents that target rapidly dividing cells.

We completed an initial Phase 1 trial in healthy volunteers for uproleselan and in May 2017 we completed enrollment in a Phase 1/2 clinical trial in patients with either relapsed/refractory or de novo/secondary AML. In December 2018, at the annual meeting of the American Society of Hematology, or ASH, we presented final clinical data from the Phase 1/2 trial that showed high remission rates, improved overall survival and improved duration of survival, all compared to historical controls derived third-party clinical trials evaluating treatment with standard chemotherapy. In November 2018, we dosed the first patient in a Phase 3 clinical trial to evaluate uproleselan in adults with relapsed/refractory AML. In addition, the data from our Phase 1/2 clinical trial suggested a favorable safety, pharmacokinetic, or PK, and biomarker profile for uproleselan. In 2018, we entered into agreements with the National Cancer Institute, or NCI, and with the Haemato Oncology Foundation for Adults in the Netherlands, or HOVON, to further evaluate uproleselan in two separate clinical trials for the treatment of specific AML patient populations.

GMI-1359

We are developing an additional clinical drug candidate, GMI-1359, that simultaneously targets both E-selectin and a chemokine receptor known as CXCR4. Since E-selectin and CXCR4 are implicated in the retention of cancer cells in the bone marrow, we believe that targeting both E-selectin and CXCR4 with a single compound could improve efficacy in the treatment of cancers that affect the bone marrow, particularly solid tumors that have a propensity to metastasize to bone, such as breast and prostate cancer. We recently completed a Phase 1 randomized, double-blind, placebo-controlled, single-dose escalation trial of GMI-1359 in healthy volunteers. In this trial, volunteer participants received a single injection of either GMI-1359 or placebo, after which they were evaluated for safety, tolerability and

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PK. This trial was conducted at a single site in the United States. GMI-1359 was generally well tolerated in this trial, with no participants experiencing serious adverse events. We anticipate initiating a Phase 1b trial of GMI-1359 in patients with metastatic breast cancer in 2019.

In addition to our clinical-stage programs described above, we are also advancing other programs. These programs include:

- **Selectin Antagonists:** As a potential life-cycle extension to uproleselan, our scientists have rationally designed an innovative antagonist of E-selectin, GMI-1687, that could be suitable for subcutaneous administration in the clinic. When given by subcutaneous injection in animal models, GMI-1687 has been observed to have equivalent activity to uproleselan, but at an approximately 1,000-fold lower dose. We believe that GMI-1687 could be developed to broaden the clinical usefulness of an E-selectin antagonist to conditions where outpatient treatment is preferred or required. We are currently conducting studies with GMI-1687 to support our planned submission of an investigational new drug application, or IND, to the FDA.
- **Galectin Antagonists:** Galectin-3 is a carbohydrate-binding protein whose expression has been shown to play a central role in fibrosis and cancer. Galectin-3 has been linked to a number of biologic processes including inflammation, aberrant cell activation and proliferation (macrophages, neutrophils, and mast cells), fibrogenesis and ultimately, organ dysfunction. Experimental data have implicated galectin-3 in a variety of diseases across a number of organ systems, including liver, kidney, lung, eye and heart. Notably, in our preclinical studies, blockage of galectin-3 has been shown to prevent fibrosis following organ damage, which we believe makes it a promising target for further evaluation and development.

Current research also indicates that galectins have important roles in modulating the immune and inflammatory response to cancer that contributes to neoplastic transformation, tumor cell survival, angiogenesis and metastasis. Applying our understanding of carbohydrate biology and chemistry, we have rationally designed several high-potency, selective, small-molecule “glycomimetic” antagonists of Galectin-3. These novel compounds have been observed to have anti-fibrotic activity in our animal models of disease.

We have retained the worldwide development and commercialization rights to all of our drug candidates other than rivipansel.

“GlycoMimetics,” the GlycoMimetics logo and other trademarks or service marks of GlycoMimetics, Inc. appearing in this Annual Report are the property of GlycoMimetics, Inc. This Annual Report contains additional trade names, trademarks and service marks of others, which are the property of their respective owners.

Our Strategy

Our goal is to be the leader in the discovery, development and commercialization of novel glycomimetic drugs to address unmet medical needs resulting from diseases in which carbohydrate biology plays a key role. Leveraging the potentially broad applicability of our proprietary glycomimetics platform, our initial focus is to internally develop and advance orphan drug candidates targeted at hematologic cancers and other diseases, and to out-license any drug candidates we may develop that are targeted at larger market opportunities. The key elements of our strategy are to:

- Complete the clinical development of and obtain regulatory approvals for uproleselan for the treatment of adults with relapsed/refractory AML. Based on the positive Phase 1/2 clinical trial results presented at ASH in 2018, we announced the design for a randomized, double-blind, placebo-controlled Phase 3 clinical trial to evaluate uproleselan in adults with relapsed/refractory AML, which design is aligned with guidance we received from the FDA. In this single pivotal trial, we plan to enroll approximately 380 adult patients with relapsed or refractory AML at centers in the United States, Canada, Europe and Australia. Enrollment began in the fourth quarter of 2018. If the results from this Phase 3 clinical trial are positive, we plan to apply for regulatory approval from the FDA and EMA.

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- Explore the potential use of uproleselan in other AML patient populations through third-party collaborations. In May 2018, we signed a Cooperative Research and Development Agreement, or CRADA, with the NCI, part of the National Institutes of Health. Under the terms of the CRADA, we will collaborate with both the NCI and the Alliance for Clinical Trials in Oncology to conduct a randomized, controlled clinical trial evaluating the addition of uproleselan to a standard Cytarabine/Daunorubicin chemotherapy regimen (7&3) in older adults with previously untreated AML who are eligible for intensive chemotherapy. The primary endpoint will be overall survival, with a planned interim analysis based on event-free survival after the first 250 patients have been enrolled in the trial. Under the terms of the CRADA, the NCI may fund additional research, including clinical trials of pediatric patients with AML as well as preclinical experiments and clinical trials evaluating alternative chemotherapy regimens. Additionally, in February 2018, we entered into an agreement with Haemato Oncology Foundation for Adults in the Netherlands, or HOVON, to initiate clinical trial startup activities evaluating uproleselan in adults with newly diagnosed AML who are not eligible for intensive chemotherapy. The trial will also evaluate patients with myelodysplastic syndrome, or MDS, who have a high risk of leukemia. The HOVON trial will be the first to evaluate uproleselan together with decitabine, a chemotherapy drug, in this underserved population of AML and MDS patients. We believe these two patient populations represent a significant potential expansion opportunity for uproleselan. HOVON intends to enroll approximately 140 patients in the clinical trial, including a control arm. Patients will be evaluated after three cycles of therapy; key efficacy endpoints will include remission rate, disease-free survival and overall survival. The trial is anticipated to be conducted in five countries across Europe.
- Advance the clinical development of GMI-1359 for the treatment of cancer. Following completion of a Phase 1 single-dose escalation trial in healthy volunteers in 2018, we anticipate initiating a Phase 1b trial of GMI-1359 in metastatic breast cancer patients in 2019.
- Support Pfizer's further development of rivipansel. We will continue to support Pfizer, as requested, with the clinical development of rivipansel, including the ongoing Phase 3 clinical trial and potential regulatory filings for marketing approval. We expect to use any milestone and royalty payments that we may receive from Pfizer to accelerate the development of our other drug candidates.
- Identify and develop additional novel selectin antagonists to address unmet medical needs with significant market potential. We believe our glycomimetics platform will enable us to develop a broad pipeline of potential drug candidates that may be orphan products or may address larger market opportunities. We have identified a highly potent E-selectin antagonist which we believe will be suitable for subcutaneous delivery and could be of value in potential major market opportunities, such as the treatment of certain cancers and cardiovascular disease.
- Apply our insights and our glycomimetics platform to other carbohydrate targets beyond selectins. We have identified additional opportunities where carbohydrates play critical roles in disease processes and where we believe we can apply our platform to create targeted glycomimetic drugs. We have designed inhibitors that specifically block the binding of galectin-3 to carbohydrate structures. We plan to optimize these compounds and conduct additional preclinical studies in 2019 to further characterize the effects of galectin-3 inhibitors on inflammation and fibrosis, as well as immune processes. We are also designing other galectin inhibitors with dual functional inhibition of E-selectin that we believe could be used to treat various diseases.

Our Platform

Our proprietary glycomimetics platform is based on our expertise in carbohydrate chemistry and our understanding of the role carbohydrates play in key biological processes. Carbohydrate structures on cell surfaces are responsible for complex carbohydrate-protein binding interactions. Inhibiting these binding interactions affects the functions of these proteins and their interactions with other molecules. We believe our expertise enables us to design specific glycomimetic molecules that can mimic carbohydrate structures and thereby inhibit their disease-related functions.

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Our initial focus is on selectin antagonists, which we believe have the potential to address unmet medical needs in a number of orphan and large market opportunities. Selectins have been shown to play a key role in a wide range of diseases, including hematologic disorders, inflammatory diseases, infection, cancer and cardiovascular disease.

Our initial drug design efforts are focused on a naturally occurring, three-dimensional complex carbohydrate core structure known as the Lewis structure. This core structure is naturally modified in a variety of ways to form many different functional carbohydrates. These variations determine the biological functions of the carbohydrates, including functions related to conditions defined above. Accordingly, we believe that this structure provides the foundation for the design of glycomimetic drug candidates that could be used to address a variety of diseases.

Once we identify a carbohydrate structure involved in a disease pathway, we design molecules that mimic that carbohydrate structure and inhibit its disease-related functions by binding to the carbohydrate's target receptor, thereby blocking the binding by the native carbohydrate itself. For example, one of the naturally modified Lewis structures binds to selectins, which play a key role in VOC. Rivipansel mimics that carbohydrate structure and accordingly binds to selectins, which we believe thereby inhibits the progression of VOC. In addition, our glycomimetic molecules are designed to have greater affinity to the carbohydrate's target receptor than does the native carbohydrate. This means that the glycomimetic molecules possess stronger intermolecular forces between themselves and the target receptors, and thus "outcompete" the native carbohydrates in binding to the relevant target receptors, thereby inhibiting their disease-related functions. Using our glycomimetics platform, we have designed and synthesized a proprietary library of these structures targeting different biological processes.

Our glycomimetics platform includes intellectual property, know-how, expertise, proprietary biological information and biochemical assays, all of which support the rational design of potent glycomimetic compounds. These include:

- Know-how to successfully mimic the Lewis structure, which is common to a number of functional carbohydrates.
- Use of empirical methods to determine critical interactions between variations of a particular functional carbohydrate and its target molecule.
- Application of the empirically determined bioactive structure of the functional carbohydrate for docking into the binding area of the crystal structure of the target molecule.
- Expertise in stabilizing the bioactive core of glycomimetic compounds and increasing the number of interaction contact points to improve affinity.
- Experience and technology in synthetic organic chemistry required for the specialized synthesis of carbohydrates and their modifications.
- Proprietary assays to determine the binding characteristics, inhibitory activity and biological activity of glycomimetic compounds.

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Our Pipeline

We have discovered our drug candidates internally through a rational drug design approach that couples our expertise in carbohydrate chemistry with our knowledge of carbohydrate biology. We are actively developing glycomimetic drug candidates based on this expertise. Our drug candidates and their target indications and development status are summarized in the chart below.

Rivipansel —Targeting Selectins to Treat VOC

Rivipansel is being developed to treat VOC with the goal of reducing duration of VOC episodes, length of hospital stay and use of opioid analgesics for pain management. In our Phase 2 clinical trial, patients treated with rivipansel plus the standard of care demonstrated improvement in these endpoints, in each case as compared to patients receiving placebo plus the standard of care.

Sickle Cell Disease and VOC

SCD is a genetic disease that, according to the Centers for Disease Control and Prevention, or CDC, affects millions of people throughout the world, including an estimated 100,000 people in the United States and an estimated 60,000 people in Europe. People living with SCD have chronic and acute damage to their tissue and organs. One of the most common and severe complications of SCD is vaso-occlusive crisis, or VOC, which is the occurrence of unpredictable episodes of acute pain, often very excruciating, in the affected parts of the body. Recurrent episodes may cause irreversible organ damage. The CDC estimates that VOC resulted in approximately 75,000 hospitalizations in the United States in 2010. According to the National Hospital Discharge Survey conducted by the National Center for Health Statistics, these hospitalizations have an average duration of approximately six days.

Among both adults and children with SCD, VOC is the most common reason for seeking medical attention resulting in hospitalization. As there are no approved therapies that interrupt VOC once it has started or that treat the underlying ischemic event, the standard of care for people experiencing VOC is limited to supportive care consisting of pain management, hydration and treatment of any precipitating events such as infection and inflammatory conditions.

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Market Opportunity for Rivipansel in SCD

We believe that effective, on-demand (as needed) treatment for VOC could provide significant clinical and pharmacoeconomic benefit. According to the U.S. Agency for Healthcare Research and Quality, the average hospital charges in the United States for a patient treated for VOC were approximately \$20,000 in 2006. In some states, these charges may be substantially higher. For example, according to the California Office of Statewide Health Planning and Development, the average hospital charges for a patient treated for VOC in California were over \$40,000 in 2006. A reduction in the length of a hospital stay following treatment with rivipansel could significantly reduce these costs of care.

Additionally, if rivipansel is shown to be safe and effective in reducing the duration of VOC in hospitalized patients, it could also be tested to determine if hospitalization could be prevented with use of rivipansel in the emergency department, or if VOC could be managed safely and effectively in the home or in an outpatient setting through a self-administered dosage form, thereby avoiding costly emergency department visits. We believe that uses in each of these settings represent potentially significant market opportunities.

The Role of Selectins in VOC

The cause of vascular occlusion involves both an inflammatory component and a mechanical component. In the inflammatory component, white blood cells begin to roll along and then adhere to the endothelium, the thin layer of cells that lines the interior surface of blood vessels. These white blood cells then become activated and express adhesion receptors known as integrins, which bind and form aggregates with platelets, red blood cells and other white blood cells. These cell aggregates are responsible for the mechanical component of vascular occlusion, in which rigid sickled red blood cells are more easily caught in the post-capillary venules, which are very small blood vessels connecting the capillaries and the veins. The resulting vascular occlusion causes slowing of blood flow in the post-capillary venules, contributing to inadequate oxygen supply in the local tissue, known as ischemia, which in turn causes further tissue inflammation and pain.

The development of VOC is illustrated in the following diagram:

Selectins are important in this process because they act as adhesion molecules and play a key role in the initial recognition and binding of white blood cells to the endothelial cells, and their formation of aggregates with platelets, red blood cells and other white blood cells. White blood cells express carbohydrates on their surfaces that bind to E-selectin that is present on inflamed vascular endothelium. White blood cells bound to E-selectin on the endothelial

cells then become activated and act as adhesion sites for platelets, red blood cells and other white blood cells, thereby leading to the formation of an occlusion. Rivipansel is a glycomimetic drug candidate designed to inhibit binding of all three types of selectins and inhibit the selectin-mediated recognition and binding of white blood cells to the endothelium. The rationale for the development of rivipansel to treat VOC is that, by blocking these steps in the vaso-occlusive process, it has the potential to decrease the duration and intensity of VOC.

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Limitations of the Current Standard of Care for VOC

Although bone marrow transplant is currently available and can be curative for SCD, its use is greatly limited by the lack of availability of matched donors and by the risk of serious complications, including graft versus host disease, infection and death.

Until 2017, the only drug approved to treat SCD was hydroxyurea. Hydroxyurea, available in both generic and branded formulations, is a once daily oral treatment intended to reduce the frequency of VOC in patients with SCD who have recurrent VOC episodes. While hydroxyurea has been shown to reduce the frequency of hospitalization due to VOC, in some patient groups, it is not effective in relieving symptoms or accelerating the resolution of an ongoing VOC episode. Moreover, hydroxyurea is not suitable for all patients. Its uptake and effectiveness can be limited by a lack of compliance to the dosing regimen, inconsistent patient responses, variable tolerability and concerns regarding long-term toxicity and other adverse side effects. In particular, hydroxyurea is labeled to inform patients that it can cause a severe decrease in the number of blood cells in a patient's bone marrow, which may increase risks that the patient will develop a serious infection or bleeding, and that it may increase the risk that the patient will develop certain cancers. Furthermore, hydroxyurea is not effective in relieving symptoms or accelerating the resolution of an ongoing VOC episode.

In July 2017, the FDA approved Endari, a twice-daily, oral, prophylactic therapy intended to reduce the acute complications of SCD in adult and pediatric patients 5 years of age and older. Common side effects of Endari include constipation, nausea, headache, abdominal pain, cough, pain in the extremities, back pain and chest pain. Since its launch in December 2017, real world experience with Endari has been limited.

Since available therapies do not address the underlying pathophysiology of an ongoing VOC episode, supportive care with opioid narcotics and hydration remain the current standard of care for VOC until the event runs its natural course. Pain management often starts with oral medications taken at home at the onset of pain. However, if the pain is not relieved, or if it progresses, patients typically seek medical attention in a clinic setting or emergency department. Pain that is not controlled in these settings typically requires hospitalization for more potent pain medications, typically administered intravenously. The patient must stay in the hospital to receive these intravenous pain medications and fluids until the VOC resolves and the pain subsides. Use of narcotics can lead to tissue or organ damage and resulting complications and morbidities, prolonged hospital stays and associated continuation of pain and suffering. Treatment of pain with IV narcotics and management of VOC-related complications typically require hospital stays ranging from a few days to a few weeks, with an average length of stay of approximately six days. Other supportive measures during hospitalization include supplemental oxygen and treatment of any concurrent infections or other conditions.

In light of the debilitating effects of VOC and the associated high costs of care, there is a significant unmet medical need for treatment that can be taken at the onset of a VOC episode that selectively targets the underlying inflammatory ischemic event in order to reduce the severity and duration of VOC in SCD patients. We believe that rivipansel can potentially satisfy this unmet medical need.

Rivipansel Clinical Results

We completed a Phase 2 clinical trial of rivipansel in sickle cell patients hospitalized for VOC. This trial was a randomized, double-blind, placebo-controlled trial at 22 sites in the United States and Canada evaluating the safety, efficacy and PK of multiple IV doses of rivipansel or placebo in 76 patients hospitalized for VOC, ranging from 12 to 60 years old. Of these patients, 43 received rivipansel and 33 received placebo, in both cases in addition to the standard of care. Patients receiving rivipansel in the trial received one of two dose levels. Patients in the low dose group received a loading dose of 20 mg/kg, followed by a 10 mg/kg dose every 12 hours. Patients in the high dose group received a loading dose of 40 mg/kg, followed by a 20 mg/kg dose every 12 hours.

In patients receiving rivipansel in this trial, there were reductions in multiple measures related to a VOC episode as compared to patients receiving placebo. Two widely used statistical methods, known as ANCOVA and Kaplan-Meier, were used to analyze the results of this trial. The time to reach resolution of VOC, the primary endpoint of the trial, was reduced in the patients receiving rivipansel by a mean of 41.0 hours, as measured by ANCOVA, with a p-value of 0.192, and reduced by a median of 63.3 hours, as measured by Kaplan-Meier, with a p-value of 0.187. P-value is a conventional statistical method for measuring the statistical significance of clinical results. A p-value of 0.05 or less represents

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statistical significance, meaning that there is a less than 1-in-20 likelihood that the observed results occurred by chance. In addition, in the patients receiving rivipansel, the time to hospital discharge was reduced by a mean of 54.7 hours, as measured by ANCOVA, with a p-value of 0.096, and a median of 83.9 hours, as measured by Kaplan-Meier, with a p-value of 0.092. The time to transition off IV analgesics was reduced by a mean of 47.0 hours, as measured by ANCOVA, with a p-value of 0.137, and a median of 75.7 hours, with a p-value of 0.089, as measured by Kaplan-Meier. The cumulative amount of opioid analgesic administered during hospitalization was reduced by 83%, as measured by ANCOVA, with a p-value of 0.01. Although the Phase 2 clinical trial was not large enough to detect statistically significant differences in these endpoints, other than with respect to the reduction in cumulative amount of opioid analgesic administered, we believe the observed reductions in these measures in patients treated with rivipansel, and the consistency of a positive response across multiple measures, demonstrate the potential benefit of rivipansel.

We believe the favorable effects we observed in our Phase 2 clinical trial are the result of mechanism-based resolution of VOC. Specifically, we believe that by inhibiting selectin-mediated adhesion of white blood cells to the endothelium, rivipansel prevents propagation of VOC and promotes early resolution. Results from the Phase 2 clinical trial provide the first clinical evidence of a positive effect of rivipansel in adult and pediatric patients experiencing VOC. No currently available therapies provide similar benefits to patients in VOC. Based on the data from our Phase 2 clinical trial for rivipansel, we believe rivipansel has the potential to become the first drug approved to treat VOC in both adult and pediatric patient populations.

If rivipansel is demonstrated to be safe and effective for the treatment of VOC, we believe it may show substantial clinical and pharmacoeconomic benefit. If patients treated with rivipansel are discharged more quickly from the hospital, there is potential to reduce the costs of hospitalization, in addition to showing clinical benefit by reduced duration of VOC episodes and reduced use of opioid analgesics for pain management. In addition, if rivipansel is shown to be safe and effective for treating VOC in hospitalized patients, it is possible that it could be tested in patients experiencing VOC who are not hospitalized to determine if hospitalization could be prevented or if pain from VOC could be managed safely and effectively in the home or in an outpatient setting. We believe that uses in each of these settings could represent significant market opportunities for rivipansel. Following the completion of the Phase 2 clinical trial, Pfizer is now responsible for the further clinical development, regulatory approval and commercialization of rivipansel.

Following transfer of the IND, Pfizer has undertaken significant activity to work toward a New Drug Application, or NDA, for rivipansel including, an approved special protocol assessment, or SPA, agreement for the design, endpoints and statistical analysis approach of the Phase 3 clinical trial. Pfizer enrolled the first patient in this Phase 3 clinical trial in June 2015. The Phase 3 trial, entitled “RESET” (Rivipansel: Evaluating Safety, Efficacy and Time to Discharge), is assessing the efficacy and safety of rivipansel for the treatment of VOC in patients hospitalized with sickle cell disease. Pfizer intends to enroll at least 350 subjects with sickle cell disease, aged six and older who are hospitalized for VOC, in this Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in order to evaluate the efficacy and safety of treatment with rivipansel. Trial participants must be receiving treatment with intravenous, or IV, opioids for their VOC and must be able to receive the first dose of rivipansel within 24 hours of initiation of intravenous opioid therapy. The primary endpoint for the trial will be time to readiness-for-discharge. Key secondary endpoints will include time to discharge, cumulative IV opioid consumption and time to discontinuation of IV opioids. Pfizer has notified us that completion of enrollment in the Phase 3 clinical trial is expected in early 2019 with top-line data available by the end of the second quarter of 2019.

Uproleselan —Targeting the Bone Marrow Microenvironment to Treat Hematologic Cancers

We are developing uproleselan, a specific E-selectin antagonist, to be used adjunctively with standard chemotherapy to treat AML and other hematologic cancers. We believe that uproleselan may be used as first-line treatment for

elderly patients with AML or, for patients with relapsed or refractory AML. Uproleselan targets interactions between cancer cells and the bone marrow microenvironment. In preclinical studies, combining uproleselan with chemotherapy made cancer cells more sensitive to chemotherapy. In other preclinical studies, uproleselan also reduced some of the toxic effects of chemotherapy, including neutropenia and mucositis, on normal cells.

Uproleselan received orphan drug designation from the FDA in May 2015 for the treatment of patients with AML. In June 2016, uproleselan received fast track designation from the FDA for the treatment of adult patients with relapsed or refractory AML and elderly patients aged 60 years or older with AML. In May 2017, uproleselan received breakthrough therapy designation from the FDA for the treatment of adult patients with relapsed or refractory AML.

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May 2017, the European Commission, based on a favorable recommendation from the EMA Committee for Orphan Medicinal Products, granted orphan designation for uproleselan for the treatment of patients with AML.

Acute Myeloid Leukemia

AML, a hematologic cancer that is characterized by the rapid growth of abnormal white blood cells that accumulate in the bone marrow and interfere with the production of normal blood cells, is a relatively rare disease, but one that accounts for the largest number of annual deaths from leukemia in the United States. According to the Surveillance, Epidemiology, and End Results Program managed by the National Cancer Institute, there were an estimated 19,520 new cases of AML diagnosed in 2018 in the United States. Approximately 352,000 patients in the world are diagnosed with AML annually. AML caused an estimated 10,670 deaths in 2018 in the United States.

AML is more commonly present in elderly patients, with a median age at diagnosis of 68 years according to the National Cancer Institute. In a review published in the Journal of Clinical Oncology, the median overall survival of patients 60 years old or older was nine months. The overall five-year relative survival rate for all AML patients is 27.4%, and only 3-8% for patients over 60 years old at diagnosis. Relative survival is a statistical measure of net survival that is calculated by comparing observed survival with expected survival from a comparable set of people who do not have AML, in order to measure the excess mortality that is associated with the AML diagnosis.

A number of published studies indicate that only some AML patients who receive chemotherapy achieve a complete response, which is defined as the disappearance of all signs of AML, and that most patients with a complete response will eventually relapse. Patients who do not enter remission are referred to as refractory, meaning that they are resistant to the chemotherapy treatment.

We believe there is a need for new treatment options for elderly patients with AML, as well as those AML patients who relapse or develop refractory disease. Most AML patients with relapsed or refractory disease have no established treatment options and, accordingly, may be referred for participation in clinical studies of potential new therapies. For patients who elect not to participate or are unable to participate, treatment options typically include chemotherapy regimens, hypomethylating agents and supportive care. Further, many elderly patients with AML are too frail to undergo chemotherapy as a result of other medical conditions, and may only be able to tolerate pain comfort or control measures. Without treatment, however, AML is uniformly fatal.

Role of E-selectin in AML

E-selectin has been shown to play important roles in the progression of AML. This has been observed in several studies, which have shown that levels of E-selectin correlate with tumor infiltration and relapse in AML. We therefore believe that our E-selectin antagonist, uproleselan, has the potential to improve the current treatment of patients with AML.

Uproleselan Preclinical Development

Some leukemia cells, known as blast cells, bind to E-selectin in the bone marrow where they are relatively protected from the effects of chemotherapy. This phenomenon is now known as environment-mediated drug resistance, or EMDR. We believe that E-selectin inhibition disrupts the cell adhesion involved in EMDR and mobilizes blasts out of the bone marrow and into the bloodstream, making them more susceptible to chemotherapy. We believe that this mechanism of action may allow uproleselan to improve chemotherapy response rates, duration of remission and, ultimately, survival in patients with hematologic cancers such as AML.

In one in vivo study in a mouse model of AML, combining uproleselan with chemotherapy, mobilized AML blast cells and significantly reduced tumor burden as compared to treatment with chemotherapy alone. In an in vitro study, AML cells once bound to E-selectin were more resistant to chemotherapy. In a related study, when treated with uproleselan, the resistance of such cells to chemotherapy was reduced. Tumor cells of patients who have relapsed AML, when tested in the laboratory, bound significantly higher levels of E-selectin than tumor cells of patients at initial diagnosis. Additional preclinical studies in mouse models of AML, in which E-selectin was observed to be upregulated, suggest that AML cells binding to E-selectin have increased chemo-resistance. This is due to the induction of tumor cell survival signaling pathways as a consequence of E-selectin binding. This effect within the bone marrow microenvironment is unique to E-selectin as compared to other vascular adhesion molecules and can be blocked by

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uproleselan. The results of this preclinical study were presented in an oral presentation at the 2017 annual ASH meeting in December 2017, and we believe the findings provide important information about how treatment with uproleselan may improve sensitivity to chemotherapy.

As uproleselan disrupts the interactions between cancer cells and bone marrow microenvironment, its mechanism of action is not limited to a single tumor type. In addition to our studies in AML, we have also tested the drug candidate in other cancer models. In in vivo studies involving animal models of multiple myeloma, chronic myelogenous leukemia and acute lymphoblastic leukemia, uproleselan, as an adjunct to standard-of-care chemotherapy, decreased tumor burden and improved survival over chemotherapy alone.

In addition to its anti-tumor effects, uproleselan, in animal models, has shown protection against some of the toxicities of chemotherapy. In particular, animals treated with uproleselan in combination with chemotherapy had less severe neutropenia and mucositis and lower bone marrow toxicity as compared to animals treated with chemotherapy alone. We believe that treatment with uproleselan results in lower bone marrow toxicity due to its inhibition of E-selectin, thereby making hematopoietic stem cells divide less frequently and protecting them from chemotherapy agents that target rapidly dividing cells. Hematopoietic stem cells are blood cells that give rise to all other types of blood cells and are heavily concentrated in the bone marrow. Similar effects have been demonstrated with rivipansel and were published in the journal *Nature Medicine* in December 2012. Based on these reductions in some of the toxicities of chemotherapy, we are evaluating these effects as secondary efficacy endpoints in our clinical trials.

Expanding the Utility of E-selectin antagonists

During the 2018 annual ASH meeting, we reported on the preclinical development of a highly potent antagonist of E-selectin, GMI-1687, which demonstrated significant activity in animal models previously reported for uproleselan but at an approximately 1,000-fold lower dose. This level of activity was obtained following injections under the skin and could alleviate the need for intravenous infusions. Based on these compound characteristics, we believe GMI-1687 could potentially be used in outpatient settings where an E-selectin antagonist has therapeutic relevance. We are currently conducting IND-enabling studies of GMI-1687.

Uproleselan Clinical Trials

In 2014, we completed a Phase 1 trial of uproleselan in healthy volunteers. The single-site Phase 1 trial was a randomized, double-blind, placebo-controlled, single ascending intravenous dose trial. In the trial, we evaluated the safety, tolerability and PK of uproleselan. Twenty-eight healthy adult subjects were enrolled in cohorts to receive study drug at three dose levels. In the trial, we observed that the subjects tolerated uproleselan well, and that the PK for uproleselan were consistent with what was predicted based on preclinical data.

In 2015, we commenced a multinational, Phase 1/2, open-label trial of uproleselan as an adjunct to standard chemotherapy in patients with AML. This trial in males and females with AML was conducted at a number of academic institutions in the United States, Ireland and Australia. The trial consisted of two parts. In the Phase 1 portion, escalation testing was performed to determine a recommended uproleselan dose in combination with standard chemotherapy to be used in the Phase 2 portion. In the Phase 2 portion of the trial, dose expansion was performed at the recommended dose of 10 mg/kg uproleselan in combination with standard chemotherapy. The primary objective of the trial was to evaluate the safety of uproleselan in combination with chemotherapy. Secondary objectives were to characterize PK and pharmacodynamics and to observe anti-leukemic activity. A total of 19 patients with relapsed or

refractory AML were enrolled and dosed with a single cycle of treatment with uproleselan and chemotherapy in the Phase 1 portion of the trial. In the Phase 2 portion, one cohort of 25 patients over 60 years of age with newly diagnosed AML and a second cohort of 47 patients with relapsed or refractory AML were enrolled. Unlike in the Phase 1 portion, some of the patients in the Phase 2 portion were eligible to receive multiple cycles of uproleselan with chemotherapy.

In December 2018, we presented final efficacy and correlative results from the Phase 1/2 trial at the 60th ASH Annual Meeting and Exposition. Key highlights from the Phase 1/2 clinical data include the following:

- Relapsed/Refractory (R/R) AML Cohort: At the recommended Phase 2 dose (RP2D), CR (complete remission)/CRi (complete remission with incomplete blood count recovery) rate was 41%, median overall survival, or OS, was 8.8 months (95% CI 5.7-11.4) and 69% of evaluable patients (11/16) achieved measurable residual disease negativity as assessed by either flow and/or DNA-based methods such as

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reverse transcription polymerase chain reaction (RT-PCR). OS will be the primary outcome measure in our company-sponsored Phase 3 trial in relapsed/refractory AML patients. In historical controls, OS of approximately 5.2-5.4 months has been observed in this population with this treatment approach. If in the Phase 3 trial we are able to achieve OS results comparable to those observed in the Phase 1/2 clinical trial, it could be a significant improvement over the results observed in these historical controls.

- Newly Diagnosed AML Cohort: At the RP2D, CR/CRi rate was 72%, median overall survival was 12.6 months (95% CI 9.9-not reached), EFS was 9.2 months (95% CI 3.0-12.6) and 56% of evaluable patients (5 out of 9) achieved measurable residual disease negativity as assessed by either flow and/or DNA-based methods such as RT-PCR. Of note, the EFS data (primary outcome measure for the interim analysis in the NCI-sponsored clinical trial in newly diagnosed AML patients) compares favorably to a range of 2.0-6.5 months for EFS in historical controls, which generally included lower risk patient populations than those treated in our Phase 1/2 trial.
- An analysis of E-selectin ligand expression on leukemic cells demonstrated that detectable levels were present on leukemic blasts for every patient tested, providing clinical evidence of biological relevance of the E-selectin ligand in this disease setting. In bone marrow samples, leukemic stem cell expression of E-selectin ligand correlated with leukemic blast E-selectin ligand expression ($p < 0.0001$), consistent with the hypothesis that E-selectin-mediated interactions are a mechanism of chemoresistance. Additionally, investigators assessed the association between baseline E-selectin ligand expression on leukemic blasts and clinical outcomes using a log-rank test. In the R/R cohort of patients evaluated, this analysis demonstrated that $\geq 10\%$ E-selectin ligand expression at baseline was correlated with prolonged survival ($p < 0.01$) for patients treated with uproleselan. We believe this observation is important because in patients not treated with uproleselan the scientific literature has instead observed that high levels of E-selectin ligand correlated with a worse clinical prognosis. The addition of uproleselan in our study appears to have reversed this trend toward worsened prognosis, and we believe this result may be achieved through the restoration of chemosensitivity.

Based on these positive results, we announced the design for a randomized, double-blind, placebo-controlled Phase 3 clinical trial to evaluate uproleselan in individuals with relapsed/refractory AML, which design is aligned with guidance received from the FDA. Based on consultations with the FDA, this single pivotal trial is planned to enroll approximately 380 adult patients with relapsed or refractory AML at centers in the United States, Canada, Europe and Australia. To best capture the full benefits of uproleselan, the primary efficacy endpoint will be overall survival; importantly, the FDA has advised us that data on overall survival will not need to be censored for transplant in the primary efficacy analysis, meaning that patients who proceed to transplant will continue to be included as part of the survival analysis. All patients will be treated with standard chemotherapy of either MEC (mitoxantrone, etoposide and cytarabine) or FAI (fludarabine, cytarabine and idarubicin), with approximately half of the patients randomized to receive uproleselan in addition to chemotherapy. Patients receiving uproleselan will be dosed for one day prior to initiation of chemotherapy, twice a day through the chemotherapy regimen, and then for two days after the end of chemotherapy, which was the same regimen as in the Phase 2 portion of the Phase 1/2 trial. The dose regimen will be fixed, rather than weight-based, which we believe will simplify administration and we will offer up to three cycles of consolidation therapy in both arms of the trial for patients who achieve remission. We believe that multiple cycles of treatment in patients who respond may drive an even deeper response in patients treated with uproleselan. If this is the case, it could lengthen the duration of remission with potential for additional benefit on survival. Key secondary endpoints of the Phase 3 trial will include the incidence of severe mucositis and remission rate, which will be assessed in a hierarchical fashion to provide supportive data. Enrollment in this pivotal trial began in the fourth quarter of 2018, and we expect top-line results from the trial to be available by the end of 2020.

In May 2018, we signed a CRADA with the NCI. Under the terms of the CRADA, we will collaborate with both the NCI and the Alliance for Clinical Trials in Oncology to conduct a Phase 2/3 randomized, controlled clinical trial testing the addition of uproleselan to a standard cytarabine/daunorubicin chemotherapy regimen (7&3) in older adults with previously untreated AML who are suitable for intensive chemotherapy. The primary endpoint will be overall survival, which is defined as the time from the date of randomization to death from any cause, with a planned interim analysis based on event-free survival after the first 250 patients have been enrolled in the trial. The full trial is expected to enroll approximately 670 patients. Under the terms of the CRADA, the NCI may also fund additional research, including clinical trials involving pediatric patients with AML as well as preclinical experiments and clinical trials

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evaluating alternative chemotherapy regimens. We will supply uproleselan as well as provide financial support to augment data analysis and monitoring for the Phase 3 program. We expect that this trial will open for enrollment in early 2019.

In February 2018, we entered into an agreement with HOVON to initiate clinical trial startup activities to evaluate uproleselan in adults with newly diagnosed AML but who cannot tolerate intensive chemotherapy, as well as in patients with MDS and a high risk of leukemia. The HOVON trial will be the first to evaluate uproleselan, together with decitabine, in this underserved population of AML and MDS patients who are not considered by their physicians to be candidates for intensive chemotherapy; these two populations represent a significant potential indication expansion opportunity for uproleselan. HOVON intends to enroll approximately 140 patients in the clinical trial, including a control arm. Patients will be evaluated after three cycles of therapy, and key efficacy endpoints will include remission rate, disease-free survival and overall survival. The trial is expected to start this year and will be conducted in five countries across Europe.

In December 2015, at the ASH annual meeting, we presented preclinical data suggesting that uproleselan could reverse resistance of certain chemotherapies seen in multiple myeloma, or MM. In September 2016, we dosed the first patient in a Phase 1 multiple dose-escalation clinical trial in defined populations of patients with MM who have not responded optimally to standard chemotherapy. In this trial, we were evaluating the efficacy, safety and PK of uproleselan, combined with bortezomib- or carfilzomib-based chemotherapy, for the treatment of MM. However, due to the changing treatment landscape of MM and subsequent enrollment challenges that we encountered, as of December 2018 we have discontinued enrollment in this trial. There have been no safety concerns identified with uproleselan in this trial.

GMI-1359 - Drug Candidate Targeting E-selectin and CXCR4

The chemokine CXCR4 has emerged as an important pro-inflammatory cytokine that is involved in cell migration throughout the body. Like E-selectin, tumor cells may also use the CXCR4 cellular pathway, contributing to chemoresistance, metastatic disease and ultimately decreased survival. We have an additional drug candidate, GMI-1359, that simultaneously targets both E-selectin and CXCR4. Since E-selectin and CXCR4 are implicated in keeping cancer cells in the bone marrow, we believe that targeting both E-selectin and CXCR4 with a single compound could improve efficacy in the treatment of cancers that affect the bone marrow, such as hematologic cancers, including AML and MM, metastases of certain solid tumors, such as breast and prostate cancer, and primary tumors of the bone such as osteosarcoma, as compared to targeting CXCR4 alone.

Leukemic blasts and circulating tumor cells derived from adenocarcinomas home to and are retained in the bone marrow via defined sinusoidal vascular gateways that express E-selectin and soluble mediators such as C-X-C motif chemokine 12 (CXCL12, also known as stem cell-derived factor 1). This homing and retention occurs through an interaction with E-selectin ligands and the chemokine receptor for CXCL12, CXCR4, which is expressed on tumor cells. Interrupting E-selectin-mediated cell activation, adhesion and homing and CXCR4-mediated homing and cell migration and retention may be synergistic and could have therapeutic benefit in many malignancies with unmet medical need. We believe the use of an E-selectin/CXCR4 dual antagonist as an adjunct to chemotherapy and possibly immunotherapy could improve response and remission rates, remission duration, and, ultimately, survival, particularly in malignancies where bone involvement is a primary hallmark of cancer growth and metastasis.

In one in vivo mouse model of bone metastatic prostate carcinoma, combining GMI-1359 with docetaxel significantly reduced tumor burden and attenuated bone destruction compared to docetaxel alone. In a mouse model of primary osteosarcoma, administration of GMI-1359 resulted in inhibition of both tumor growth and spread to the lung. These results were presented during the 2015 and 2018 meetings of the American Association of Cancer Research, respectively. In both mouse models, GMI-1359 showed single agent activity.

GMI-1359 recently completed a Phase 1 single-dose escalation trial in healthy volunteers. In this trial, volunteer participants received a single injection of GMI-1359, after which they were evaluated for safety, tolerability, PK and pharmacodynamics. This randomized, double-blind, placebo-controlled, dose-escalation trial was conducted at a single site in the United States. GMI-1359 was generally well tolerated in this trial, with no subjects experiencing serious adverse events. We have completed a protocol design for a Phase 1b trial of GMI-1359 in patients with metastatic breast cancer and anticipate study initiation in 2019.

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Galectin Inhibitors

Using our glycomimetics platform, we have designed galectin-3 inhibitors that specifically block the binding of galectin-3 to carbohydrate structures. Galectin-3 is a protein that is known to play critical roles in many pathological processes, including fibrosis, checkpoints in T-cell exhaustion during cancer immunotherapy, chemotherapy resistance and cardiovascular disease. We plan to continue to optimize these compounds and conduct additional preclinical experiments in 2019 to further characterize the effects of our galectin-3 inhibitors on immune processes and fibrosis. One such compound, GMI-1757, is a dual antagonist of both E-selectin and galectin-3 and was shown to inhibit thrombus formation in a vena cava model and fibrosis in a corneal neovascularization model. These results were presented during the 2018 meeting of the American Society of Hematology.

Our License Agreement with Pfizer for Rivipansel

Overview

In October 2011, we entered into a license agreement with Pfizer, under which we granted Pfizer an exclusive worldwide license to develop and commercialize rivipansel, for all fields and uses. The products licensed under the agreement also include certain backup compounds, along with modifications of and improvements to rivipansel that meet defined chemical properties.

Under the terms of the agreement, we received a \$22.5 million upfront payment and are eligible to earn up to \$115.0 million upon the achievement of specified development milestones, including the dosing of the first patients in Phase 3 clinical trials for up to two indications and the first commercial sale of a licensed product in the United States and selected European countries for up to two indications, up to \$70.0 million upon the achievement of specified regulatory milestones, including the acceptance of our filings for regulatory approval by regulatory authorities in the United States and Europe for up to two indications, and up to \$135.0 million upon the achievement of specified levels of annual net sales of licensed products. We are also eligible to receive tiered royalties for each licensed product, with percentages ranging from the low double digits to the low teens, based on net sales of rivipansel worldwide, subject to reductions in specified circumstances. The first potential milestone payment under the Pfizer agreement was \$35.0 million upon the initiation of dosing of the first patient in a Phase 3 trial of rivipansel by Pfizer. Under the license agreement, Pfizer made a \$15.0 million non-refundable payment to us in May 2014, and the dosing of the first patient in the Phase 3 clinical trial triggered the remaining \$20.0 million milestone payment to us, which we received in August 2015. There have been no additional payments received from Pfizer since 2015.

Development and Commercialization Obligations

Pfizer will initially develop and seek approval for rivipansel in the field of sickle cell disease under the agreement. We were responsible for completion of the Phase 2 clinical trial relating to VOC associated with sickle cell disease. Following the completion of the Phase 2 clinical trial, we now have no further development or commercialization obligations, and Pfizer is required to use commercially reasonable efforts, at its expense, to develop, obtain regulatory approval for and commercialize rivipansel for sickle cell disease in the United States. Pfizer generally must notify us in writing promptly of any decision to cease development activities, efforts to obtain regulatory approval or commercialization of rivipansel for the first approved indication.

Governance

The agreement establishes a non-voting, joint steering committee to facilitate the exchange of information regarding the development of licensed products and the initial commercialization plans for such products.

Exclusivity Restrictions

During the term of the agreement, we may not directly or indirectly commercialize any pharmaceutical compound or product that is labeled for the treatment, prevention or prophylaxis of a vaso-occlusive or painful crisis associated with sickle cell disease anywhere in the world, subject to specified exceptions if we or our affiliates were to undergo a change of control.

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Term and Termination

The agreement will expire on a licensed product-by-licensed product and country-by-country basis on the date of termination of the applicable royalty term with respect to each licensed product in each country and in its entirety upon the expiration of all applicable royalty terms for all licensed products in all countries. The royalty term for each licensed product in each country is the period commencing with the first commercial sale in the applicable country and ending on the expiration of specified patent coverage or 10 years following the first commercial sale in the applicable country, whichever is later. Pfizer has the right to terminate the agreement, subject to certain notice requirements. The agreement may also be terminated in its entirety either by Pfizer or by us in the event of an uncured material breach by the other party or in the event the other party becomes subject to specified bankruptcy, insolvency or similar circumstances.

Effects of Termination

Upon termination of the agreement by Pfizer for convenience or by us, all rights and licenses granted to Pfizer under the agreement will terminate and Pfizer is obligated to grant us a non-exclusive worldwide license to specified Pfizer proprietary rights to develop and commercialize licensed products in the form being used or sold by Pfizer at the time of such termination, to transfer to us specified data and regulatory materials and approvals, and to provide for the continued supply of licensed products subject to specified terms. If Pfizer has completed additional clinical trials for the applicable licensed product and we obtain such a license or obtain such data and materials and commercialize a licensed product, then, for a period of 10 years from the first commercial sale of such licensed product, Pfizer is eligible to receive royalties at defined percentages in the low single-digits on net sales of such licensed product worldwide, up to a defined aggregate payment cap. The applicable royalty rate and maximum royalty payment cap depend on the stage of clinical development at the time of such termination.

Research Services Agreement with University of Basel

We entered into a research services agreement with the University of Basel, or the University, for the discovery and evaluation of selectin antagonists. The research under this agreement has been completed; however, certain patents covering the rivipansel compound remain subject to provisions of the research services agreement. Under the terms of the research services agreement, if we receive any future milestone payments or royalties from Pfizer with respect to rivipansel, we agreed to pay the University 10% of those amounts, subject to specified exceptions. In 2016, we paid \$2.0 million to the University based upon our receipt of a \$20.0 million non-refundable milestone payment from Pfizer in 2015. There have been no additional payments due to the University since 2015. The research services agreement remains in effect until we are no longer obligated to make any potential payments.

Intellectual Property

We strive to protect the intellectual property that we believe is important to our business, including seeking and maintaining patent protection intended to cover the composition of matter of our drug candidates and their methods of use. We have issued patents directed to rivipansel and methods of use that are expected to expire between 2023 and 2030. We also have issued patents which cover uproleselan and methods of use that are expected to expire between 2032 and 2033. In addition, we have several pending patent applications covering uproleselan and/or methods of

using it, the last expiring of which, if issued, currently would be predicted to expire in 2038. We also rely on trade secret protection for our confidential and proprietary information and careful monitoring of such information to protect aspects of our business.

Our success will depend significantly on our ability to obtain and maintain patent and other proprietary protection for commercially important inventions and know-how related to our business, defend and enforce our patents, preserve the confidentiality of our trade secrets and operate without infringing the valid and enforceable patents and other proprietary rights of third parties. We also rely on know-how and continuing technological innovation to develop, strengthen and maintain our proprietary position in the field of glycomimetics.

A third party may hold intellectual property, including patent rights that are important or necessary to the development of our drug candidates. It may be necessary for us to use the patented or proprietary technology of third parties to commercialize our drug candidates, in which case we would be required to obtain a license from these third parties. If we are not able to obtain such a license, or are not able to obtain such a license on commercially reasonable terms, our business could be materially harmed.

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We plan to continue to expand our intellectual property estate by filing patent applications directed to additional glycomimetic compounds and their derivatives, compositions and formulations containing them and methods of using them. Additionally, we will seek patent protection in the United States and internationally for novel compositions of matter covering the compounds and their use in a variety of therapies.

The patent positions of biotechnology companies like us are generally uncertain and involve complex legal, scientific and factual questions. In addition, the coverage claimed in a patent application can be significantly reduced before the patent is issued, and its scope can be reinterpreted after issuance, including where a reissue application is filed in relation to an issued patent to correct issues or errors arising during prosecution that may render claims of the issued patent either wholly or partially invalid or unenforceable. Consequently, we do not know whether any of our drug candidates will be protectable or remain protected by enforceable patents. We cannot predict whether the patent applications we are currently pursuing will issue as patents in any particular jurisdiction or whether the claims of any issued patents will provide sufficient proprietary protection from competitors. Any patents that we hold may be challenged, circumvented or invalidated by third parties.

Because patent applications in the United States and certain other jurisdictions are maintained in secrecy for 18 months, and since publication of discoveries in the scientific or patent literature often lags behind actual discoveries, we cannot be certain of the priority of inventions covered by pending patent applications. Moreover, we may have to participate in interference proceedings declared by the U.S. Patent and Trademark Office, or USPTO, or a foreign patent office to determine priority of invention or in post-grant challenge proceedings, such as oppositions, that challenge priority of invention or other features of patentability. Such proceedings could result in substantial cost, even if the eventual outcome is favorable to us.

Manufacturing

We do not have any manufacturing facilities or personnel. We currently rely, and expect to continue to rely, on third parties for the manufacturing of our drug candidates for preclinical and clinical testing, as well as for commercial manufacturing if our drug candidates receive marketing approval.

In the case of rivipansel, the initial process development, manufacturing and scale-up was managed by us and performed under contract by third parties. Under our license agreement with Pfizer, responsibility for manufacturing rivipansel has now transferred to Pfizer. With respect to our other drug candidates, we anticipate continuing to manage process development, scale-up and manufacturing under contracts with third parties. For uproleselan, we expect a significant increase in manufacturing as we scale up for our planned Phase 3 clinical trial and prepare for potential filings for marketing approval.

All of our drug candidates are small molecules and are manufactured in reliable and reproducible synthetic processes from readily available starting materials. The chemistry does not require unusual equipment in the manufacturing process. We expect to continue to develop drug candidates that can be produced cost-effectively at contract manufacturing facilities.

Commercialization

We have not yet established a sales, marketing or drug distribution infrastructure. With the exception of rivipansel, to which we have granted Pfizer exclusive commercialization rights, we generally expect to retain commercial rights in the United States for our current drug candidates, all of which are still in preclinical or early clinical development. We believe that it will be possible for us to access the U.S. market for those drug candidates through a focused, specialized sales force.

Subject to receiving marketing approvals, we expect to commence commercialization activities by building a focused sales and marketing organization in the United States to sell our drugs. We believe that such an organization will be able to target the community of physicians who are the key specialists in treating the patient populations for which our drug candidates are being developed. Outside the United States, we expect to enter into distribution and other marketing arrangements with third parties for any of our drug candidates that obtain marketing approval.

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We also plan to build a marketing and sales management organization to create and implement marketing strategies for any drugs that we market through our own sales organization and to oversee and support our sales force. The responsibilities of the marketing organization would include developing educational initiatives with respect to approved drugs and establishing relationships with thought leaders in relevant fields of medicine.

Competition

The biotechnology and pharmaceutical industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary drugs. While we believe that our knowledge, experience and scientific resources provide us with competitive advantages, we face potential competition from many different sources, including major pharmaceutical, specialty pharmaceutical and biotechnology companies, academic institutions and governmental agencies and public and private research institutions. Any drug candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future.

The key competitive factors affecting the success of all of our drug candidates, if approved, are likely to be their safety, efficacy, convenience, price, the level of generic competition and the availability of coverage and reimbursement from government and other third-party payors.

Rivipansel: Sickle Cell Disease

Hydroxyurea and Endari are approved as prophylactic therapies for SCD. Based on publicly available information, we are not aware of any drugs currently approved in the United States as on-demand (as needed) for the treatment of SCD patients experiencing an acute VOC episode. There are a number of compounds that are in clinical development as either on-demand, prophylactic or gene therapy/blood transfusion approaches to treat patients with SCD, including:

- On Demand Approaches: Modus Therapeutics (sevuparin);
- Prophylactic Approaches: Novartis Pharmaceuticals Corporation (crizanlizumab, formerly SelG1) and Global Blood Therapeutics (voxelotor, formerly GBT440); and
- Gene Therapy/Blood Transfusion Approaches: Blue Bird Bio (Lentiglobin BB305); Sangamo Biosciences/Bioverativ (ZFN Knockout); CRISPR Therapeutics/Vertex (CTX001); Intellia/Novartis (BCL11a knockout) and Bellicum Pharmaceuticals (BPX-501).

Attempts to develop a cure for SCD through gene therapy remain at an early stage of development, with significant variability observed to date in achieving target levels of anti-sickling hemoglobin. Should one or more of these prophylactic agents or gene therapy approaches be commercialized prior to rivipansel, they could reduce the number

of VOC episodes each year, reducing the market opportunity for rivipansel.

Uproleselan: AML

Our drug discovery, development and commercialization activities in oncology face, and will continue to face, intense competition from organizations such as pharmaceutical and biotechnology companies, as well as academic and research institutions and government agencies. As the treatment landscape for AML changes, there is substantial risk that uproleselan might not provide additional benefit over other existing therapies.

Relapsed/refractory AML, the initial cancer indication for which we intend to commercialize uproleselan, has alternative established therapies. A key consideration in the treatment of these AML patients is the patient's suitability for intensive salvage chemotherapy. The patient population being studied in our ongoing Phase 3 clinical trial of uproleselan includes AML patients deemed able to tolerate salvage chemotherapy. While there is no commonly accepted single standard approach for salvage chemotherapy, existing options for the treatment of relapsed/refractory AML patients who can tolerate salvage chemotherapy include cytarabine-based combinations. In addition, we are aware of several other product candidates that are in development as potential treatment options for AML patients. Some of the patient populations being studied for these product candidates in development overlap with the patient population studied in the uproleselan Phase 3 clinical trial. The existence of established treatment options and the development of

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competing therapies for relapsed/refractory AML patients could negatively impact our ability to successfully commercialize uproleselan.

The following therapies have been approved by the FDA for the treatment of AML in the past two years:

- RYDAPT® (midostaurin), an oral prescription medicine commercialized by Novartis to be used in combination with certain chemotherapy medicines to treat adults with newly diagnosed AML who have a defect in a gene called FLT3;
- IDHIFA® (enasidenib), a prescription medicine commercialized by Celgene intended to treat people with AML with an isocitrate dehydrogenase-2 (IDH2) mutation whose disease has come back or has not improved after previous treatments;
- VYXEOSTM (daunorubicin and cytarabine), commercialized by Jazz Pharmaceuticals, which is indicated for the treatment of adults with newly-diagnosed therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC);
- MYLOTARGTM (gemtuzumab ozogamicin), commercialized by Pfizer, which is indicated for the treatment for the treatment of newly-diagnosed CD33-positive AML in adults (in combination with daunorubicin and cytarabine) and for treatment of relapsed or refractory CD33-positive AML in adults and in pediatric patients 2 years and older as a stand-alone treatment;
- TIBSOVO® (ivosidenib), a prescription medicine commercialized by Agios intended to treat people with AML with an isocitrate dehydrogenase-1 (IDH1) mutation whose disease has come back or has not improved after previous treatments;
- XOSPATA® (gilteritinib), an oral prescription medicine commercialized by Astellas intended to treat people with AML with a FLT3 gene mutation whose disease has come back or has not improved after previous treatments;
- DAURISMO (glasdigib), an oral prescription medicine commercialized by Pfizer to be used in combination with low-dose cytarabine, for the treatment of newly-diagnosed AML in adult patients who are ≥75 years old or who have comorbidities that preclude use of intensive induction chemotherapy; and
- VENCLEXTA® (venetoclax), an oral prescription medicine commercialized by Abbvie/Genentech to be used in combination with azacitidine, or decitabine, or low-dose cytarabine to treat adults with newly-diagnosed AML who are either 75 years of age or older, or have other medical conditions that prevent the use of standard chemotherapy.

While many chemotherapies in development for hematologic malignancies will likely be complementary to uproleselan, there are also therapies in development that could be directly competitive with uproleselan. In particular, there are a number of CXCR4 antagonists in clinical development that target the bone marrow microenvironment in order to mobilize and sensitize cancer cells to chemotherapy, including candidates developed by Sanofi-Aventis (Mozobil), Bristol Myers Squibb (BMS-936564), NOXXON Pharma (NOX-A12), Eli Lilly (LY2510924) and BioLine RX (BL-8040).

Many of the companies against which we are competing, or against which we may compete in the future, have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved drugs than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller or early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing

clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

Government Regulation and Product Approval

Government authorities in the United States, at the federal, state and local levels, and in other countries, extensively regulate, among other things, the research, development, testing, manufacture, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, import and export of pharmaceutical products, such as those we are developing. The processes for obtaining regulatory approvals in the United States and in foreign

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countries, along with subsequent compliance with applicable statutes and regulations, require the expenditure of substantial time and financial resources.

United States Government Regulation

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and its 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 United States requirements at any time during the drug development process, approval process or after approval, may subject an applicant to a variety of administrative or judicial sanctions, such as the FDA's refusal to approve pending new drug applications, or NDAs, withdrawal of an approval, imposition of a clinical hold, issuance of warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement or civil or criminal penalties.

The process required by the FDA before a drug may be marketed in the United States generally involves:

- 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 become effective before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, at each clinical site before each trial may be initiated;
- performance of human clinical trials, including adequate and well-controlled clinical trials, in accordance with good clinical practices, or GCP, to establish the safety and efficacy of the proposed drug for each indication;
- submission to the FDA of an NDA;
- satisfactory completion of an FDA advisory committee review, if applicable;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with current good manufacturing practices, or cGMP, and to assure that the facilities, methods and controls are adequate to preserve the drug's identity, strength, quality and purity, as well as satisfactory completion of an FDA inspection of selected clinical sites to determine GCP compliance; and
- FDA review and approval of the NDA.

Preclinical Studies

Preclinical studies include laboratory evaluation of product chemistry, toxicity and formulation, as well as animal studies to assess potential safety and efficacy. An IND sponsor must submit the results of the preclinical studies, together with manufacturing information, analytical data and any available clinical data or literature, among other things, to the FDA as part of an IND. Some preclinical testing may continue even after the IND is submitted. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to one or more proposed clinical trials and places the clinical trial on a clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. As a result, submission of an IND may not result in the FDA allowing clinical trials to commence.

Clinical Trials

Clinical trials involve the administration of the investigational new drug to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include the requirement that all research subjects provide their informed consent in writing for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, the objectives of the trial, 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

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submitted to the FDA as part of the IND. In addition, an IRB at 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 continue to oversee the clinical trial while it is being conducted. Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health, or NIH, for public dissemination on their ClinicalTrials.gov website.

Human clinical trials are typically conducted in three sequential phases, which may overlap or be combined. In Phase 1, the drug is initially introduced into healthy human subjects or patients with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an initial indication of its effectiveness. In Phase 2, the drug typically 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. In 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 safety and efficacy 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 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.

A sponsor may request a Special Protocol Assessment, or SPA, the purpose of which is to reach agreement with the FDA on the Phase 3 clinical trial protocol design and analysis that will form the primary basis of an efficacy claim. According to FDA's published guidance on the SPA process, a sponsor that meets the prerequisites may make a specific request for an SPA and provide information regarding the design and size of the proposed clinical trial. The FDA is supposed to evaluate the protocol within 45 days of the request to assess whether the protocol design and planned analysis of the trial are acceptable to support regulatory approval of the product candidate with respect to effectiveness of the indication studied, and that evaluation may result in discussions and a request for additional information. An SPA request must be made before the proposed trial begins, and all open issues must be resolved before the trial begins for an SPA to be approved. If a written agreement is reached, it will be documented in an SPA letter or the minutes of a meeting between the sponsor and the FDA and made part of the administrative record.

Even if the FDA agrees to the design, execution and analyses proposed in protocols reviewed under the SPA process, the FDA may revoke or alter its agreement under the following circumstances:

- public health concerns emerge that were unrecognized at the time of the protocol assessment, or the director of the review division determines that a substantial scientific issue essential to determining safety or efficacy has been identified after testing has begun;
- a sponsor fails to follow a protocol that was agreed upon with the FDA; or
- the relevant data, assumptions, or information provided by the sponsor in a request for SPA change, are found to be false statements or misstatements, or are found to omit relevant facts.

A documented SPA may be modified, and such modification will be deemed binding on the FDA review division, except under the circumstances described above, if the FDA and the sponsor agree in writing to modify the protocol and such modification is intended to improve the study. An SPA, however, does not guarantee that a trial will be

successful.

Marketing Approval

Assuming successful completion of the required clinical testing, 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 product for one or more indications. In most cases, the submission of an NDA is subject to a substantial application user fee. Under the

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Prescription Drug User Fee Act, or PDUFA, guidelines that are currently in effect, the FDA has agreed to certain performance goals regarding the timing of its review of an application.

In addition, under the Pediatric Research Equity Act, an NDA or supplement to an NDA must contain data that are adequate to assess the safety and effectiveness of the drug 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. 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. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation.

The FDA also may require submission of a risk evaluation and mitigation strategy, or REMS, plan to mitigate any identified or suspected serious risks. The REMS plan could include medication guides, physician communication plans, assessment plans and elements to assure safe use, such as restricted distribution methods, patient registries or other risk minimization tools.

The FDA conducts a preliminary review of all NDAs within the first 60 days after submission, before accepting them for filing, to determine whether they are 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 reviews an NDA to determine, among other things, whether the drug is safe and effective and whether the facility in which it is manufactured, processed, packaged or held meets standards designed to assure the product's continued safety, quality and purity.

The FDA typically refers questions regarding novel drugs to an external advisory committee. 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.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is manufactured. 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 trial sites to assure compliance with GCP.

The testing and approval process for an NDA requires substantial time, effort and financial resources, and takes several years to complete. Data obtained from preclinical and clinical testing are not always conclusive and may be susceptible to varying interpretations, which could delay, limit or prevent regulatory approval. The FDA may not grant approval of an NDA on a timely basis, or at all.

After evaluating the NDA and all related information, including the advisory committee recommendation, if any, and inspection reports regarding the manufacturing facilities and clinical trial sites, the FDA may issue an approval letter, or, in some cases, a complete response letter. A complete response letter generally contains a statement of specific conditions that must be met in order to secure final approval of the NDA and may require additional clinical or preclinical testing in order for FDA to reconsider the application. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. If and when those conditions have been met to the FDA's satisfaction, the FDA will typically issue an approval letter. An approval

letter authorizes commercial marketing of the drug with specific prescribing information for specific indications.

Special FDA Expedited Review and Approval Programs

The FDA has various programs, including fast track designation, accelerated approval, priority review, and breakthrough therapy designation, which are intended to expedite or simplify the process for the development and FDA

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review of drugs that are intended for the treatment of serious or life threatening diseases or conditions and demonstrate the potential to address unmet medical needs. The purpose of these programs is to provide important new drugs to patients earlier than under standard FDA review procedures.

To be eligible for a fast track designation, the FDA must determine, based on the request of a sponsor, that a product is intended to treat a serious or life-threatening disease or condition and demonstrates the potential to address an unmet medical need. The FDA will determine that a product will fill an unmet medical need if it will provide a therapy where none exists or provide a therapy that may be potentially superior to existing therapy based on efficacy or safety factors. The FDA may review sections of the NDA for a fast track product on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the NDA, the FDA agrees to accept sections of the NDA and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the NDA.

The FDA may give a priority review designation to drugs that offer major advances in treatment, or provide a treatment where no adequate therapy exists. A priority review means that the goal for the FDA to review an application is six months, rather than the standard review of ten months under current PDUFA guidelines. These six and ten month review periods are measured from the “filing” date rather than the receipt date for NDAs for new molecular entities, which typically adds approximately two months to the timeline for review and decision from the date of submission. Most products that are eligible for fast track designation are also likely to be considered appropriate to receive a priority review.

In addition, products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may be eligible for accelerated approval and may be approved on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity or prevalence of the condition and the availability or lack of alternative treatments. As a condition of approval, the FDA may require a sponsor of a drug receiving accelerated approval to perform post-marketing studies to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical endpoint, and the drug may be subject to accelerated withdrawal procedures.

A sponsor can also request designation of a product candidate as a “breakthrough therapy.” 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. Drugs designated as breakthrough therapies are also eligible for accelerated approval. The FDA must take certain actions, such as holding timely meetings and providing advice, intended to expedite the development and review of an application for approval of a breakthrough therapy.

Even if a product qualifies for one or more of these programs, the FDA may later decide that the product no longer meets the conditions for qualification or decide that the time period for FDA review or approval will not be shortened. We may explore some of these opportunities for our product candidates as appropriate.

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, manufacturing changes or other labeling claims, are subject to further testing requirements and prior FDA review and approval. There also are continuing annual user fee requirements for any marketed products, as well as application fees for supplemental applications with clinical data.

Even if the FDA approves a product, it may limit the approved indications for use of the product, require that contraindications, warnings or precautions be included in the product labeling, including a boxed warning, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess a drug's safety after approval,

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require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms under a 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-marketing studies or surveillance programs.

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

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market.

Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in mandatory 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. Although physicians, in the practice of medicine, may prescribe approved drugs for unapproved indications, pharmaceutical companies generally are required to promote their drug products 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.

Federal and State Fraud and Abuse, Data Privacy and Security, and Transparency Laws and Regulations

In addition to FDA restrictions on marketing of pharmaceutical products, federal and state healthcare laws and regulations restrict business practices in the biopharmaceutical industry. These laws include anti-kickback and false claims laws and regulations, data privacy and security, and transparency laws and regulations.

The federal Anti-Kickback Statute prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration to induce or in return for purchasing, leasing, ordering or arranging for or recommending the purchase, lease or order of any item or service reimbursable under Medicare, Medicaid or other federal healthcare programs. The term “remuneration” has been broadly interpreted to include anything of value. The

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Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on one hand and prescribers, purchasers and formulary managers on the other. Although there are a number of statutory exemptions and regulatory safe harbors protecting some common activities from prosecution, the exemptions and safe harbors are drawn narrowly. Practices that involve remuneration that may be alleged to be intended to induce prescribing, purchases or recommendations may be subject to scrutiny if they do not qualify for an exemption or safe harbor. Several courts have interpreted the statute's intent requirement to mean that if any one purpose of an arrangement involving remuneration is to induce referrals of federal healthcare covered business, the statute has been violated.

The reach of the federal Anti-Kickback Statute was also broadened by the Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively PPACA, which, among other things, amended the intent requirement of the federal Anti-Kickback Statute such that a person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it in order to have committed a violation. In addition, PPACA provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act or the civil monetary penalties statute, which imposes penalties against any person who is determined to have presented or caused to be presented a claim to a federal health program that the person knows or should know is for an item or service that was not provided as claimed or is false or fraudulent.

Federal false claims laws, including the federal civil False Claims Act prohibits any person from knowingly presenting, or causing to be presented, a false claim for payment to the federal government or knowingly making, using or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government. A claim includes "any request or demand" for money or property presented to the U.S. government. Several pharmaceutical and other healthcare companies have been prosecuted under these laws for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. Other companies have been prosecuted for causing false claims to be submitted because of the companies' marketing of products for unapproved, and thus non-reimbursable, uses. The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, created additional federal criminal statutes that prohibit, among other things, knowingly and willfully executing a scheme to defraud any healthcare benefit program, including private third-party payors and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. Also, many states have similar fraud and abuse statutes or regulations that apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor.

In addition, we may be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and their respective implementing regulations, including the Final HIPAA Omnibus Rule published on January 25, 2013, imposes specified requirements on certain types of individuals and entities relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA's security standards directly applicable to "business associates," defined as independent contractors or agents of covered entities that create, receive, maintain or transmit protected health information in connection with providing a service for or on behalf of a covered entity. HITECH also increased the civil and criminal penalties that may be imposed against covered entities, business associates and possibly other persons, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in certain circumstances, many of which are not pre-empted by HIPAA, differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

The federal Physician Payments Sunshine Act requires certain manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program, with specific exceptions, to report annually to the Centers for Medicare & Medicaid Services, or CMS, information related to payments or other transfers of value made to physicians and teaching hospitals, and applicable manufacturers and applicable group purchasing organizations to report annually to CMS ownership and investment interests held by the physicians and their immediate family members.

We may also be subject to state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal

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government, as well as state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures.

Because of the breadth of these laws and the narrowness of available statutory and regulatory exemptions, it is possible that some of our business activities could be subject to challenge under one or more of such laws. If our operations are found to be in violation of any of the federal and state laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including criminal and significant civil monetary penalties, damages, fines, individual imprisonment, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, contractual damages, reputational harm, diminished profits and future earnings, disgorgement, exclusion from participation in government healthcare programs and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. To the extent that any of our products are sold in a foreign country, we may be subject to similar foreign laws and regulations, which may include, for instance, applicable post-marketing requirements, including safety surveillance, anti-fraud and abuse laws and implementation of corporate compliance programs and reporting of payments or transfers of value to healthcare professionals.

Coverage and Reimbursement

The future commercial success of our drug candidates or any of our collaborators' ability to commercialize any approved drug candidates successfully will depend in part on the extent to which governmental payor programs at the federal and state levels, including Medicare and Medicaid, private health insurers and other third-party payors provide coverage for and establish adequate reimbursement levels for our drug candidates. Government health administration authorities, private health insurers and other organizations generally decide which drugs they will pay for and establish reimbursement levels for healthcare. In particular, in the United States, private health insurers and other third-party payors often provide reimbursement for products and services based on the level at which the government, through the Medicare or Medicaid programs, provides reimbursement for such treatments. In the United States, the EU and other potentially significant markets for our drug candidates, government authorities and third party payors are increasingly attempting to limit or regulate the price of medical products and services, particularly for new and innovative products and therapies, which often has resulted in average selling prices lower than they would otherwise be. Further, the increased emphasis on managed healthcare in the United States and on country and regional pricing and reimbursement controls in the EU will put additional pressure on product pricing, reimbursement and usage, which may adversely affect our future product sales and results of operations. These pressures can arise from rules and practices of managed care groups, judicial decisions and laws and regulations related to Medicare, Medicaid and healthcare reform, pharmaceutical coverage and reimbursement policies and pricing in general.

Third-party payors are increasingly imposing additional requirements and restrictions on coverage and limiting reimbursement levels for medical products. For example, federal and state governments reimburse covered prescription drugs at varying rates generally below average wholesale price. These restrictions and limitations influence the purchase of healthcare services and products. Third-party payors may limit coverage to specific drug products on an approved list, or formulary, which might not include all of the FDA-approved drug products for a particular indication. Third-party payors are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. We may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of our products, in addition to the costs required to obtain the FDA approvals. Our drug candidates may not be considered medically necessary or cost-effective. A payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Further, one payor's determination to provide coverage for a drug product does not assure that other payors will also provide coverage for the drug product. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an

appropriate return on our investment in drug development. Legislative proposals to reform healthcare or reduce costs under government insurance programs may result in lower reimbursement for our drugs and drug candidates or exclusion of our drugs and drug candidates from coverage. The cost containment measures that healthcare payors and providers are instituting and any healthcare reform could significantly reduce our revenues from the sale of any approved drug candidates. We cannot provide any assurances that we will be able to obtain and maintain third party coverage or adequate reimbursement for our drug candidates in whole or in part.

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Impact of Healthcare Reform on our Business

The United States and some foreign jurisdictions are considering enacting or have enacted a number of additional legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to sell our products profitably. Among policy makers and payors in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts, which include major legislative initiatives to reduce the cost of care through changes in the healthcare system, including limits on the pricing, coverage, and reimbursement of pharmaceutical and biopharmaceutical products, especially under government-funded health care programs, and increased governmental control of drug pricing.

There have been several U.S. government initiatives over the past few years to fund and incentivize certain comparative effectiveness research, including creation of the Patient-Centered Outcomes Research Institute under PPACA. Although the results of the comparative effectiveness studies are not intended to mandate coverage policies for public or private payors, it is not clear what effect, if any, the research will have on the sales of any product, if any such product or the condition that it is intended to treat is the subject of a study. It is also possible that comparative effectiveness research demonstrating benefits in a competitor's product could adversely affect the sales of our product candidates. If third-party payors do not consider our drug candidates to be cost-effective compared to other available therapies, they may not cover our drug candidates, once approved, as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow us to sell our drugs on a profitable basis. PPACA became law in March 2010 and substantially changed the way healthcare is financed by both governmental and private insurers. Among other measures that may have an impact on our business, PPACA establishes an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents; a new Medicare Part D coverage gap discount program; and a new formula that increases the rebates a manufacturer must pay under the Medicaid Drug Rebate Program. Additionally, PPACA extends manufacturers' Medicaid rebate liability, expands eligibility criteria for Medicaid programs, and expands entities eligible for discounts under the Public Health Service pharmaceutical pricing program. At this time, we are unsure of the full impact that PPACA will have on our business. There have been judicial and Congressional challenges to certain aspects of PPACA, as well as recent efforts by the Trump administration to repeal or replace certain aspects of the PPACA, and we expect such challenges and amendments to continue.

Since January 2017, President Trump has signed two Executive Orders designed to delay the implementation of any certain provisions of the PPACA or otherwise circumvent some of the requirements for health insurance mandated by the PPACA. Concurrently, Congress has considered legislation that would repeal or repeal and replace all or part of the PPACA. While Congress has not passed comprehensive repeal legislation, two bills affecting the implementation of certain taxes under the PPACA have been signed into law. The Tax Cuts and Jobs Act of 2017 includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the PPACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate". Additionally, on January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain PPACA-mandated fees, including the so-called "Cadillac" tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share and the medical device excise tax on non-exempt medical devices.

In addition, there has been increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices. Specifically, there have been several recent U.S. Congressional inquiries and proposed federal and proposed and enacted state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. At the federal level, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. At the state

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

As a result of PPACA, Medicare payments are increasingly tied to quality of care and value measures, and reporting of related data by providers such as physicians and hospitals. So called “value based reimbursement” measures may present challenges as well as potential opportunities for biopharmaceutical manufacturers. Medicare incentives for providers meeting certain quality measures may ultimately prove beneficial for manufacturers that are able to establish

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that their products may help providers to meet such measures. However, manufacturers' ability to market their drug products based on quality or value is highly regulated and not always permissible. In addition, the potentially decreased Medicare reimbursement to those providers that fail to adequately comply with quality reporting requirements could translate to decreased resources available to purchase products and may negatively impact marketing or utilization of our drug candidates if they are approved for marketing. We cannot predict at this time what impact, if any, the longer-term shift towards value based reimbursement will have on any of our drug candidates in either the Medicare program, or in any other third party payor programs that may similarly tie payment to provider quality.

In addition, other legislative changes have been proposed and adopted since PPACA was enacted. In August 2011, the President signed into law the Budget Control Act of 2011, as amended, which, among other things, created the Joint Select Committee on Deficit Reduction to recommend proposals in spending reductions to Congress. The Joint Select Committee on Deficit Reduction did not achieve its targeted deficit reduction of at least \$1.2 trillion for the years 2013 through 2021, triggering the legislation's automatic reductions to several government programs. These reductions include aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which began in 2013 and, following passage of the Bipartisan Budget Act of 2015, will continue through 2025 unless additional Congressional action is taken. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These and other healthcare reform initiatives may result in additional reductions in Medicare and other healthcare funding.

Exclusivity and Approval of Competing Products

Hatch-Waxman Patent Listing

In seeking approval for a drug through an NDA, applicants are required to list with the FDA each patent with claims that cover the applicant's product or a method of using the product. Upon approval of a drug, each of the patents listed in the application for the drug is then published in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the Orange Book. Drugs listed in the Orange Book can, in turn, be cited by potential competitors in support of approval of an abbreviated new drug application, or ANDA, or 505(b)(2) NDA. Generally, an ANDA provides for marketing of a drug product that has the same active ingredients in the same strengths, dosage form and route of administration as the listed drug and has been shown to be bioequivalent through in vitro or in vivo testing or otherwise to the listed drug. ANDA applicants are not required to conduct or submit results of preclinical or clinical tests to prove the safety or efficacy of their drug product, other than the requirement for bioequivalence testing. Drugs approved in this way are commonly referred to as "generic equivalents" to the listed drug, and can often be substituted by pharmacists under prescriptions written for the original listed drug. 505(b)(2) NDAs generally are submitted for changes to a previously approved drug product, such as a new dosage form or indication.

The ANDA or 505(b)(2) NDA applicant is required to certify to the FDA concerning any patents listed for the approved product in the FDA's Orange Book, except for patents covering methods of use for which the ANDA applicant is not seeking approval. Specifically, the applicant must certify with respect to each patent that:

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

Generally, the ANDA or 505(b)(2) NDA cannot be approved until all listed patents have expired, except when the ANDA or 505(b)(2) NDA applicant challenges a listed drug. A certification that the proposed 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 indicate that it is not seeking approval of a patented method of use, the ANDA or 505(b)(2) NDA application will not be approved until all the listed patents claiming the referenced product have expired.

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If the ANDA or 505(b)(2) NDA 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 application has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of notice of the Paragraph IV certification automatically prevents the FDA from approving the ANDA or 505(b)(2) NDA until the earlier of 30 months, expiration of the patent, settlement of the lawsuit or a decision in the infringement case that is favorable to the ANDA applicant.

Hatch-Waxman Non-Patent Exclusivity

Market and data exclusivity provisions under the FDCA also can delay the submission or the approval of certain applications for competing products. The FDCA provides a five-year period of non-patent data exclusivity within the United States to the first applicant to gain approval of an NDA for a new chemical entity. A drug is a new chemical entity if the FDA has not previously approved any other new drug containing the same active moiety, which is the molecule or ion responsible for the activity of the drug substance. During the exclusivity period, the FDA may not accept for review an ANDA or a 505(b)(2) NDA submitted by another company that contains the previously approved active moiety. However, an ANDA or 505(b)(2) NDA may be submitted after four years if it contains a certification of patent invalidity or noninfringement.

The FDCA also provides three years of marketing exclusivity for an NDA, 505(b)(2) NDA or supplement to an existing NDA or 505(b)(2) NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant, are deemed by the FDA to be essential to the approval of the application or supplement. Three-year exclusivity may be awarded for changes to a previously approved drug product, such as new indications, dosages, strengths or dosage forms of an existing drug. This three-year exclusivity covers only the conditions of use associated with the new clinical investigations and, as a general matter, does not prohibit the FDA from approving ANDAs or 505(b)(2) NDAs for generic versions of the original, unmodified drug product. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA; however, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the preclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness.

Orphan Drug Exclusivity

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug or biological product intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making a drug or biological product available in the United States for this type of disease or condition will be recovered from sales of the product. Orphan designation must be requested before submitting an NDA or biologics license application. Orphan designation does not convey any advantage in or shorten the duration of the regulatory review and approval process. We have received orphan drug designation for rivipansel and uproleselan, and we intend to seek orphan drug designation and exclusivity for our other drug candidates whenever it is available.

If a product that has orphan designation subsequently receives the first FDA approval for such drug for the disease or condition for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications to market the same drug or biological product for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity. Competitors, however, may receive approval of different products for the indication for which the orphan product has exclusivity or obtain approval for the same product but for a different indication for which the orphan product has exclusivity. If a drug or biological product designated as an orphan product receives marketing approval

for an indication broader than what is designated, it may not be entitled to orphan product exclusivity. Orphan drug status in the EU has similar, but not identical, benefits.

Pediatric Exclusivity

Pediatric exclusivity is another type of non-patent marketing exclusivity in the United States and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity, including the non-patent and orphan drug exclusivity periods described above. This six-month exclusivity

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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 FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or Orange Book listed patent protection cover the drug 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 an ANDA or 505(b)(2) application owing to regulatory exclusivity or listed patents. If any of our drug candidates is approved, we anticipate seeking pediatric exclusivity when it is appropriate.

Foreign Regulation

In order to market any product outside of the United States, we would need to comply with numerous and varying regulatory requirements of other countries regarding safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of our drug candidates. For example, in the EU, we must obtain authorization of a clinical trial application, or CTA, in each member state in which we intend to conduct a clinical trial. Whether or not we obtain FDA approval for a drug, we would need to obtain the necessary approvals by the comparable regulatory authorities of foreign countries before we can commence clinical trials or marketing of the drug in those countries. The approval process varies from country to country and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may negatively impact the regulatory process in others.

Employees

As of December 31, 2018, we had 50 full-time employees, all of whom are located in the United States. None of our employees is represented by a labor union or covered by a collective bargaining agreement. We consider our relationship with our employees to be good.

Legal Proceedings

We are not currently a party to any material legal proceedings, and we are not aware of any pending or threatened legal proceeding against us that we believe could have a material adverse effect on our business, operating results or financial condition.

Customer Concentration and Geographic Information

We did not recognize any material revenue during the years ended December 31, 2018 or 2017. All of our long-lived assets are located in the United States.

Corporate Information

We were incorporated under the laws of the State of Delaware in April 2003 and commenced operations in May 2003. Our principal executive offices are located at 9708 Medical Center Drive, Rockville, Maryland 20850. Our telephone number is (240) 243-1201.

Available Information

Our internet website address is www.glycomimetics.com. In addition to the information contained in this Annual Report, information about us can be found on our website. Our website and information included in or linked to our website are not part of this Annual Report.

Our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended, are available free of charge through our website as soon as reasonably practicable after they are electronically filed with or furnished to the Securities and Exchange Commission, or SEC. Additionally the SEC maintains an internet site that

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contains reports, proxy and information statements and other information. The address of the SEC's website is www.sec.gov.

ITEM 1A.RISK FACTORS

Our business is subject to numerous risks. You should carefully consider the following risks, as well as general economic and business risks, and all of the other information contained in this Annual Report, together with any other documents we file with the SEC. Any of the following risks could have a material adverse effect on our business, operating results and financial condition and cause the trading price of our common stock to decline.

Risks Related to Our Financial Position and Capital Needs

We have incurred significant losses since our inception. We expect to continue to incur losses over the next several years and may never achieve or maintain profitability.

Since inception, we have incurred significant operating losses. As of December 31, 2018, we had an accumulated deficit of \$200.6 million. Since our initial public offering in 2014, we have primarily financed our operations with proceeds from additional registered public offerings of our common stock and milestone payments under our license agreement with Pfizer. We have not generated any meaningful revenue since our inception other than from the upfront and milestone payments from Pfizer.

We have devoted substantially all of our financial resources and efforts to research and development, including preclinical studies and clinical trials. We are still in the early stages of development of our drug candidates, and we have not completed development of any drugs. We expect to continue to incur significant expenses and operating losses over the next several years. Our net losses may fluctuate significantly from quarter to quarter and year to year. Although responsibility for further development, regulatory approval and potential commercialization of our first drug candidate, rivipansel, has transferred to Pfizer under our license agreement with them following the completion of our Phase 2 clinical trial, we anticipate that our expenses will increase substantially as we:

- conduct clinical trials of uproleselan in AML;
- conduct clinical trials of GMI-1359;
- continue the research and development of our other drug candidates;
- seek to discover and develop additional drug candidates;
- seek regulatory approvals for any drug candidates that successfully complete clinical trials;
- ultimately establish a sales, marketing and distribution infrastructure and scale up external manufacturing capabilities to commercialize any drugs other than rivipansel for which we may obtain regulatory approval;
- maintain, expand and protect our intellectual property portfolio;
- hire additional clinical, quality control and scientific personnel;
- add operational, financial and management information systems and personnel, including personnel to support our drug development and planned future commercialization efforts; and
- incur additional legal, accounting and other expenses in operating as a public company.

To become and remain profitable, we must succeed in developing and eventually commercializing drugs that generate significant revenue. This will require us to be successful in a range of challenging activities, including completing preclinical testing and clinical trials of our drug candidates other than rivipansel, obtaining regulatory approval for these drug candidates and manufacturing and commercializing any drugs for which we may obtain regulatory approval, as well as discovering additional drug candidates. We are only in the preliminary stages of most of these activities. We may never succeed in these activities and, even if we do, may never generate revenue that is significant

enough to achieve profitability.

In the case of rivipansel, our ability to generate revenue is dependent upon the achievement of development, regulatory and commercial milestones and sales sufficient to generate royalties under our license agreement with Pfizer,

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and the achievement of such milestones is largely out of our control. If Pfizer fails, or chooses not to continue, to further develop, seek regulatory approval for or commercialize rivipansel, our ability to generate revenue with respect to rivipansel will be significantly reduced or eliminated. Because all of our drug candidates other than rivipansel are still in preclinical or early clinical development, if we are unable to generate revenue from our license agreement with Pfizer, we may never become profitable, and we may not be able to invest in the further development of our other drug candidates.

Because of the numerous risks and uncertainties associated with drug development, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able to achieve profitability. If we are required by regulatory authorities to perform studies in addition to those currently expected, or if there are any delays in completing our clinical trials or the development of any of our drug candidates, our expenses could increase.

Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would depress the value of our company and could impair our ability to raise capital, expand our business, maintain our research and development efforts or even continue our operations. A decline in the value of our company could also cause you to lose all or part of your investment.

We will need substantial additional funding to pursue our business objectives. If we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate our drug development programs or potential commercialization efforts.

We believe that our cash and cash equivalents as of December 31, 2018 will enable us to fund our operating expenses and capital expenditure requirements at least through our receipt of top-line results from our Phase 3 clinical trial of uproleselan in individuals with relapsed/refractory AML, which we expect to occur by the end of 2020, without giving effect to any potential milestone payments we may receive under our agreement with Pfizer. However, we will need to obtain substantial additional funding in connection with our continuing operations. Our future capital requirements will depend on many factors, including:

- our agreement with Pfizer remaining in effect and our ability to achieve milestones under this and any other license or collaboration agreement that we may enter into in the future;
- the progress and results of the Phase 3 clinical trial of rivipansel;
- the scope, progress, results and costs of preclinical development, laboratory testing and clinical trials for our other drug candidates, including our ongoing and planned clinical trials of uproleselan and GMI-1359;
- the number and development requirements of other drug candidates that we may pursue;
- the costs, timing and outcome of regulatory review of our drug candidates;
 - the costs and timing of future commercialization activities, including product manufacturing, marketing, sales and distribution, for any of our drug candidates other than rivipansel for which we receive marketing approval;
- any royalties we receive from Pfizer with respect to sales of rivipansel, if it receives marketing approval;
- the revenue, if any, received from commercial sales of our drug candidates other than rivipansel for which we receive marketing approval;
- the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending any intellectual property-related claims; and
- the extent to which we acquire or in-license other drug candidates and technologies.

Identifying potential drug candidates and conducting preclinical testing and clinical trials is a time consuming, expensive and uncertain process that takes years to complete, and we and Pfizer or any future collaborators may never generate the necessary data or results required to obtain regulatory approval and achieve product sales. In addition, our drug candidates, if approved, may not achieve commercial success. Our commercial revenue, if any, will be derived from the sale of drugs that we do not expect to be commercially available for many years, if at all. Accordingly, we

will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all. If we are unable to raise capital when needed or on attractive terms, we

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could be forced to delay, reduce or eliminate our research and development programs or any future commercialization efforts.

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

Until such time, if ever, as we can generate substantial revenue from the sale of our drugs, we expect to finance our cash needs through a combination of equity offerings, debt financings and license and development agreements. We do not currently have any committed external source of funds other than possible milestone payments and possible royalties under our license agreement with Pfizer. To the extent that we raise additional capital through the sale of equity or convertible debt securities, your ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a common stockholder. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends.

If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may be required to relinquish valuable rights to our research programs or drug candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings or other arrangements with third parties when needed, we may be required to delay, limit, reduce or terminate our drug development or future commercialization efforts or grant rights to third parties to develop and market drug candidates that we would otherwise prefer to develop and market ourselves.

Our operating history may make it difficult for you to evaluate the success of our business to date and to assess our future viability.

We commenced operations in 2003, and our operations to date have been largely focused on raising capital, developing our expertise in carbohydrate chemistry and knowledge of carbohydrate biology, identifying potential drug candidates, undertaking preclinical studies and conducting clinical trials. We have three drug candidates in clinical development, but we have not yet demonstrated our ability to successfully complete later stage clinical trials, obtain regulatory approvals, manufacture a commercial scale drug, or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful commercialization.

We may encounter unforeseen expenses, difficulties, complications, delays and other known or unknown factors in achieving our business objectives. With respect to our drug candidates other than rivipansel, we will need to transition at some point from a company with a research and development focus to a company capable of supporting commercial activities. We may not be successful in such a transition.

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

Our ability to use net operating losses to offset future taxable income may be subject to limitations.

As of December 31, 2018, we had federal and state net operating loss carryforwards of \$151.5 million, research and development tax credit carryforwards of \$8.5 million and \$19.6 million of orphan drug tax credit carryforwards. The federal and state net operating loss carryforwards will begin to expire, if not utilized, beginning in 2026, the research and development tax credits in 2023 and the orphan drug tax credit in 2033. These net operating loss and tax credit carryforwards could expire unused and be unavailable to offset future income tax liabilities. Under federal income tax laws, federal net operating losses incurred in 2018 and in future years may be carried forward indefinitely, but the

deductibility of such federal net operating losses is limited. It is uncertain if and to what extent various states will conform to the federal tax laws. In addition, under Section 382 of the Internal Revenue Code of 1986, as amended, and corresponding provisions of state law, if a corporation undergoes an “ownership change,” which is generally defined as a greater than 50% change, by value, in its equity ownership over a three-year period, the corporation’s ability to use its pre-change net operating loss carryforwards and other pre-change tax attributes to offset its post-change income or taxes may be limited. We could experience ownership changes in the future that would limit our ability to use our net operating loss carryforwards.

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Risks Related to the Discovery and Development of Our Drug Candidates

Our research and development is focused on discovering and developing novel glycomimetic drugs, and we are taking an innovative approach to discovering and developing drugs, which may never lead to marketable drugs.

A key element of our strategy is to use and expand our platform to build a pipeline of novel glycomimetic drug candidates and progress these drug candidates through clinical development for the treatment of a variety of diseases. The discovery of therapeutic drugs based on molecules that mimic the structure of carbohydrates is an emerging field, and the scientific discoveries that form the basis for our efforts to discover and develop drug candidates are relatively new. The scientific evidence to support the feasibility of developing drug candidates based on these discoveries is both preliminary and limited. Although our research and development efforts to date have resulted in a pipeline of glycomimetic drug candidates, we may not be able to develop drug candidates that are safe and effective. Even if we are successful in continuing to build our pipeline, the potential drug candidates that we identify may not be suitable for clinical development, including as a result of being shown to have harmful side effects or other characteristics that indicate that they are unlikely to be drugs that will receive marketing approval and achieve market acceptance. If we do not successfully develop and commercialize drug candidates based upon our glycomimetics platform, we will not be able to obtain product revenue in future periods, which likely would result in significant harm to our financial position and adversely affect our stock price.

We are very early in our development efforts and have only three drug candidates that are in clinical trials. All of our other drug candidates are still in preclinical development. If we or our collaborators are unable to commercialize our drug candidates or experience significant delays in doing so, our business will be materially harmed.

We are very early in our development efforts and rivipansel, uproleselan and GMI-1359 are our only drug candidates that are in clinical trials. Our other drug candidates are still in preclinical development. We have not completed the development of any drug candidates, we currently generate no revenue from the sale of any drugs and we may never be able to develop a marketable drug. We have invested substantially all of our efforts and financial resources in the development of our glycomimetics platform, the identification of potential drug candidates using that platform and the development of our drug candidates. Other than with respect to rivipansel, for which our collaborator Pfizer now has the responsibility for further development and commercialization, our ability to generate revenue from our other drug candidates, which we do not expect will occur for many years, if ever, will depend heavily on their successful development and eventual commercialization. The success of those drug candidates will depend on several factors, including:

- successful completion of preclinical studies and clinical trials;
- receipt of marketing approvals from applicable regulatory authorities;
- obtaining and maintaining patent and trade secret protection and regulatory exclusivity for our drug candidates;
- making arrangements with third-party manufacturers for, or establishing, commercial manufacturing capabilities;
- launching commercial sales of the drugs, if and when approved, whether alone or in collaboration with others;
- acceptance of the drugs, if and when approved, by patients, the medical community and third-party payors;
- effectively competing with other therapies;
- obtaining and maintaining healthcare coverage and adequate reimbursement;
- protecting our rights in our intellectual property portfolio; and
- maintaining a continued acceptable safety profile of the drugs following approval.

If we do not achieve one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize our drug candidates, which would materially harm our business.

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

All but three of our drug candidates are in preclinical development, and their risk of failure is high. It is impossible to predict when or if any of our drug candidates will prove safe or effective in humans or will receive regulatory approval. Before obtaining marketing approval from regulatory authorities for the sale of any drug candidate, we or a collaborator must complete preclinical development and then conduct extensive clinical trials to demonstrate the safety and efficacy of the drug candidate in humans. Clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. A failure of one or more clinical trials can occur at any stage of development. The outcome of preclinical testing and early clinical trials may not be predictive of the success of later clinical trials, and interim results of a clinical trial do not necessarily predict final results. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their drug candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval of their drugs.

As described in this report, we are currently conducting a Phase 3 clinical trial of our candidate uproleselan, from which we currently expect top-line results to be available by the end of 2020. However, the timing of these preliminary results could be delayed for a number of reasons. Similarly, we or our current or future collaborators may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent our or their ability to receive marketing approval or commercialize our drug candidates, including:

- regulators or institutional review boards may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- we may experience delays in reaching, or fail to reach, agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites;
- clinical trials of our drug candidates may produce negative or inconclusive results, including failure to demonstrate statistical significance, and we may decide, or regulators may require us, to conduct additional clinical trials or abandon drug development programs;
 - the number of patients required for clinical trials of our drug candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate or participants may drop out of these clinical trials at a higher rate than we anticipate;
- our third-party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;
- regulators or institutional review boards may require that we or our investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks;
- the cost of clinical trials of our drug candidates may be greater than we anticipate;
- the supply or quality of our drug candidates or other materials necessary to conduct clinical trials of our drug candidates may be insufficient or inadequate; and
- our drug candidates may have undesirable side effects or other unexpected characteristics, causing us or our investigators, regulators or institutional review boards to suspend or terminate the trials.

If we are required to conduct additional clinical trials or other testing of our drug candidates beyond those that we currently contemplate, if we are unable to successfully complete clinical trials of our drug candidates or other testing, if the results of these clinical trials or tests are not positive or are only modestly positive or if there are safety concerns, we may:

- be delayed in obtaining marketing approval for our drug candidates;
- not obtain marketing approval at all;

- obtain approval for indications or patient populations that are not as broad as intended or desired;

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- obtain approval with labeling that includes significant use or distribution restrictions or safety warnings;
- be subject to additional post-marketing testing requirements; or
- have the drug removed from the market after obtaining marketing approval.

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

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

We or our collaborators may not be able to initiate or continue clinical trials for our drug 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 our lead drug candidates are intended to treat patients with orphan diseases such as sickle cell disease and AML, our or our collaborators' ability to enroll eligible patients may be limited or may result in slower enrollment than we anticipate. In addition, some of our competitors have ongoing clinical trials for drug candidates that treat the same or similar indications as our drug candidates, and patients who would otherwise be eligible for our clinical trials may instead enroll in clinical trials of our competitors' drug candidates. Patient enrollment is also affected by other factors, including:

- the severity of the disease or condition under investigation;
- the eligibility criteria for the trial;
- the perceived risks and benefits of the drug candidate;
 - the availability of drugs approved to treat the disease or condition under investigation;
- 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 or our collaborators' inability to enroll a sufficient number of patients for clinical trials would result in significant delays and could require us or them to abandon one or more clinical trials altogether. Enrollment delays in these clinical trials may result in increased development costs for our drug candidates, which would cause the value of our company to decline and limit our ability to obtain additional financing.

If serious adverse or unacceptable side effects are identified during the development of our drug candidates, we may need to abandon or limit the development of some of our drug candidates.

If our drug candidates are associated with undesirable side effects in clinical trials or have characteristics that are unexpected, we may need to abandon their development or limit their development to more narrow uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective. Many drug candidates that initially showed promise in early stage testing have later been found to cause side effects that prevented their further development.

We may expend our limited resources to pursue a particular drug candidate or indication and fail to capitalize on drug candidates or indications that may be more profitable or for which there is a greater likelihood of success.

Because we have limited financial and management resources, we focus on a limited number of research programs and drug candidates. As a result, we may forego or delay pursuit of opportunities with other drug candidates or for

other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail

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to capitalize on viable commercial drugs or profitable market opportunities. Our spending on current and future research and development programs and drug candidates for specific indications may not yield any commercially viable drugs. If we do not accurately evaluate the commercial potential or target market for a particular drug candidate, we may relinquish valuable rights to that drug candidate through collaboration, licensing or other arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights.

Risks Related to Our Dependence on Third Parties

Our success is highly dependent on our existing collaboration with Pfizer, and future collaborations may also be important to us. If we are unable to maintain any of these collaborations, or if these collaborations are not successful, our business could be adversely affected.

We have limited capabilities for drug development and do not yet have any capabilities for sales, marketing or distribution. Under our license agreement with Pfizer, Pfizer is responsible for all further development, regulatory approval and potential commercialization efforts with respect to rivipansel. Other than rivipansel, uproleselan and GMI-1359, all of our drug candidates are still in preclinical development, and therefore our success is highly dependent on our collaboration with Pfizer. We cannot assure you that Pfizer will continue to develop rivipansel in a timely manner, or at all, or, if it achieves regulatory approval, that Pfizer will successfully commercialize rivipansel. For example, we have announced that Pfizer expects to receive top-line results from the Phase 3 clinical trial of rivipansel by the end of the second quarter of 2019. As we rely on Pfizer for the conduct of the Phase 3 trial and communications with regulatory agencies, the timing of the top-line results may be further delayed for reasons outside of our control.

Our Pfizer collaboration, and any future collaborations we might enter into, may pose a number of risks, including:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may not perform their obligations as expected;
- collaborators may not pursue the commercialization of any drug candidates that achieve regulatory approval or may elect not to pursue, continue or renew development or commercialization of drug candidates based on clinical trial results, changes in such collaborators' strategic focus or available funding or external factors, such as an acquisition, that divert resources or create competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a drug candidate, repeat or conduct new clinical trials or require a new formulation of a drug candidate for clinical testing;
- collaborators could experience delays in initiating or conducting clinical trials for any number of reasons;
- collaborators could independently develop, or develop with third parties, drugs that compete directly or indirectly with our drugs or drug candidates if such collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- drug candidates discovered in collaboration with us may be viewed by our collaborators as competitive with their own drug candidates or drugs, which may cause such collaborators to cease to devote resources to the commercialization of our drug candidates;
- a collaborator with marketing and distribution rights to one or more of our drug candidates that achieve regulatory approval may not commit sufficient resources to the marketing and distribution of such drug or drugs;
- disagreements with collaborators, including disagreements over proprietary rights, contract interpretation or the preferred course of development, might cause delays or termination of the research, development or commercialization of drug candidates, might lead to additional responsibilities for us with respect to drug candidates or might result in litigation or arbitration, any of which would be time consuming and expensive;

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- collaborators may not properly maintain or defend our or their intellectual property rights or may use our or their proprietary information in such a way as to invite litigation that could jeopardize or invalidate such intellectual property or proprietary information or expose us to potential litigation;
- collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability; and
- collaborations may be terminated for the convenience of the collaborator and, if terminated, we could be required to raise additional capital to pursue further development or commercialization of the applicable drug candidates.

If our collaboration with Pfizer or any other collaborations we might enter into in the future do not result in the successful development and commercialization of drugs, or if one of our collaborators terminates its agreement with us, we may not receive any future research funding or milestone or royalty payments under the collaboration. In addition, even if we are eligible to receive these payments, they could be substantially delayed. For example, under our license agreement, Pfizer has the option to commence another Phase 2 clinical trial of rivipansel, and such commencement would delay or inhibit our ability to receive some of the milestone payments we might otherwise have received under the agreement. If we do not receive the funding we expect under these agreements, the development of our drug candidates could be delayed and we may need additional resources to develop our drug candidates. All of the risks relating to drug development, regulatory approval and commercialization described in this report also apply to the activities of our collaborators.

If Pfizer or a future collaborator of ours is involved in a business combination, the collaborator might deemphasize or terminate development or commercialization of any drug candidate licensed to it by us. If one of our collaborators terminates its agreement with us, we may find it more difficult to attract new collaborators and our reputation in the business and financial communities could be adversely affected. For our drug candidates other than rivipansel, we may in the future determine to collaborate with pharmaceutical and biotechnology companies for their development and potential commercialization. We face significant competition in seeking appropriate collaborators. Our ability to reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of a collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. If we are unable to reach agreements with suitable collaborators on a timely basis, on acceptable terms, or at all, we may have to curtail the development of a drug candidate, reduce or delay its development or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to fund and undertake development or commercialization activities on our own, we may need to obtain additional expertise and additional capital, which may not be available to us on acceptable terms or at all. If we fail to enter into collaborations and do not have sufficient funds or expertise to undertake the necessary development and commercialization activities, we may not be able to further develop our drug candidates or bring them to market, which would impair our business prospects.

We expect to rely on third parties to conduct our future clinical trials for drug candidates other than rivipansel, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials.

We currently expect to engage a third-party contract research organization, or CRO, to conduct our ongoing and planned clinical trials for uproleselan and GMI-1359 and any of our other drug candidates that may progress to clinical development. We expect to continue to rely on third parties, such as CROs, clinical data management organizations, medical institutions and clinical investigators, to conduct those clinical trials. Agreements with such third parties might terminate for a variety of reasons, including a failure to perform by the third parties. If we need to enter into alternative arrangements, that would delay our drug development activities.

Our reliance on these third parties for research and development activities will reduce our control over these activities, but will not relieve us of our responsibilities. For example, we will remain 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 requires us to comply with standards, commonly referred to as good clinical practices, or GCPs, for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and

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accurate and that the rights, integrity and confidentiality of trial participants are protected. We also are required to register ongoing clinical trials and post the results of completed clinical trials on a government-sponsored database, ClinicalTrials.gov, within specified timeframes. Failure to do so can result in fines, adverse publicity and significant civil and criminal sanctions.

Furthermore, these third parties may also have relationships with other entities, some of which may be our competitors. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our clinical trials in accordance with regulatory requirements or our stated protocols, we will not be able to obtain, or may be delayed in obtaining, marketing approvals for our drug candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our drug candidates.

We also expect to rely on other third parties to store and distribute drug supplies for our clinical trials. Any performance failure on the part of our distributors could delay clinical development or marketing approval of our drug candidates or commercialization of our drugs, producing additional losses and depriving us of potential revenue.

We contract with third parties for the manufacturing of some of our drug candidates for preclinical and clinical testing and expect to continue to do so for commercialization. This reliance on third parties increases the risk that we will not have sufficient quantities of our drug candidates or drugs, or such quantities at an acceptable cost, which could delay, prevent or impair our development or commercialization efforts.

We do not have any manufacturing facilities or personnel. For our drug candidates other than rivipansel, for which manufacturing responsibility has shifted to Pfizer, we rely, and expect to continue to rely, on third parties for the manufacturing of our drug candidates for preclinical and clinical testing, as well as for commercial manufacture if any of our drug candidates receive marketing approval. This reliance on third parties increases the risk that we will not have sufficient quantities of our drug candidates or drugs, or such quantities at an acceptable cost or quality, which could delay, prevent or impair our ability to timely conduct our clinical trials or our other development or commercialization efforts.

We also expect to rely on third-party manufacturers or third-party collaborators for the manufacturing of commercial supply of any other drug candidates for which we or our collaborators obtain marketing approval. We may be unable to establish any agreements with third-party manufacturers or to do so on acceptable terms. Even if we are able to establish agreements with third-party manufacturers, reliance on third-party manufacturers entails additional risks, including:

- reliance on the third party for regulatory compliance and quality assurance;
- the possible breach of the manufacturing agreement by the third party;
- the possible misappropriation of our proprietary information, including our trade secrets and know-how; and
- the possible termination or non-renewal of the agreement by the third party at a time that is costly or inconvenient for us.

Third-party manufacturers may not be able to comply with current good manufacturing practices, or cGMP, regulations or similar regulatory requirements outside the United States. Our failure, or the failure of our third-party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us, including clinical holds, fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of drug candidates or drugs, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our drugs.

In addition, in the event that any of our third-party manufacturers fails to comply with such requirements or to perform its obligations to us in relation to quality, timing or otherwise, or if our supply of components or other materials becomes limited or interrupted for other reasons, we may be forced to manufacture the materials ourselves,

for which we currently do not have the capabilities or resources, or enter into an agreement with another third party, which we may not be able to do on commercially reasonable terms, if at all. We do not currently have arrangements in place for redundant supply or a second source for bulk drug substance. If our current contract manufacturers cannot perform as agreed, we may be required to replace such manufacturers and we may incur added costs and delays in identifying and qualifying any such replacement. Any replacement of our manufacturers could require significant effort and expertise because there

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may be a limited number of qualified replacements. If we are required to change manufacturers for any reason, we will be required to verify that the new manufacturer maintains facilities and procedures that comply with quality standards and with all applicable regulations and guidelines. The delays associated with the verification of a new manufacturer could negatively affect our ability to develop our drug candidates in a timely manner or within budget.

Our current and anticipated future dependence upon others for the manufacturing of our drug candidates or drugs may adversely affect our future profit margins and our ability to commercialize any drugs that receive marketing approval on a timely and competitive basis.

We, or our third-party manufacturers, may be unable to successfully scale-up manufacturing of our drug candidates in sufficient quality and quantity, which would delay or prevent us from conducting our ongoing and planned clinical trials and developing our drug candidates.

In order to conduct our ongoing and planned clinical trials of our drug candidates, we will need to manufacture them in large quantities. We, or our manufacturing partners, may be unable to successfully increase the manufacturing capacity for any of our drug candidates in a timely or cost-effective manner, or at all. In addition, quality issues may arise during scale-up activities. If we or our manufacturing partners are unable to successfully scale up the manufacture of our drug candidates in sufficient quality and quantity, the development, testing and clinical trials of that drug candidate may be delayed or become infeasible, and marketing approval or commercial launch of any resulting drug may be delayed or not obtained, which could significantly harm our business.

Risks Related to the Commercialization of Our Drug Candidates

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

If any of our drug candidates receives marketing approval, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community. If our drug candidates do not achieve an adequate level of acceptance, we may not generate significant revenue from drug sales 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 efficacy and potential advantages compared to alternative treatments;
- our ability to offer our drugs for sale at competitive prices;
- the convenience and ease of administration compared to alternative treatments;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the strength of marketing and distribution support;
- the availability of third-party coverage and adequate reimbursement;
- the prevalence and severity of any side effects; and
- any restrictions on the use of our drugs together with other medications.

If we are unable to establish sales, marketing and distribution capabilities for drug candidates other than rivipansel, we may not be successful in commercializing those drug candidates if and when they are approved.

We do not have a sales or marketing infrastructure and have no experience in the sale, marketing or distribution of pharmaceutical drugs. Under our license agreement with Pfizer, Pfizer is responsible for the commercialization of rivipansel, our first drug candidate, if it receives regulatory approval. To achieve commercial success for any other drug candidate for which we may obtain marketing approval, we will need to establish a sales and marketing organization to market or co-promote such drugs. There are risks involved with establishing our own sales, marketing and distribution capabilities. For example, recruiting and training a sales force is expensive and time consuming and

could delay any product launch. If the commercial launch of a drug candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these

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commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

Factors that may inhibit our efforts to commercialize our drugs on our own include:

- our inability to recruit, train and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future drugs;
- the lack of complementary drugs to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more products; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

If we are unable to establish our own sales, marketing and distribution capabilities and enter into arrangements with third parties to perform these services, our revenue and our profitability, if any, are likely to be lower than if we were to sell, market and distribute any drugs that we develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to sell, market and distribute our drug candidates or may be unable to do so on terms that are favorable to us. We likely will have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our drugs effectively. If we do not establish sales, marketing and distribution capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our drug candidates.

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

The development and commercialization of new drugs is highly competitive. We face competition with respect to our current drug candidates, and we will face competition with respect to any drug candidates that we may seek to develop or commercialize in the future, from major pharmaceutical companies, specialty pharmaceutical companies, biotechnology companies, academic institutions, governmental agencies and public and private research institutions. Should any competitors' drug candidates receive regulatory or marketing approval prior to ours, they may establish a strong market position and be difficult to displace or diminish the need for our drug candidates.

The key competitive factors affecting the success of all of our drug candidates, if approved, are likely to be their safety, efficacy, convenience, price, the level of generic competition and the availability of coverage and reimbursement from government and other third-party payors. As described above under "Business—Competition," we expect that both rivipansel and uproleselan will compete with approved therapies and those currently in development by other companies. To the extent that competitive drugs or drug candidates developed by others are successful in treating our target indications, it could reduce the market opportunity for our drug candidates.

Many of the companies against which we are competing, or against which we may compete in the future, have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved drugs than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller or early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize drugs that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any drugs that we may develop. Our competitors also may obtain FDA or other regulatory approval for their drugs more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market.

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In addition, because we have no patents with respect to our glycomimetics platform, our competitors may use our methods, or acquire similar expertise, in order to develop glycomimetic drug candidates and progress these drug candidates through clinical development and commercialization, which could impair our ability to successfully commercialize our drug candidates or otherwise limit our commercial opportunities.

Even if we or our collaborators are able to commercialize any of our drug candidates, the drugs may become subject to unfavorable pricing regulations or third-party coverage and reimbursement policies.

Our and our collaborators' ability to commercialize any of our drug candidates successfully will depend, in part, on the extent to which coverage and adequate reimbursement for these drugs and related treatments will be available from government payor programs at the federal and state levels authorities, including Medicare and Medicaid, private health insurers, managed care plans and other organizations. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels. A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. Increasingly, third-party payors are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for drugs. Coverage and reimbursement may not be available for any drug that we or our collaborators commercialize and, even if these are available, the level of reimbursement may not be satisfactory. Inadequate reimbursement levels may adversely affect the demand for, or the price of, any drug candidate for which we or our collaborators obtain marketing approval. Obtaining and maintaining adequate reimbursement for our drugs may be difficult. We may be required to conduct expensive pharmacoeconomic studies to justify coverage and reimbursement or the level of reimbursement relative to other therapies. If coverage and adequate reimbursement are not available or reimbursement is available only to limited levels, we or our collaborators may not be able to successfully commercialize any drug candidates for which marketing approval is obtained.

There may be significant delays in obtaining coverage and reimbursement for newly approved drugs, and coverage may be more limited than the indications for which the drug is approved by the FDA or similar regulatory authorities outside the United States. Moreover, eligibility for coverage and reimbursement does not imply that a drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution expenses. Interim reimbursement levels for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement rates may vary according to the use of the drug and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost drugs and may be incorporated into existing payments for other services. Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement policies. However, one payor's determination to provide coverage for a drug does not assure that other payors will also provide coverage for the drug. Our or our collaborators' inability to promptly obtain coverage and adequate reimbursement rates from both government-funded and private payors for any approved drugs that we develop could adversely affect our operating results, our ability to raise capital needed to commercialize drugs and our overall financial condition.

The regulations that govern marketing approvals, pricing, coverage and reimbursement for new drugs vary widely from country to country. Current and future legislation may significantly change the approval requirements in ways that could involve additional costs and cause delays in obtaining approvals. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we or our collaborators might

obtain marketing approval for a drug in a particular country, but then be subject to price regulations that delay commercial launch of the drug, possibly for lengthy time periods, and negatively impact our ability to generate revenue from the sale of the drug in that country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more drug candidates, even if our drug candidates obtain marketing approval.

There can be no assurance that our drug candidates, if they are approved for sale in the United States or in other countries, will be considered medically reasonable and necessary for a specific indication, that they will be considered cost-effective by third-party payors, that coverage or an adequate level of reimbursement will be available or that third-

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party payors' reimbursement policies will not adversely affect our ability to sell our drug candidates profitably if they are approved for sale.

Product liability lawsuits against us could cause us to incur substantial liabilities and to limit commercialization of any drugs that we may develop.

We face an inherent risk of product liability exposure related to the testing of our drug candidates in human clinical trials, and will face an even greater risk if we commercially sell any drugs that we may develop. If we cannot successfully defend ourselves against claims that our drug candidates or drugs caused injuries, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for any drug candidates or drugs that we may develop;
- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants;
- significant costs to defend the related litigation;
- substantial monetary awards paid to trial participants or patients;
- loss of revenue;
- reduced resources of our management to pursue our business strategy; and
- the inability to commercialize any drugs that we may develop.

We currently hold \$10.0 million of clinical trial insurance coverage in the aggregate for our clinical trials being conducted in the United States, with a per incident limit of \$5.0 million, which may not be adequate to cover all liabilities that we may incur. In addition, we have increased our clinical coverage above this amount in foreign countries where we plan to have sites as part of our clinical trials for uproleselan, including Ireland, Australia, Netherlands, Germany and England. We may need to further increase our insurance coverage as we expand our clinical trials or if we commence commercialization of our drug candidates. Insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise.

Risks Related to Our Intellectual Property

If we are unable to obtain and maintain patent protection for our drug candidates, or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize drug candidates similar or identical to ours, and our ability to successfully commercialize our drug candidates may be impaired.

Our success depends in large part on our ability to obtain and maintain patent protection in the United States and other countries with respect to our drug candidates. We seek to protect our proprietary position by filing patent applications in the United States and abroad related to our drug candidates.

The patent prosecution process is expensive and time consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. We may not have the right to control the preparation, filing and prosecution of patent applications, or to maintain the rights to patents licensed to third parties. Therefore, these patents and applications may not be prosecuted and enforced in a manner consistent with the best interests of our business.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation. In addition, the laws of foreign countries may not protect our rights to the same extent as the laws of the United States, or vice versa. For example, European patent law restricts the patentability of methods of treatment of the human body more than U.S. law does.

Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing or, in some cases, not at all. Therefore, we cannot know with certainty whether we were the first to make the inventions claimed in our patents or pending patent applications, or that we were the first to file for patent protection of such inventions. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly

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uncertain. Our pending and future patent applications may not result in patents being issued that protect our drug candidates, in whole or in part, or which effectively prevent others from commercializing competitive drug candidates. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection.

Recent patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents. On September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith Act includes a number of significant changes to U.S. patent law. These include provisions that affect the way patent applications are prosecuted and may also affect patent litigation. The U.S. Patent and Trademark Office recently developed new regulations and procedures to govern administration of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act, and in particular, the first to file provisions, only became effective on March 16, 2013. Accordingly, it is not clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business and financial condition.

Moreover, we may be subject to a third-party preissuance submission of prior art to the U.S. Patent and Trademark Office, or become involved in opposition, derivation, reexamination, inter partes review, post-grant review or interference proceedings challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our drug candidates and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize drugs without infringing third-party patent rights. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future drug candidates.

Even if our patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Our competitors may be able to circumvent our patents by developing similar or alternative drug candidates in a non-infringing manner.

In addition, the issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our patents may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in loss of exclusivity or freedom to operate or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical drug candidates, or limit the duration of the patent protection of our drug candidates. Given the amount of time required for the development, testing and regulatory review of new drug candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our patent portfolio may not provide us with sufficient rights to exclude others from commercializing drugs similar or identical to ours.

We may become involved in lawsuits to protect or enforce our patents or other intellectual property, which could be expensive, time consuming and unsuccessful.

Competitors may infringe our issued patents or other intellectual property. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their patents. In addition, in a patent infringement proceeding, a court may decide that a patent of ours is invalid or unenforceable, in whole or in part, construe the patent's claims narrowly or refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology. An adverse result in

any litigation proceeding could put one or more of our patents at risk of being invalidated or interpreted narrowly.

We may need to license intellectual property from third parties, and such licenses may not be available or may not be available on commercially reasonable terms.

A third party may hold intellectual property, including patent, rights that are important or necessary to the development of our drug candidates. It may be necessary for us to use patented or proprietary technology of third parties

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to commercialize our drug candidates, in which case we would be required to obtain a license from these third parties on commercially reasonable terms, or our business could be harmed, possibly materially.

Third parties may initiate legal proceedings alleging that we are infringing their intellectual property rights, the outcome of which would be uncertain and could have a material adverse effect on the success of our business.

Our commercial success depends upon our ability, and the ability of our collaborators, to develop, manufacture, market and sell our drug candidates without infringing the proprietary rights of third parties. There is considerable intellectual property litigation in the biotechnology and pharmaceutical industries. We may become party to, or threatened with, future adversarial proceedings or litigation regarding intellectual property rights with respect to our drug candidates, including interference or derivation proceedings before the U.S. Patent and Trademark Office. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future.

If we are found to infringe a third party's intellectual property rights, we could be required to obtain a license from such third party to continue developing and marketing our drug candidates. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. We could be forced, including by court order, to cease commercializing the infringing drug. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees if we are found to have willfully infringed a patent. A finding of infringement could prevent us from commercializing our drug candidates or force us to cease some of our business operations. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business.

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

Many of our employees were previously employed at universities or other biotechnology or pharmaceutical companies. Although we try to ensure that our employees do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that these employees or we have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such employee's former employer. Litigation may be necessary to defend against these claims.

In addition, while it is our policy to require our employees and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own. Our and their assignment agreements may not be self-executing or may be breached, and we may be forced to bring claims against third parties, or defend claims they may bring against us, to determine the ownership of what we regard as our intellectual property.

If we fail in prosecuting or defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to management.

Intellectual property litigation could cause us to spend substantial resources and distract our personnel from their normal responsibilities.

Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses, and could distract our technical and management personnel from their normal

responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments, and if securities analysts or investors perceive these results to be negative it could have a substantial adverse effect on the price of our common stock. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities. We may not have sufficient financial or other resources to conduct such litigation or proceedings adequately. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could compromise our ability to compete in the marketplace.

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

In addition to seeking patents for our drug candidates, we also rely on trade secrets, including unpatented know-how, technology and other proprietary information, to maintain our competitive position. For example, our platform is based on trade secrets that consist largely of expertise in carbohydrate chemistry and knowledge of carbohydrate biology. We do not believe that we can obtain patent protection for our platform. Thus, our competitors may use our methods, or acquire similar expertise, in order to develop glycomimetic drug candidates and progress these drug candidates through clinical development and commercialization, which could impair our ability to successfully commercialize our drug candidates.

We seek to protect our trade secrets, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, corporate collaborators, outside scientific collaborators, contract manufacturers, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time consuming, and the outcome is unpredictable. In addition, some courts inside and outside the United States are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent them, or those to whom they communicate it, from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor, our competitive position would be harmed.

Risks Related to Regulatory Approval of Our Drug Candidates and Other Legal Compliance Matters

If we or our collaborators are not able to obtain, or if there are delays in obtaining, required regulatory approvals, we or they will not be able to commercialize our drug candidates and our ability to generate revenue will be materially impaired.

Our drug candidates and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, are subject to comprehensive regulation by the FDA and other regulatory agencies in the United States and by the European Medicines Agency, or EMA, and similar regulatory authorities outside the United States. Failure to obtain marketing approval for a drug candidate will prevent us or our collaborators from commercializing the drug candidate. We have not received approval to market any of our drug candidates from regulatory authorities in any jurisdiction. We have only limited experience in filing and supporting the applications necessary to gain marketing approvals and expect to rely on third-party CROs to assist us in this process for drug candidates other than rivipansel. Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information to regulatory authorities for each therapeutic indication to establish the drug candidate's safety and efficacy. Securing marketing approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, applicable regulatory authorities. Our drug candidates may not be effective, may be only moderately effective or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our ability to obtain marketing approval or prevent or limit commercial use. If any of our drug candidates receives marketing approval, the accompanying label may limit the approved use of our drug, which could limit sales of the drug.

The process of obtaining marketing approvals, both in the United States and abroad, is expensive and may take many years if additional clinical trials are required, if approval is obtained at all, and can vary substantially based upon a

variety of factors, including the type, complexity and novelty of the drug candidates involved. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations or changes in regulatory review for each submitted drug application may cause delays in the approval or rejection of an application. Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application, or may decide that our data is insufficient for approval and require additional preclinical, clinical or other studies. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent marketing approval of a drug candidate. Any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved drug not commercially viable.

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For marketing exclusivity in the treatment of an ongoing VOC episode in sickle cell disease, we expect to rely primarily on the orphan drug designation that the FDA has granted us for rivipansel, which includes the treatment of the complications of sickle cell disease. We have similarly received orphan drug designation for uproleselan from the FDA as well as from the EMA in the European Union as a potential treatment for AML. However, in order to obtain marketing exclusivity in a particular jurisdiction, we must receive the first marketing approval of the drug for its intended indication. In addition, the orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review or approval process.

If we experience delays in obtaining approval or if we fail to obtain approval of our drug candidates, the commercial prospects for our drug candidates may be harmed and our ability to generate revenue will be materially impaired.

Even though we have obtained orphan drug designation for our most advanced drug candidate, rivipansel, and for uproleselan, we may not be able to obtain orphan drug marketing exclusivity for these drug candidates or any of our other drug candidates.

Regulatory authorities in some jurisdictions, including the United States and the European Union, or EU, may designate drugs for relatively small patient populations as orphan drugs. Under the Orphan Drug Act, the FDA may designate a drug as an orphan drug if it is 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. We have obtained orphan drug designation from the FDA and the EMA for rivipansel for the treatment of VOC. We have also obtained orphan drug designation from the FDA for uproleselan for the treatment of AML. Generally, if a drug with an orphan drug designation subsequently receives the first marketing approval for the indication for which it has such designation, the drug is entitled to a period of marketing exclusivity, which precludes the FDA or the EMA from approving another marketing application for the same drug for the same indication for that time period. The applicable period is seven years in the United States and 10 years in the EU. The EU exclusivity period can be reduced to six years if a drug no longer meets the 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 drug candidate, that exclusivity may not effectively protect the candidate from competition because different drugs can be approved for the same condition. Even after an orphan drug is approved, the FDA can subsequently approve another drug with the same active moiety 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.

The FDA fast track designation for rivipansel and uproleselan and additional breakthrough therapy designation for uproleselan may not actually lead to a faster development or regulatory review or approval process.

If a drug is intended for the treatment of a serious or life-threatening disease or condition and the drug demonstrates the potential to address unmet medical needs for this disease or condition, the drug sponsor may apply for FDA fast track designation. If fast track designation is obtained, the FDA may initiate review of sections of a new drug application, or NDA, before the application is complete. This “rolling review” is available if the applicant provides, and the FDA approves, a schedule for submission of the individual sections of the application.

Although we have obtained a fast track designation from the FDA for rivipansel to treat VOC and for uproleselan to treat AML and breakthrough therapy designation for uproleselan to treat AML, we may not experience a faster development process, review or approval compared to conventional FDA procedures. Our fast track designation may be withdrawn by the FDA if it believes that the designation is no longer supported by data from our clinical

development programs. Our fast track designation does not guarantee that we will qualify for or be able to take advantage of the expedited review procedures or that we will ultimately obtain regulatory approval of rivipansel or uproleselan.

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Failure to obtain marketing approval in international jurisdictions would prevent our drug candidates from being marketed abroad.

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

A variety of risks associated with marketing our drug candidates internationally could hurt our business.

We or our collaborators may seek regulatory approval for rivipansel and our other drug candidates outside of the United States and, accordingly, we expect that we will be subject to additional risks related to operating in foreign countries if we obtain the necessary approvals, including:

- differing regulatory requirements in foreign countries;
- the potential for so-called parallel importing, which is what happens when a local seller, faced with high or higher local prices, opts to import goods from a foreign market with low or lower prices rather than buying them locally;
- unexpected changes in tariffs, trade barriers, price and exchange controls and other regulatory requirements;
- economic weakness, including inflation or political instability in particular foreign economies and markets;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- foreign taxes, including withholding of payroll taxes;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations related to doing business in another country;
- difficulties staffing and managing foreign operations;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- potential liability under the Foreign Corrupt Practices Act or comparable foreign regulations;
- challenges enforcing our contractual and intellectual property rights, especially in foreign countries that do not respect and protect intellectual property rights to the same extent as the United States;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geo-political actions, including war and terrorism.

These and other risks associated with our potential international operations may compromise our ability to achieve or maintain profitability.

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Any drug candidate for which we obtain marketing approval could be subject to post-marketing restrictions or recall or withdrawal from the market, and we may therefore be subject to penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with our drug candidates, when and if any of them are approved.

Any drug candidate for which we obtain marketing approval, along with manufacturing processes, post-approval clinical data, labeling, advertising and promotional activities for such drug candidate, 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 drug candidate is granted, the approval may be subject to limitations on the indicated uses for which the drug may be marketed or to the conditions of approval, including the requirement to implement a risk evaluation and mitigation strategy. If any of our drug candidates receives marketing approval, the accompanying label may limit the approved use of our drug, which could limit its sales.

The FDA may also impose requirements for costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of the drug. The FDA closely regulates the post-approval marketing and promotion of drugs to ensure drugs are marketed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA imposes stringent restrictions on manufacturers' communications regarding off-label use, and if we do not market our drugs for their approved indications, we may be subject to enforcement action for off-label marketing. Violations of the Federal Food, Drug, and Cosmetic Act relating to the promotion of prescription drugs may lead to investigations alleging violations of federal and state healthcare fraud and abuse laws, as well as state consumer protection laws.

In addition, later discovery of previously unknown adverse events or other problems with our drugs, manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may have negative consequences, including:

- restrictions on such drugs, manufacturers or manufacturing processes;
- restrictions on the labeling or marketing of a drug;
- restrictions on product distribution or use;
- requirements to conduct post-marketing studies or clinical trials;