

RIGEL PHARMACEUTICALS INC  
Form 10-K  
February 28, 2019  
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, D.C. 20549

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FORM 10 K

(Mark One)

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

For the fiscal year ended December 31, 2018

or

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

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Commission file number 0 29889

RIGEL PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

Delaware	94 3248524
(State or other jurisdiction of	(IRS Employer
incorporation or organization)	Identification No.)
1180 Veterans Blvd.	
South San Francisco, California	94080
(Address of principal executive offices)	(Zip Code)

(650) 624 1100

(Registrant's telephone number, including area code)

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

Title of each class:	Name of each exchange on which registered:
Common Stock, par value \$.001 per share	The Nasdaq Global Market

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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 (§ 229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

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

<input type="checkbox"/> Large accelerated filer	<input type="checkbox"/> Accelerated filer	<input type="checkbox"/> Non-accelerated filer	<input type="checkbox"/> Smaller reporting company
			<input type="checkbox"/> 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 a check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☐

The approximate aggregate market value of the Common Stock held by non-affiliates of the registrant, based upon the closing price of the registrant's Common Stock as reported on the Nasdaq Global Market on June 30, 2018, the last business day of the registrant's most recently completed second fiscal quarter, was \$470,773,135. Shares of the registrant's outstanding Common Stock held by each executive officer, director and affiliates of the registrant's outstanding Common Stock have been excluded. The determination of affiliate status for the purposes of this calculation is not necessarily a conclusive determination for other purposes.

As of February 21, 2019, there were 167,171,505 shares of the registrant's Common Stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

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Items 10, 11, 12, 13 and 14 of Part III of this Annual Report on Form 10-K incorporate information by reference from the definitive proxy statement for the registrant's 2019 Annual Meeting of Stockholders to be filed with the Securities and Exchange Commission pursuant to Regulation 14A not later than 120 days after the end of the fiscal year covered by this Annual Report on Form 10-K.

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FORWARD LOOKING STATEMENTS

This Annual Report on Form 10 K contains statements indicating expectations about future performance and other forward looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended (the Securities Act), Section 21E of the Securities Exchange Act of 1934, as amended (the Exchange Act), and the Private Securities Litigation Reform Act of 1995, that involve risks and uncertainties. We usually use words such as “may,” “will,” “should,” “could,” “expect,” “plan,” “anticipate,” “might,” “believe,” “estimate,” “predict,” “intend” or the negative of similar expressions to identify these forward looking statements. These statements appear throughout this Annual Report on Form 10 K and are statements regarding our current intent, belief or expectation, primarily with respect to our operations and related industry developments. Examples of these statements include, but are not limited to, statements regarding the following: our business and scientific strategies; the progress of our product development programs, including clinical testing, and the timing of commencement and results thereof; our corporate collaborations, and revenues that may be received from collaborations and the timing of those potential payments; our drug discovery technologies; our research and development expenses; protection of our intellectual property; and sufficiency of our cash resources and need for additional capital. You should not place undue reliance on these forward looking statements. Our actual results could differ materially from those anticipated in these forward looking statements for many reasons, including as a result of the risks and uncertainties discussed under the heading “Risk Factors” in Part I, Item 1A of this Annual Report on Form 10 K. A forward looking statement speaks only as of the date on which it is made, and, except as required by law, we undertake no obligation to update any forward looking statement to reflect events or circumstances after the date on which the statement is made or to reflect the occurrence of unanticipated events. New factors emerge from time to time, and it is not possible for us to predict which factors will arise. In addition, we cannot assess the impact of each factor on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward looking statements.

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PART I

Item 1. Business

Overview

Rigel Pharmaceuticals, Inc., is a biotechnology company dedicated to discovering, developing and providing novel small molecule drugs that significantly improve the lives of patients with immune and hematologic disorders, cancer and rare diseases. Our pioneering research focuses on signaling pathways that are critical to disease mechanisms. Our first U.S. Food and Drug Administration (FDA) approved product is TAVALISSE® (fostamatinib disodium hexahydrate), an oral spleen tyrosine kinase (SYK) inhibitor, for the treatment of adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment. Our current clinical programs include an upcoming Phase 3 study of fostamatinib in autoimmune hemolytic anemia (AIHA) and an ongoing Phase 1 study of R835, a proprietary molecule from our interleukin receptor associated kinase (IRAK) program. In addition, we have product candidates in development with partners BerGenBio ASA (BerGenBio), Daiichi Sankyo (Daiichi), Aclaris Therapeutics (Aclaris), and AstraZeneca AB (AZ).

Business Update

In April 2018, we received FDA approval of our first product TAVALISSE® (fostamatinib disodium hexahydrate), an oral SYK inhibitor, for the treatment of adult patients with chronic immune thrombocytopenia who have had an insufficient response to a previous treatment. TAVALISSE was launched in the U.S. on May 29, 2018. Sales grew approximately 50% in the fourth quarter of 2018 compared to the third quarter of 2018, which was driven, in part, by continued use of the product as an early treatment option in steroid refractory patients and strong continuation of therapy among patients. For the year ended December 31, 2018, we reported \$13.9 million in net product sales of TAVALISSE. With our fully integrated commercial team consisting of sales, marketing, market access, and commercial operations functions, we continue to execute on our commercial strategy to access the U.S. ITP market estimated to be over \$1.0 billion annually.

Our execution of our global strategy for commercialization of fostamatinib outside of the U.S. has made significant progress since the fourth quarter of 2018. Our recent commercial collaborations with Kissei Pharmaceutical Co., Ltd. (Kissei) and Grifols, S.A. (Grifols), lay the groundwork for us to advance fostamatinib globally and to access the worldwide ITP market which is estimated to be over \$1.8 billion annually. Kissei is a leading Japanese pharmaceutical company with significant development experience and a track record of commercial success in Asian markets. Grifols is one of the largest intravenous immunoglobulin (IVIG) providers globally that has established relationships with European hematologists and hematologist/oncologists, as well as a distribution infrastructure across the E.U. Fostamatinib is on track for potential E.U. approval by the end of 2019, which could enable a product launch in

initial European markets as early as 2020.

In October 2018, we entered into an exclusive license and supply agreement with Kissei to develop and commercialize fostamatinib in all current and potential indications in Japan, China, Taiwan and the Republic of Korea. Under the agreement, we received an upfront payment of \$33.0 million with the potential for up to \$147 million in development, regulatory and commercial milestone payments. We will also receive product transfer price payments in the mid to upper twenty percent range based on tiered net sales for the exclusive supply of fostamatinib to Kissei.

In January 2019, we entered into an exclusive license agreement with Grifols to commercialize fostamatinib in all indications, including chronic ITP, AIHA, and IgAN, in Europe and Turkey. Under the agreement, we received an upfront payment of \$30.0 million, with the potential for \$297.5 million in total regulatory and commercial milestones, which includes a \$20 million payment upon approval from the European Medicines Agency (EMA) for fostamatinib in chronic ITP. We will also receive stepped double-digit royalty payments based on tiered net sales which may reach 30% of net sales. In return, Grifols receives exclusive rights to fostamatinib in human diseases, including chronic ITP, AIHA, and IgAN, in Europe and Turkey. In the event that, in 2021, after the second anniversary of the agreement, fostamatinib has not been approved by the EMA for the treatment of ITP in Europe, Grifols will have the option during a six-month time-frame to terminate the entire agreement which would terminate all their rights to ITP, AIHA, and all other

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indications. In this limited circumstance, we will pay Grifols \$25.0 million and regain all rights to fostamatinib in Europe and other territories. We retain the global rights to fostamatinib outside the Kissei and Grifols territories.

In November 2018, our pivotal Phase 3 trial design for fostamatinib in warm AIHA was submitted to the FDA. Results from our recent Phase 2 suggest that fostamatinib could potentially be an effective treatment option. Preparations for patient enrollment in our pivotal trial have begun and we are on track for study initiation in the first half of 2019. For the site selection process, we are leveraging the locations and relationships from our Phase 3 trial in chronic ITP. Additionally, in January 2018, the FDA awarded Orphan Drug Designation to fostamatinib for the treatment of warm AIHA.

In June 2018, we initiated a Phase 1 study to assess safety, tolerability, pharmacokinetics and pharmacodynamics of R835, a proprietary molecule from our IRAK program, in healthy subjects. We have several additional molecules which were discovered in our labs that are currently under development.

In May 2018, we completed an underwritten public offering in which we sold 18,400,000 shares of our common stock pursuant to an effective registration statement at a price to the public of \$3.90 per share and received net proceeds of approximately \$67.2 million after deducting underwriting discounts and commissions and offering expenses.

## Executive Team Appointments

In May 2018, we announced that Dean Schorno was appointed as the Company's Executive Vice President and Chief Financial Officer. In March 2018, we announced that Stacy Markel was appointed as the Company's Executive Vice President of Human Resources.

## Strategy

Our goal is to become a successful commercial stage biopharmaceutical company. We aim to expand our commercial business in the U.S. on our own and globally through partnerships, and continue our research and development of novel small molecule drugs that significantly improve the lives of patients with immune and hematological disorders, cancer and rare diseases through our innovative drug discovery platform. We continue to build and maintain a strong commercial team in the U.S. to execute successfully on our commercialization strategy for TAVALISSE in chronic ITP. We also entered into partnerships for the expansion of fostamatinib into Europe and Asia, and will be concentrating on the further development of the utility of fostamatinib in other indications on our own or by our partners.



The key elements to our business and scientific strategy are to:

- maximize the opportunity to successfully commercialize TAVALISSE in the United States, where we believe a company our size can effectively compete in rare disease markets;
- assist our global commercialization partners in Europe and Asia in maximizing the revenue potential for fostamatinib;
  - develop and commercialize fostamatinib for possible additional indications, including AIHA;
- develop drug candidates and establish strategic collaborations with pharmaceutical and biotechnology companies to further develop and market our product candidates.
- develop a diverse portfolio of drug candidates that address focused therapeutic indications or that represent significant market opportunities; and
- utilize our research engine to discover and validate new product candidates in focused therapeutic indications.

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### Our Product Portfolio

The following table summarizes our portfolio:

#### Product in Commercial Launch

##### TAVALISSE in ITP

Disease background. Chronic ITP affects an estimated 65,000 adult patients in the U.S. In patients with ITP, the immune system attacks and destroys the body's own blood platelets, which play an active role in blood clotting and healing. ITP patients can suffer extraordinary bruising, bleeding and fatigue as a result of low platelet counts. Current therapies for ITP include steroids, blood platelet production boosters that imitate thrombopoietin (TPOs) and splenectomy.

Orally-available fostamatinib program. Taken in tablet form, fostamatinib blocks the activation of SYK inside immune cells. ITP is typically characterized by the body producing antibodies that attach to healthy platelets in the blood stream. Immune cells recognize these antibodies and affix to them, which activates the SYK enzyme inside the immune cell, and triggers the destruction of the antibody and the attached platelet. When SYK is inhibited by fostamatinib, it interrupts this immune cell function and allows the platelets to escape destruction. The results of our Phase 2 clinical trial, in which fostamatinib was orally administered to sixteen adults with chronic ITP, published in *Blood*, showed that fostamatinib significantly increased the platelet counts of certain ITP patients, including those who had failed other currently available agents.

We designed a Phase 3 clinical program, called fostamatinib in thrombocytopenia (FIT), in which a total of 150 ITP patients were randomized into two identical multi-center, double-blind, placebo-controlled clinical trials. The patients were diagnosed with persistent or chronic ITP, and had blood platelet counts consistently below 30,000 per microliter of blood. Two-thirds of the subjects received fostamatinib orally at 100 mg bid (twice daily) and the other third received placebo on the same schedule. Subjects were expected to remain on treatment for up to 24 weeks. At week four of treatment, subjects who failed to meet certain platelet count and met certain tolerability thresholds could have their dosage of fostamatinib (or corresponding placebo) increased to 150 mg bid. The primary efficacy endpoint of this program was a stable platelet response by week 24 with platelet counts at or above 50,000 per microliter of blood for at least four of the final six qualifying blood draws. In August 2015, the FDA granted our request for Orphan Drug designation for fostamatinib for the treatment of ITP.

On August 30, 2016, we announced the results of the first study, reporting that fostamatinib met the study's primary efficacy endpoint. The study showed that 18% of patients receiving fostamatinib achieved a stable platelet response compared to none receiving a placebo control ( $p=0.0261$ ). On October 20, 2016, we announced the results of the second study, reporting that the response rate was 18%, consistent with the first study. However, one patient in the

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placebo group (4%) achieved a stable platelet response, therefore the difference between those on treatment and those on placebo did not reach statistical significance ( $p=0.152$ ) and the study did not meet its primary endpoint. Using the most conservative sensitivity analysis, rather than the protocol's prespecified analysis, one more patient in the second study is considered a non-responder, resulting in 8 of 50 (16%) responders on fostamatinib ( $p = 0.256$  vs. placebo). When the data from both studies are combined, however, this difference is statistically significant ( $p=0.007$ ).

Patients from the FIT studies were given the option to enroll in a long-term open-label extension study and receive treatment with fostamatinib, also a Phase 3 trial. A total of 123 patients enrolled in this study. All the patients who responded to fostamatinib in the FIT studies and enrolled in the long-term open-label extension study maintained a median platelet count of 106,500/uL at a median of 16 months. In addition, there were 44 placebo non-responders that enrolled in the long-term open-label extension study. 41 of these patients had at least 12 weeks of follow-up. Of those, 9 patients (22%) have achieved a prospectively defined stable platelet response, which is statistically significant ( $p=0.0078$ ) and similar to the response rate fostamatinib achieved in the parent studies.

A stable response was defined as a patient achieving platelet counts of greater than 50,000/uL on more than 4 of the 6 visits between weeks 14 and 24, without rescue medication. In the post-study analysis we performed, a clinically-relevant platelet response was defined to include patients achieving one platelet count over 50,000/uL during the first 12 weeks of treatment, in absence of rescue medication, but who did not otherwise meet the stable response criteria. Once the platelet count of greater than 50,000/uL is achieved, a loss of response was defined as two consecutive platelet counts of less than 30,000/uL in any subsequent visits. In the combined dataset of both stable and clinically-relevant platelet responders for the FIT studies, the response rate was 43% (43/101), compared to 14% (7/49) for placebo ( $p=0.0006$ ).

The most frequent adverse events were gastrointestinal-related, and the safety profile of the product was consistent with prior clinical experience, with no new or unusual safety issues uncovered.

On April 17, 2018, we announced that the FDA had approved TAVALISSE for the treatment of thrombocytopenia in adult patients with chronic ITP who have had an insufficient response to a previous treatment. On April 30, 2018, we announced that the American Journal of Hematology published positive results from the FIT Phase 3 clinical program. We launched TAVALISSE in the U.S. on our own in May 2018. In October 2018, we announced that the EMA has validated the MAA for fostamatinib in adult chronic immune thrombocytopenia, which initiated the MAA review process. We anticipate a decision from the CHMP of the EMA by the fourth quarter of 2019.

Commercial launch activities, including sales and marketing

A significant portion of our operating expenses in 2018 is related to our commercial launch activities for TAVALISSE. Specifically, our marketing and sales efforts are focused on targeting hematologists and

hematologist-oncologists in the United States, who manage chronic adult ITP patients.

We have a fully integrated commercial team consisting of sales, marketing, market access, and commercial operations functions. Our sales team promotes TAVALISSE in the U.S. wherein, in the ordinary course of the business, we use customary pharmaceutical company practices to market our products in the U.S. and concentrate our efforts on hematologists and hematologists-oncologists. TAVALISSE is sold initially through third-party wholesale distribution and specialty pharmacy channels and group purchasing organizations before being ultimately prescribed to patients. To facilitate our commercial activities in the U.S., we also enter into arrangements with various third-parties, including advertising agencies, market research firms and other sales-support-related services as needed. We believe that our commercial team and distribution practices are adequate to ensure that our marketing efforts reach our target customers and deliver our products to patients in a timely and compliant fashion. Also, to help ensure that all eligible patients in the U.S. have appropriate access to TAVALISSE, we have established a comprehensive reimbursement and patient support program called Rigel One Care (ROC). Through ROC, we provide co-pay assistance to qualified, commercially insured patients to help minimize out-of-pocket costs and provide free drug to uninsured or under-insured patients who meet certain clinical and financial criteria. In addition, ROC is designed to provide comprehensive reimbursement support services, such as prior authorization support, benefits investigation and appeals support.

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### Competitive landscape for TAVALISSE

Our industry is intensely competitive and subject to rapid and significant technological change. TAVALISSE is competing with other existing therapies. In addition, a number of companies are pursuing the development of pharmaceuticals that target the same diseases and conditions that we are targeting. For example, there are existing therapies and drug candidates in development for the treatment of ITP that may be alternative therapies to TAVALISSE.

Currently, corticosteroids remain the most common first line therapy for ITP, occasionally in conjunction with intravenous immunoglobulin (IVIg) or anti-Rh(D) to help further augment platelet count recovery, particularly in emergency situations. However, it has been estimated that frontline agents lead to durable remissions in only a small percentage of newly-diagnosed adults with ITP. Moreover, concerns with steroid-related side effects often restrict therapy to approximately four weeks. As such, many patients progress to persistent or chronic ITP, requiring other forms of therapeutic intervention. In long-term treatment of chronic ITP, patients are often cycled through several therapies over time in order to maintain a sufficient response to the disease.

Other approaches to treat ITP are varied in their mechanism of action, and there is no consensus about the sequence of their use, according to the most recent ITP guideline from the American Society of Hematology. Options include splenectomy, thrombopoietin receptor agonists (TPO-RAs) and various immunosuppressants (such as rituximab). The response rate criteria of the above-mentioned options vary, precluding a comparison of response rates for individual therapies.

Even with the above treatment options, a significant number of patients remain severely thrombocytopenic for long durations and are subject to risk of spontaneous or trauma-induced hemorrhage. The addition of fostamatinib to the treatment options could be beneficial since it has a different mechanism of action than any of the therapies that are currently available. Fostamatinib is a potent and relatively selective SYK inhibitor, and its inhibition of Fc receptors and B-cell receptors of signaling pathways make it a potentially broad immunomodulatory agent.

Other products in the U.S. that are approved by the FDA to increase platelet production through binding and TPO receptors on megakaryocyte precursors include PROMACTA® (Novartis) and Nplate® (Amgen, Inc.).

### Fostamatinib in Global Markets

#### Fostamatinib in Europe/Turkey

In January 2019, we entered into an exclusive commercialization license agreement with Grifols to commercialize fostamatinib for the treatment, palliation, or prevention of human diseases, including chronic or persistent ITP, AIHA, and IgAN in Europe and Turkey. Pursuant to the terms of the license agreement, Grifols received exclusive rights to commercialize, and non-exclusive rights to develop, fostamatinib in Europe and Turkey. Grifols also received an exclusive option to expand the territory under its exclusive and non-exclusive licenses to include the Middle East, North Africa and Russia (including Commonwealth of Independent States). The parties' collaboration is governed through a joint governance committee.

We are responsible for performing and funding certain development activities for fostamatinib for ITP and AIHA in Europe and Turkey and Grifols is responsible for all other development activities for fostamatinib in such territory. We will retain the global rights to fostamatinib outside the Grifols territories and those rights previously granted to Kissei. We remain responsible for the manufacture and supply of fostamatinib for all development and commercialization activities under the agreement. In connection with the agreement, we will enter into a supply agreement with Grifols pursuant to which we will supply Grifols with filled and finished product for use under the license agreement.

Under the terms of the agreement, we received an upfront cash payment of \$30.0 million and will be eligible to receive regulatory and commercial milestones of up to \$297.5 million, which includes a \$17.5 million payment for EMA approval of fostamatinib for the first indication, currently anticipated to be for the treatment of chronic ITP, and a \$2.5 million creditable advance royalty payment due upon EMA approval of fostamatinib in the first indication. We will

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also receive tiered royalty payments ranging from the mid-teens to 30% of net sales of fostamatinib in Europe and Turkey. In return, Grifols receives exclusive rights to fostamatinib in human diseases, including chronic ITP, AIHA, and IgAN, in Europe and Turkey. In the event that, in 2021, after the second anniversary of the agreement, fostamatinib has not been approved by the EMA for the treatment of ITP in Europe, Grifols will have the option during a six-month time-frame to terminate the entire agreement which would terminate all their rights to ITP, AIHA, and all other indications. In this limited circumstance, we will pay Grifols \$25.0 million and regain all rights to fostamatinib in Europe and other territories. We retain the global rights to fostamatinib outside the Kissei and Grifols territories.

### Fostamatinib in Japan/Asia

In October 2018, we entered into an exclusive license and supply agreement with Kissei to develop and commercialize fostamatinib in all current and potential indications in Japan, China, Taiwan and the Republic of Korea. Kissei is a Japan-based pharmaceutical company addressing patients' unmet medical needs through its research, development and commercialization efforts, as well as through collaborations with partners.

Under the terms of the agreement, Rigel received an upfront cash payment of \$33.0 million, with the potential for an additional \$147 million in development and commercial milestone payments, and will receive product transfer price payments in the mid to upper twenty percent range based on tiered net sales for the exclusive supply of fostamatinib. Kissei receives exclusive rights to fostamatinib in ITP and all future indications in Japan, China, Taiwan, and the Republic of Korea. Rigel retains the global rights, excluding these Asian countries, to develop and commercialize fostamatinib in ITP and any additional indications.

Kissei will initially seek local country approval for fostamatinib in ITP and conduct clinical studies as required by the country's Pharmaceuticals and Medical Devices Agency. Japan has the third highest prevalence of chronic ITP in the world behind the U.S. and EU.

### Clinical Stage Programs

#### Fostamatinib—AIHA

Disease background. AIHA is a rare, serious blood disorder where the immune system produces antibodies that result in the destruction of the body's own red blood cells. Symptoms can include fatigue, shortness of breath, rapid heartbeat, jaundice or enlarged spleen. While no medical treatments are currently approved for AIHA, physicians generally treat acute and chronic cases of the disorder with corticosteroids, other immuno-suppressants, or



splenectomy. Research has shown that inhibiting SYK with fostamatinib may reduce the destruction of red blood cells. This disorder affects an estimated 40,000 Americans, for whom no approved treatment options currently exist.

Orally available fostamatinib program. We conducted our Phase 2 clinical trial, also known as the SOAR study, in patients with warm AIHA. This trial was an open-label, multi-center, two-stage study that evaluated the efficacy and safety of fostamatinib in patients with warm AIHA who had previously received treatment for the disorder, but have relapsed. The primary efficacy endpoint of this study was to achieve increased hemoglobin levels by week 12 of greater than 10 g/dL, and greater than or equal to 2 g/dL higher than baseline.

In October 2017, we announced that, on a top-line, preliminary basis, Stage 1 of the AIHA study enrolled 17 patients who have had at least one post-baseline hemoglobin measure. In January 2018, we also announced the updated top-line data as of December 2017 for this open-label study in which 47% of these patients (8 patients out of 17) have responded to fostamatinib treatment. Of the 17, six patients, including the last two patients enrolled, responded during the 12-week evaluation period and an additional two patients met the response criteria in the extension study after 12 weeks of dosing. In February 2018, an additional patient in the Stage 1 extension study met the response criteria. As of February 2018, 53% of evaluable patients (9 of 17) have responded to fostamatinib treatment. The safety profile was consistent with the existing fostamatinib safety database. Given that the Stage 1 of the study met its primary efficacy endpoint, we began enrollment of Stage 2 of this study, in which we planned to enroll 20 patients under the same protocol. After we met with the FDA regarding the pathway of our AIHA program, we stopped enrollment of Stage 2 of this study at the end of August 2018 and planned to proceed with the pivotal Phase 3 trial.

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We submitted our pivotal Phase 3 trial design for the treatment of warm AIHA to the FDA in November 2018. The trial is a placebo-controlled study of approximately 80 patients with primary or secondary warm AIHA who have failed at least one prior treatment. The primary endpoint is anticipated to be a durable hemoglobin response by week 24, defined as Hgb > 10 g/dL and > 2 g/dL greater than baseline and durability response, with the response not being attributed to rescue therapy. Enrollment is expected to begin in the first half of 2019.

In January 2018, the FDA granted our request for Orphan Drug designation for fostamatinib for the treatment of AIHA.

### Fostamatinib—IgAN

**Disease background.** IgAN is an autoimmune disease that severely affects the functioning of the kidneys. An estimated 12,000 Americans are diagnosed with this type of glomerulonephritis each year, with 25% of whom will eventually require dialysis and/or kidney transplantation over time. IgAN is characterized by the deposition of IgA immune complexes in the glomeruli of the kidneys leading to an inflammatory response and subsequent tissue damage that ultimately disrupts the normal filtering function of the kidneys. By inhibiting SYK in kidney cells, fostamatinib may block the signaling of IgA immune complex receptors, reduce the deposition of IgA immune complexes and arrest or slow destruction of the glomeruli.

**Orally-available fostamatinib program.** Our Phase 2 clinical trial in patients with IgAN, called SIGN (SYK Inhibition for Glomerulonephritis) completed enrollment for its first and second cohorts. In January 2017, we announced that the first cohort in the Phase 2 study of fostamatinib in IgAN was completed in various centers throughout Asia, the U.S. and Europe. This cohort evaluated the efficacy, safety, and tolerability of the lower dose of fostamatinib (100mg BID, n=26; placebo n=12) as measured by change in proteinuria, renal function, and histology (comparing the pre- and post-study renal biopsies). The primary efficacy endpoint was the mean change in proteinuria from baseline at 24 weeks. The study found that at 24 weeks, fostamatinib was well tolerated with a good safety profile. The second cohort evaluated a higher dose of fostamatinib (150mg BID) and completed enrollment in August 2017.

In April 2018, we announced that trial did not achieve statistical significance for its primary endpoint, which was mean change in proteinuria comparing fostamatinib dose groups to placebo controls in all patients studied. However, in a pre-specified subgroup analysis of patients with greater than 1 gram/day of proteinuria at baseline, the initial data showed a greater reduction in proteinuria in fostamatinib-treated patients relative to placebo patients (this finding did not reach statistical significance). Patients with greater than 1 gram/day of proteinuria have an increased risk of disease progression and represent an unmet medical need. Current guidance for clinical trials in IgAN recommends studying patients with greater than 1 gram/day of proteinuria at entry. We decided to stop any further internal development of this program in the U.S.

R835, an Oral IRAK1/4 Inhibitor for Autoimmune and Inflammatory Diseases

Orally Available IRAK 1/4 Inhibitor Program. During the second quarter of 2018, we selected R835, a proprietary molecule from our IRAK preclinical development program, for human clinical trials. This investigational candidate, R835, is an orally available, potent and selective inhibitor of IRAK1 and IRAK4 that blocks inflammatory cytokine production in response to toll-like receptor (TLR) and the interleukin-1 (IL-1R) family receptor signaling. TLRs and IL-1Rs play a critical role in the innate immune response and dysregulation of these pathways can lead to a variety of inflammatory conditions including psoriasis, rheumatoid arthritis, inflammatory bowel disease and gout (among others). R835 prevents cytokine release in response to TLR and IL-1R activation in vitro. R835 is active in multiple rodent models of inflammatory disease including psoriasis, arthritis, lupus, multiple sclerosis and gout. Preclinical studies show that R835 inhibits both the IRAK1 and IRAK4 signaling pathways, which play a key role in inflammation and immune responses to tissue damage. Dual inhibition of IRAK1 and IRAK4 allows for more complete suppression of pro-inflammatory cytokine release.

We initiated a Phase 1 study to assess safety, tolerability, pharmacokinetics and pharmacodynamics of R835 in healthy subjects in the second quarter of 2018. This Phase 1 study is a randomized, placebo-controlled, double-blind trial

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in up to 91 healthy subjects, ages 18 to 55. The study design aims to assess the tolerability and safety of R835 in both single ascending and multiple ascending doses. We expect to complete our Phase 1 study in 2019.

### Partnered Clinical Programs

#### R548 (ATI-501 and ATI-502) - Aclaris

Aclaris is developing ATI-501 and ATI-502, an oral and topical Janus Kinase (JAK) 1/3 inhibitor. ATI- 501 is being developed as an oral treatment for patients with alopecia areata (AA), including the more severe forms of AA that result in total scalp hair loss, known as alopecia totalis (AT), and total hair loss on the scalp and body, known as alopecia universalis (AU). Aclaris recently started a Phase 2 clinical trial of its investigational JAK inhibitor ATI-501 oral suspension in patients with AA, including AT and AU. In December 2018, Aclaris announced that it has completed enrollment of AUAT-201 Oral, a randomized, double-blinded, parallel-group, placebo-controlled trial to evaluate the safety, efficacy and dose response of three concentrations of ATI-501 oral suspension for the treatment of AA. Topline data from the AUAT-201 Oral trial are expected in the third quarter of 2019.

In 2017, three Phase 2 studies with the topical treatment ATI-502 in AA and Vitiligo were initiated. AA-202 Topical and AUATB-201 Topical are ongoing Phase 2 clinical trials of ATI-502 for the treatment of AA in the U.S. and Australia, respectively. In November 2018, Aclaris completed enrollment of AA-201 Topical, a randomized, double-blinded, parallel-group, placebo-controlled trial to evaluate the safety, efficacy and dose response of two concentrations of ATI-502 for the treatment of AA. Topline data from the AA-201 Topical trial are expected in the second quarter of 2019.

#### BGB324 - BerGenBio

BerGenBio is conducting Phase 1/2 studies with BGB324 (bemcentinib), a first-in-class selective AXL kinase inhibitor, as a single agent in relapsed acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS); and in combination with erlotinib (Tarceva®) in advanced (EGFR-positive) non-small-cell lung carcinoma. BerGenBio is also conducting Phase 2 studies with BGB324 in combination with KEYTRUDA® (pembrolizumab) in non-small cell adenocarcinoma of the lung and triple negative breast cancer in collaboration with another company. In October 2018, BerGenBio announced that the first patient had been dosed in the second stage of the Phase 2 studies in BGB324 in combination with KEYTRUDA®.

#### DS-3032 - Daiichi

DS-3032 is an investigational oral selective inhibitor of the murine double minute 2 (MDM2) protein currently being investigated by Daiichi in three Phase 1 clinical trials for solid and hematological malignancies including AML, acute lymphocytic leukemia, chronic myeloid leukemia in blast phase, lymphoma and MDS.

Preliminary safety and efficacy data from a Phase 1 study of DS-3032 suggests that DS-3032 may be a promising treatment for hematological malignancies including relapsed/refractory AML and high-risk MDS. Evaluation of additional dosing schedules of DS-3032 is underway and combination studies with fostamatinib are currently being conducted by Daiichi.

AZ-D0449 – AZ

AZ is currently conducting a Phase 1 study in healthy volunteers and patients with mild asthma to investigate the safety, anti-inflammatory effect of inhaled AZ-D0449. The study, which follows the single and multiple ascending doses, is currently recruiting patients.

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### Research/Preclinical Programs

We are conducting proprietary research in the broad disease areas of inflammation/immunology, immuno-oncology and cancers. Within these disease areas, our researchers are investigating mechanisms of action as well as screening compounds against potential novel targets and optimizing those leads that appear to have the greatest potential.

### Sponsored Research and License Agreements

We conduct research and development programs independently and in connection with our corporate collaborators. As of December 31, 2018, we are a party to a collaboration agreement with ongoing performance obligations, with Kissei for the development and commercialization of fostamatinib in Japan, China, Taiwan and the Republic of Korea. As of December 31, 2018, we are also a party to collaboration agreements, but do not have ongoing performance obligations with Aclaris for the development and commercialization of JAK inhibitors for the treatment of AA and other dermatological conditions, AZ for the development and commercialization of R256, an inhaled JAK inhibitor, BerGenBio for the development and commercialization of AXL inhibitors in oncology, and Daiichi to pursue research related to MDM2 inhibitors, a novel class of drug targets called ligases. All of the abovementioned agreements fall under the scope of Accounting Standards Codification (ASC) Topic 808, Collaboration Arrangements, but are accounted for following ASC Topic 606, Revenue From Contracts with Customers, as allowed under ASC Topic 808.

Under these agreements, which we entered into in the ordinary course of business, we received or may be entitled to receive upfront cash payments, payments contingent upon specified events achieved by such partners and royalties on any net sales of products sold by such partners under the agreements. Total future contingent payments to us under all of these agreements could exceed \$369.9 million if all potential product candidates achieved all of the payment triggering events under all of our current agreements (based on a single product candidate under each agreement). Of this amount, up to \$58.0 million relates to the achievement of development events, up to \$220.6 million relates to the achievement of regulatory events and up to \$91.3 million relates to the achievement of certain commercial or launch events. This estimated future contingent amount does not include any estimated royalties that could be due to us if the partners successfully commercialize any of the licensed products. Future events that may trigger payments to us under the agreements are based solely on our partners' future efforts and achievements of specified development, regulatory and/or commercial events.

### Kissei License Agreement

In October 2018, we entered into an exclusive license and supply agreement with Kissei to develop and commercialize fostamatinib in all current and potential indications in Japan, China, Taiwan and the Republic of Korea. Kissei is responsible for performing and funding all development activities for fostamatinib in the above-mentioned territories. We received an upfront cash payment of \$33.0 million with the potential for up to an additional \$147.0 million in development, regulatory and commercial milestone payments, and will receive mid to upper twenty percent, tiered, escalated net sales-based payments for the supply of fostamatinib. Under the agreement, we are obligated to grant Kissei the license rights on fostamatinib on the territories above, as well as supply Kissei

with drug product for use in clinical trials and pre-commercialization activities. We remain responsible for the manufacture and supply of fostamatinib for all development and commercialization activities under the agreement.

We accounted for this agreement following ASC 606 and identified the following distinct performance obligations at inception of the agreement namely: (a) granting of the license, (b) supply of fostamatinib for clinical use and (c) material right associated with discounted fostamatinib that are supplied for use other than clinical or commercial. We concluded that the granting of the license is distinct relative to the other performance obligations. Moreover, we determined that the upfront fee of \$33.0 million represents the transaction price and was allocated to the performance obligations based on our best estimate of the relative standalone selling price as follows: (a) for the license, we estimated the standalone selling price using the adjusted market assessment approach to estimate its standalone selling price in the licensed territories; (b) for the supply of fostamatinib and the material right associated with discounted fostamatinib, we estimated the standalone selling price using the cost plus expected margin approach. Variable consideration of \$147.0 million related to future development and regulatory milestones was fully constrained due to the fact that it was probable that a significant reversal of cumulative revenue would occur, given the inherent uncertainty of success with

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these future milestones. We will recognize revenues related to the supply of fostamatinib and material right upon delivery of fostamatinib to Kissei. For sales-based milestones and royalties, we determined that the license is the predominant item to which the royalties or sales-based milestones relate to. Accordingly, we will recognize revenue at the later of (i) when the related sales occur, or (ii) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied). We will re-evaluate the transaction price in each reporting period and as uncertain events are resolved or other changes in circumstances occur.

As of December 31, 2018, we have granted Kissei the license rights over fostamatinib. Accordingly, we recognized \$30.6 million of the \$33.0 million upfront fee as allocated revenue for the delivered license during the year ended December 31, 2018. At December 31, 2018, performance obligations related to the supply of fostamatinib and material right associated with discounted fostamatinib supply have not yet been satisfied. Accordingly, as of December 31, 2018, the allocated transaction price of \$2.4 million on these two unsatisfied performance obligations were recorded as deferred revenue in the balance sheet.

### BMS Collaboration Agreement

In February 2015, we entered into a collaboration agreement with Bristol-Myers Squibb Company (BMS) for the discovery, development and commercialization of cancer immunotherapies based on our extensive portfolio of small molecule TGF beta receptor kinase inhibitors. Under the collaboration agreement, BMS will have exclusive rights and will be solely responsible for the clinical development and commercialization of any products. Pursuant to the collaboration agreement with BMS, we received a noncreditable and non-refundable upfront payment of \$30.0 million in March 2015. We were also entitled to receive development and regulatory contingent fees that could exceed \$309.0 million for a successful compound approved in certain indications. In addition, we were eligible to receive tiered royalties on the net sales of any products from the collaboration. BMS also agreed to reimburse us for agreed upon costs based on a contractual cost per full-time equivalent employee in connection with the performance of research activities during the research term. Under the collaboration agreement, we were obligated to provide the following deliverables: (i) granting of license rights to our program, (ii) participation in the Joint Research Committee, and (iii) performance of research activities. We concluded that these deliverables were a single unit of accounting as the license did not have stand-alone value apart from the other deliverables. Accordingly, the \$30.0 million upfront payment was recognized ratably as revenue from the effective date of the agreement and was fully amortized in September 2016, the end of the research term. We believed that straight-line recognition of this revenue was appropriate as the research was performed ratably over the research period. During the year ended December 31, 2016, we recognized revenue of \$13.4 million relating to the upfront payment and \$290,000 and relating to the research activities we performed. As of September 30, 2016, all deliverables under the agreement had been delivered. In November 2016, we were notified by BMS that it has designated one compound as an early drug candidate and received \$3.0 million in December 2016, triggered by this development event. In July 2018, BMS notified us that they will discontinue their participation in the preclinical collaboration of cancer immunotherapies based on our small molecule TGF beta receptor kinase inhibitors which originally commenced in 2015. The agreement was terminated in August 2018.

### BerGenBio License Agreement



In June 2011, we entered into an exclusive license agreement with BerGenBio, pursuant to which BerGenBio has exclusive rights for the development and commercialization of an oncology program. Pursuant to the agreement, we are entitled to receive milestone and royalty payments in certain circumstances, and revenue share payments in certain circumstances. Where the revenue share payment provisions are triggered, the milestone and royalty payment provisions cease to be applicable. BerGenBio is responsible for all activities it wishes to perform under the license we granted to it. In February 2017, we received \$3.3 million from BerGenBio as a result of BerGenBio advancing BGB324, an AXL kinase inhibitor licensed under the agreement, to a Phase 2 clinical study. In June 2016, we received contingent payments of \$1.7 million relating to a time-based non-refundable fee and \$2.0 million relating to BerGenBio's exercise of certain option rights before the prescription period to exercise the rights expired. All deliverables under the agreement had been previously delivered, as such, the above payments of \$3.3 million in 2017 and \$3.7 million in 2016, triggered by the above time-based and contingent events were recognized as revenue during the years ended December 31, 2017 and 2016, respectively.

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In September 2018, BerGenBio served us with a notice of arbitration seeking declaratory relief related to the interpretation of provisions under the license agreement, particularly as they relate to the rights and obligations of the parties in the event of the license or sale of a product by BerGenBio and/or the sale of BerGenBio to a third party. The arbitration panel dismissed four of the six declarations sought by BerGenBio, and we thereafter consented to one of the remaining declarations requested by BerGenBio. On February 27, 2019, the arbitration panel issued a determination granting the declaration sought by BerGenBio on the remaining issue, and held that in the event of a sale of shares by BerGenBio's shareholders where there is no monetary benefit to BerGenBio, we would not be entitled to a portion of the proceeds from such a sale. In this circumstance, where the revenue share is not triggered, the milestone and royalty payment provisions remain in effect. We are still reviewing this determination. We believe the determination will not have a material adverse effect on our operations, cash flows or financial condition.

## Our Discovery Engine

The approaches that we use in connection with both our proprietary product development programs and our corporate collaborations are designed to identify protein targets for compound screening and validate the role of those targets in the disease process. Unlike genomics based approaches, which begin by identifying genes and then searching for their functions, our approach identifies proteins that are demonstrated to have an important role in a specific disease pathway. By understanding the disease pathway, we attempt to avoid studying genes that will not make good drug targets and focus only on the subset of expressed proteins of genes that we believe are specifically implicated in the disease process.

We begin by developing assays that model the key events in a disease process at the cellular level. We then identify potential protein targets. In addition, we identify the proteins involved in the intracellular process and prepare a map of their interactions, thus giving us a comprehensive picture of the intracellular disease pathway. We believe that our approach has a number of advantages, including:

- improved target identification: it focuses only on the subset of expressed proteins of genes believed to be specifically implicated in the disease process;
- rapid validation of protein targets: it produces validated protein targets quickly because it uses key events in the disease process as the basis to design the functional, disease based screen;
- improved disease pathway mapping: it produces a comprehensive map of the intracellular disease pathway, enabling the identification of a large number of potential protein targets;
- informed target selection: it provides a variety of different types of targets and information concerning the role each plays in their endogenous state to better select targets more susceptible to pharmaceutical intervention;
- efficient compound screening: it increases the probability and speed with which compound screening will identify "hits" because it provides detailed knowledge of the target that can be used to guide the design of the compound screen; and
- risk reduction: it may reduce the risk of failure in the product development process due to serious side effects, including toxicity or other reasons, by selecting only targets that are specific to the disease in question and that have no apparent role in other cell types or signaling pathways.

Because of the very large numbers of screens employed, our technology is labor intensive. The complexity of our technology requires a high degree of skill and diligence to perform successfully. We believe we have been and will continue to be able to meet these challenges successfully and increase our ability to identify targets for drug discovery.

## Pharmacology and Preclinical Development



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We believe that the rapid characterization and optimization of compounds identified in high throughput screening (HTS) will generate high quality preclinical development candidates. Our pharmacology and preclinical development group facilitates lead optimization by characterizing lead compounds with respect to pharmacokinetics, potency, efficacy and selectivity. The generation of proof of principle data in animals and the establishment of standard pharmacological models with which to assess lead compounds represent integral components of lead optimization. As programs move through the lead optimization stage, our pharmacology and preclinical development groups support our chemists and biologists by performing the necessary studies, including toxicology, for IND application submissions.

## Clinical Development

We have assembled a team of experts in drug development to design and implement clinical trials and to analyze the data derived from these trials. The clinical development group possesses expertise in project management and regulatory affairs. We work with external clinical research organizations with expertise in managing clinical trials, drug formulation, and the manufacture of clinical trial supplies to support our drug development efforts.

## Intellectual Property

We are able to protect our technology from unauthorized use by third parties only to the extent that it is covered by valid and enforceable patents or is effectively maintained as a trade secret. Accordingly, patents and other proprietary rights are an essential element of our business. As of December 31, 2018, we had 60 pending patent applications and 386 issued and active patents in the United States, as well as corresponding pending foreign patent applications and issued foreign patents. Our policy is to file patent applications to protect technology, inventions and improvements to inventions that are commercially important to the development of our business. We seek U.S. and international patent protection for a variety of technologies, including new screening methodologies and other research tools, target molecules that are associated with disease states identified in our screens, and lead compounds that can affect disease pathways. We also intend to seek patent protection or rely upon trade secret rights to protect other technologies that may be used to discover and validate targets and that may be used to identify and develop novel drugs. We seek protection, in part, through confidentiality and proprietary information agreements. We are a party to various license agreements that give us rights to use technologies in our research and development

We currently hold a number of issued patents in the United States, as well as corresponding applications that allow us to pursue patents in other countries, some of which have been allowed and/or granted and others of which we expect to be granted. Specifically, in most cases where we hold a U.S. issued patent, the subject matter is covered at least by an application filed under the Patent Cooperation Treaty (PCT), which is then used or has been used to pursue protection in certain countries that are members of the treaty. Our patents extend for varying periods according to the date of patent filing or grant and the legal term of patents in the various countries where patent protection is obtained. Some of these patents may be eligible for patent term extensions, depending on their subject matter and length of time required to conduct clinical trials. Our material patents relate to fostamatinib, an oral SYK inhibitor, that is the active pharmaceutical ingredient in TAVALISSE, and R406, the active metabolite of fostamatinib. These patents will expire in 2023, 2026, 2028, 2030, 2031, 2032 and 2034.

Fostamatinib. Fostamatinib is covered as a composition of matter in a U.S. issued patent that has an expected expiration date of September 2031, after taking into account a patent term adjustment and extension rules.

Fostamatinib is also covered under broader composition of matter claims in a U.S. issued patent that has an expiration date in March 2026, after taking into account a patent term adjustment. Additional patents covering fostamatinib composition of matter, methods for use, formulations, methods for making and intermediates expire in 2023, 2026, 2028, 2030, 2032 and 2034. Corresponding applications have been filed in foreign jurisdictions under the PCT, and are at various stages of prosecution. Of note, a patent covering fostamatinib as a composition of matter and in compositions for use treating various diseases has been granted by the European Patent Office.

R406. R406 is covered as a composition of matter in a U.S. issued patent and, with a patent term adjustment, has an expiration date in February 2025. R406 is also covered under two broader composition of matter patents issued in the U.S. expiring in February 2023 and July 2024. Methods of using R406 to treat various indications and compositions of matter covering certain intermediates used to make R406 are also covered under patents described above.

Corresponding applications have been filed in foreign jurisdictions under the PCT and are at various stages of

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prosecution.

## Competition

The biotechnology and pharmaceutical industries are intensely competitive and subject to rapid and significant technological change. Many of the drugs that we are attempting to discover will be competing with existing therapies. In addition, a number of companies are pursuing the development of pharmaceuticals that target the same diseases and conditions that we are targeting.

There are existing therapies and drug candidates in development for the treatment of ITP that may be alternative therapies to TAVALISSE. Currently, corticosteroids remain the most common first line therapy for ITP, occasionally in conjunction with intravenous immunoglobulin (IVIg) or anti-Rh(D) as added agents to help further augment platelet count recovery, particularly in emergency situations. However, it has been estimated that frontline agents lead to durable remissions in only a small percentage of newly-diagnosed adults with ITP. Moreover, concerns with steroid-related side effects often restrict therapy to approximately four weeks. As such, many patients progress to persistent or chronic ITP, requiring other forms of therapeutic intervention.

Other approaches to treat ITP are varied in their mechanism of action, and there is no consensus about the sequence of their use, according to the most recent ITP guideline from the American Society of Hematology. Options include splenectomy, TPO-RAs and various immunosuppressants (such as rituximab). The response rate criteria of the above-mentioned options vary, precluding a comparison of response rates for individual therapies.

Even with the above treatment options, a significant number of patients remain severely thrombocytopenic for long durations and are subject to risk of spontaneous or trauma-induced hemorrhage. The addition of fostamatinib to the treatment options could be beneficial since it has a different mechanism of action than the TPO agonists. Fostamatinib is a potent and relatively selective SYK inhibitor, and its inhibition of Fc receptors and B-cell receptors signaling pathways make it a potentially broad immunomodulatory agent.

Other products in the U.S. that are approved by the FDA to increase platelet production through binding and TPO receptors on megakaryocyte precursors include PROMACTA® (Novartis) and Nplate® (Amgen, Inc.).

We face, and will continue to face, intense competition from pharmaceutical and biotechnology companies, as well as from academic and research institutions and government agencies, both in the United States and abroad. Some of these competitors are pursuing the development of pharmaceuticals that target the same diseases and conditions as our research programs. Our major competitors include fully integrated pharmaceutical companies that have extensive drug discovery efforts and are developing novel small molecule pharmaceuticals. We also face significant competition from organizations that are pursuing the same or similar technologies, including the discovery of targets that are useful in compound screening, as the technologies used by us in our drug discovery efforts.

Competition may also arise from:

- new or better methods of target identification or validation;
- other drug development technologies and methods of preventing or reducing the incidence of disease;
- new small molecules; or
- other classes of therapeutic agents.

Our competitors or their collaborative partners may utilize discovery technologies and techniques or partner with collaborators in order to develop products more rapidly or successfully than we or our collaborators are able to do.

Many of our competitors, particularly large pharmaceutical companies, have substantially greater financial, technical and human resources and larger research and development staffs than we do. In addition, academic institutions, government agencies and other public and private organizations conducting research may seek patent protection with respect to

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potentially competitive products or technologies and may establish exclusive collaborative or licensing relationships with our competitors.

We believe that our ability to compete is dependent, in part, upon our ability to create, maintain and license scientifically advanced technology and upon our and our collaborators' ability to develop and commercialize pharmaceutical products based on this technology, as well as our ability to attract and retain qualified personnel, obtain patent protection or otherwise develop proprietary technology or processes and secure sufficient capital resources for the expected substantial time period between technological conception and commercial sales of products based upon our technology. The failure by any of our collaborators or us, including our commercial team, in any of those areas may prevent the successful commercialization of our potential drug targets.

Many of our competitors, either alone or together with their collaborative partners, have significantly greater experience than we do in:

- identifying and validating targets;
- screening compounds against targets; and
- undertaking preclinical testing and clinical trials.

Accordingly, our competitors may succeed in obtaining patent protection, identifying or validating new targets or discovering new drug compounds before we do.

Our competitors might develop technologies and drugs that are more effective or less costly than any that are being developed by us or that would render our technology and product candidates obsolete and noncompetitive. In addition, our competitors may succeed in obtaining the approval of the FDA or other regulatory agencies for product candidates more rapidly. Companies that complete clinical trials, obtain required regulatory agency approvals and commence commercial sale of their drugs before us may achieve a significant competitive advantage, including certain patent and FDA marketing exclusivity rights that would delay or prevent our ability to market certain products. Any drugs resulting from our research and development efforts, or from our joint efforts with our existing or future collaborative partners, might not be able to compete successfully with competitors' existing or future products or obtain regulatory approval in the United States or elsewhere.

We face and will continue to face intense competition from other companies for commercial and collaborative arrangements with pharmaceutical and biotechnology companies, for establishing relationships with academic and research institutions and for licenses to additional technologies. These competitors, either alone or with their collaborative partners, may succeed in developing technologies or products that are more effective than ours.

Our ability to compete successfully will depend, in part, on our ability to:

- identify and validate targets;
- discover candidate drug compounds that interact with the targets we identify;
- attract and retain scientific and product development personnel;
- obtain patent or other proprietary protection for our new drug compounds and technologies; and
- enter commercialization agreements for our new drug compounds.

## Operating Expenses

A significant portion of our operating expenses in 2018 is related to our commercial launch activities for TAVALISSE and research and development activities. Specifically, our marketing and sales efforts is focused on targeting hematologists and hematologist-oncologists in the United States, who manage chronic adult ITP patients. To support these efforts, we have hired experienced commercial professionals, including sales representatives in the





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hematology area, and commercial operations, marketing, and market access professionals. In the ordinary course of business, we also entered into contractual agreements with third parties to support our commercial activities. Additionally, we intend to maintain our strong commitment to research and development. We plan to develop and commercialize fostamatinib for possible additional indications, including AIHA. See “Item 8. Financial Statements and Supplementary Data” of this Annual Report on Form 10-K for costs and expenses related to research and development, and other financial information for each of the fiscal years 2018, 2017 and 2016.

## Government Regulation

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

## Review and Approval of Drugs in the United States

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

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

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

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

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

Before an applicant begins testing a compound with potential therapeutic value in humans, the drug candidate enters the preclinical testing stage. Preclinical studies include laboratory evaluation as well as in vitro and animal studies to assess the safety and activity of the drug for initial testing in humans and to establish a rationale for therapeutic use. The results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical studies, among other things, are submitted to the FDA as part of an IND. Some long-term preclinical testing, such as animal tests of reproductive adverse events and carcinogenicity, and long term toxicity studies, may continue after the IND is submitted.

In support of the IND, applicants must submit a protocol for each clinical trial and any subsequent protocol amendments. In addition, the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature, among other things, are submitted to the FDA as part of an IND. The FDA requires a 30-day waiting period after the submission of each IND before clinical trials may begin. At any time during this 30-day period, or thereafter, the FDA may raise concerns or questions about the conduct of the trials as outlined in the IND and impose a clinical hold or partial clinical hold. In this case, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can begin or resume. An IRB representing each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct continuing review and reapprove the study at least annually. An IRB can suspend or terminate approval of a clinical trial.

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include, among other things, the requirement that all research subjects provide their informed consent in writing before their participation in any clinical trial. Human clinical trials are typically conducted in sequential phases, which may overlap or be combined:

- Phase 1. The drug is initially introduced into a small number of healthy human subjects or, in certain indications such as cancer, patients with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an early indication of its effectiveness and to determine optimal dosage.
- Phase 2. The drug is administered to a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage.
- Phase 3. These clinical trials are commonly referred to as “pivotal” studies, which denote a study that presents the data that the FDA or other relevant regulatory agency will use to determine whether or not to approve a drug. The drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well-controlled clinical trials to generate enough data to statistically evaluate the efficacy and safety of the product for approval, identify adverse effects, establish the overall risk-benefit profile of the product and to provide adequate information for the labeling of the product.
- Phase 4. Post-approval studies may be conducted after initial marketing approval. These studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication.

The FDA or the sponsor or the data monitoring committee 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.

Review of an NDA by the FDA

If clinical trials are successful, the next step in the drug development process is the preparation and submission to the FDA of a NDA. The NDA is the vehicle through which drug applicants formally propose that the FDA approve a new drug for marketing and sale in the United States for one or more indications. The NDA must contain a description of the manufacturing process and quality control methods, as well as results of preclinical tests, toxicology studies, clinical trials and proposed labeling, among other things. The submission of most NDAs is subject to an application user fee and

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the sponsor of an approved NDA is also subject to annual product and establishment user fees. These fees are typically increased annually.

Following submission of an NDA, the FDA conducts a preliminary review of an NDA to determine whether the application is sufficiently complete to permit substantive review. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA has agreed to goals to review and act within ten months from filing for standard review NDAs and within six months for NDAs that have been designated for “priority review”.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is or will be 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 sites to assure compliance with GCP. In addition, as a condition of approval, the FDA may require an applicant to develop a REMS. REMS use risk minimization strategies beyond the professional labeling to ensure that the benefits of the product outweigh the potential risks. To determine whether a REMS is needed, the FDA will consider the size of the population likely to use the product, seriousness of the disease, expected benefit of the product, expected duration of treatment, seriousness of known or potential adverse events, and whether the product is a new molecular entity.

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

On the basis of the FDA’s evaluation of the NDA and accompanying information, including the results of the inspection of the manufacturing facilities, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA’s satisfaction in a resubmission of the NDA, the FDA will issue an approval letter.

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

## Post-Approval Requirements

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to prior

FDA review and approval. 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

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

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

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

### Orphan Drug Designation and Exclusivity

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

If a product with orphan designation receives the first FDA approval for the disease or condition for which it has such designation, the product generally will receive orphan drug exclusivity. Orphan drug exclusivity means that the FDA may not approve another sponsor’s marketing application for the same drug for the same indication for seven years, except in certain limited circumstances. Orphan exclusivity does not block the approval of a different drug for the same rare disease or condition, nor does it block the approval of the same drug for different indications. If a drug designated as an orphan drug ultimately receives marketing approval for an indication broader than what was designated in its orphan drug application, it may not be entitled to exclusivity. Orphan exclusivity will not bar approval of another product under certain circumstances, including if a subsequent product with the same drug for the same indication is shown to be clinically superior to the approved product on the basis of greater efficacy or safety, or providing a major contribution to patient care, or if the company with orphan drug exclusivity is not able to meet market demand.

### Pharmaceutical Coverage, Pricing and Reimbursement

In the United States and markets in other countries, patients who are prescribed treatments for their conditions and providers performing the prescribed services generally rely on third-party payors to reimburse all or part of the associated healthcare costs. Third-party payors include federal and state government health programs such as Medicare and Medicaid, commercial health insurers, managed care organizations, and other organizations. Significant uncertainty exists as to the coverage and reimbursement status of products approved by the FDA and other government authorities. For example, there have been several recent U.S. Congressional inquiries and proposed federal legislation designed to, among other things, bring more transparency to drug pricing, review the relationship



between pricing and manufacturer patient programs, reduce the cost of drugs under Medicare, and reform government program reimbursement methodologies for drugs. Further, 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 have increasingly passed legislation and implemented 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, to encourage importation from other countries and bulk purchasing. Thus, even if a product candidate is approved, sales of the product will depend, in part, on the

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extent to which third-party payors provide coverage and establish adequate reimbursement levels for the product. It is likely that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for a pharmaceutical manufacturer's products or additional pricing pressure.

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

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

## Healthcare Law and Regulation

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

- the federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, paying, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made, in whole or in part, under a federal healthcare program such as Medicare and Medicaid. The term "remuneration" has been broadly interpreted to include anything of value. The intent standard under the federal Anti-Kickback Statute was amended by the Patient Protection and Affordable Care Act and the Health Care and Education Reconciliation Act, or the Affordable Care Act, to a stricter standard such that a person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it, in order to have committed a violation. Moreover, 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;

- the federal civil and criminal false claims laws, including the civil False Claims Act, and civil monetary penalties laws, which prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false, fictitious or fraudulent or knowingly making, using or causing to made or used a false record or statement to avoid, decrease or conceal an obligation to pay money to the federal government.
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which imposes criminal and civil liability for, among other things, executing or attempting to execute a scheme to defraud any healthcare benefit program, including any third-party payors, knowingly and willfully embezzling or

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stealing from a healthcare benefit program, willfully obstructing a criminal investigation of a healthcare offense, and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statements or representations, or making false statements relating to healthcare benefits, items or services. Similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it to have committed a violation;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, and their respective implementing regulations, which impose obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information, including PHI. HITECH also created new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce HIPAA laws and seek attorneys' fees and costs associated with pursuing federal civil actions;
- the federal transparency requirements known as the federal Physician Payments Sunshine Act, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report annually to the Centers for Medicare & Medicaid Services, or CMS, within the United States Department of Health and Human Services, information related to payments and other transfers of value made by that entity to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members; and
- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, which may apply to sales or marketing arrangements and claims involving healthcare items or services that are reimbursed by non-governmental third-party payors, including private insurers.

Some state, local and foreign laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, restrict payments that may be made to healthcare providers and other potential referral sources, and/or require drug manufacturers to report information related to payments and transfers of value made to physicians and other health care providers or entities or marketing expenditures. In addition, there are local laws that require the licensure of sales representatives; state laws that require drug manufacturers to report information related to drug pricing; data privacy and security laws and regulations in foreign jurisdictions that may be more stringent than those in the United States (such as the European Union (E.U.), which adopted the General Data Protection Regulation, which became effective in May 2018); state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts; and state laws related to insurance fraud in the case of claims involving private insurers.

Efforts to ensure that our business arrangements will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental and enforcement authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law interpreting applicable fraud and abuse or other healthcare laws and regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of civil, criminal and administrative penalties, damages, disgorgement, monetary fines, individual imprisonment, additional reporting obligations and oversight if we become subject to a corporate integrity agreement or other agreement to resolve allegations of non-compliance with these laws, possible exclusion from participation in federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, and curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

## Healthcare Reform

The United States and state governments continue to propose and pass legislation designed to reduce the cost of healthcare. In March 2010, the United States Congress enacted the Affordable Care Act which included changes to the

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coverage and payment for drug products under government health care programs. Some of the provisions of the Affordable Care Act have yet to be implemented, and there have been judicial and Congressional challenges to certain aspects of the Affordable Care Act, as well as recent efforts by the Trump administration to repeal or replace certain aspects of the Affordable Care Act. Since January 2017, President Trump has signed two Executive Orders designed to delay the implementation of certain provisions of the Affordable Care Act or otherwise circumvent some of the requirements for health insurance mandated by the Affordable Care Act. Concurrently, Congress has considered legislation that would repeal or repeal and replace all or part of the Affordable Care Act. While Congress has not passed comprehensive repeal legislation, two bills affecting the implementation of certain taxes under the Affordable Care Act have been enacted. 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 Affordable Care Act 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”. On January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain mandated fees under the Affordable Care Act, 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 July 2018, CMS published a final rule permitting further collections and payments to and from certain Affordable Care Act qualified health plans and health insurance issuers under the Affordable Care Act risk adjustment program in response to the outcome of federal district court litigation regarding the method CMS uses to determine this risk adjustment. On December 14, 2018, a U.S. District Court Judge in the Northern District of Texas ruled that the individual mandate is a critical and inseparable feature of the Affordable Care Act, and because it was repealed as part of the Tax Act, the remaining provisions of the Affordable Care Act are invalid as well. While neither the Texas District Court Judge, Trump administration nor CMS have stated that the ruling will have an immediate effect, it is unclear how this decision, subsequent appeals, if any, and other efforts will impact the Affordable Care Act.

Outside the United States, ensuring adequate coverage and payment for our products will face challenges. Pricing of prescription pharmaceuticals is subject to governmental control in many countries. Pricing negotiations with governmental authorities can extend well beyond the receipt of regulatory approval for a product and may require us to conduct a clinical trial that compares the cost effectiveness of our product candidates or products to other available therapies. The conduct of such a clinical trial could be expensive and result in delays in our commercialization efforts. Third-party payors are challenging the prices charged for medical products and services, and many third-party payors limit reimbursement for newly-approved health care products. Recent budgetary pressures in many E.U. countries are also causing governments to consider or implement various cost-containment measures, such as price freezes, increased price cuts and rebates. If budget pressures continue, governments may implement additional cost-containment measures. Cost-control initiatives could decrease the price we might establish for products that we may develop or sell, which would result in lower product revenues or royalties payable to us. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our products.

## Manufacturing and Raw Materials

We do not own or operate manufacturing or distribution facilities or resources for clinical or commercial production and distribution of our product for commercial use or for preclinical and clinical trials. We assign internal personnel to manage and oversee third parties working on our behalf under contract. These third parties manufacture raw materials, the active pharmaceutical ingredient, or API, and finished drug product for commercial distribution and for use in clinical studies. We currently rely on, and will continue to rely on these third-party contract manufacturers to produce sufficient quantities of our products.

## Employees

As of December 31, 2018, we had 158 employees. None of our employees are represented by a collective bargaining arrangement, and we believe our relationship with our employees is good. Recruiting and retaining experienced and qualified sales and marketing personnel to successfully commercialize our product and scientific personnel to continue to perform research and development work in the future will be critical to our business success. We may not be able to attract and retain personnel on acceptable terms given the competition among pharmaceutical and

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biotechnology companies, academic and research institutions and government agencies for experienced scientists.

### Scientific and Medical Advisors

We utilize scientists, key opinion leaders and physicians to advise us on scientific and medical matters as part of our ongoing research and product development efforts, including experts in clinical trial design, preclinical development work, chemistry, biology, immunology, oncology and immuno-oncology. Certain of our consultants receive non employee options to purchase our common stock and certain of our scientific and medical advisors receive honorarium for time spent assisting us.

### Available Information

Our website is located at [www.rigel.com](http://www.rigel.com). The information found on our website is not part of or incorporated by reference into this Annual Report on Form 10 K. We electronically file with the Securities and Exchange Commission (SEC) our Annual Report on Form 10 K, Quarterly Reports on Form 10 Q, Current Reports on Form 8 K and amendments to the reports filed or furnished pursuant to Section 13(a) or 15(d) of the Exchange Act. We make available free of charge on or through our website copies of these reports as soon as reasonably practicable after we electronically file these reports with, or furnish them to, the SEC. Further, copies of these reports are available at the SEC's Public Reference Room at 100 F Street, NE, Washington, D.C. 20549. Information on the operation of the Public Reference Room can be obtained by calling the SEC at 1 800 SEC 0330. The SEC also maintains an internet site that contains reports, proxy and information statements and other information regarding issuers that file electronically with the SEC at [www.sec.gov](http://www.sec.gov).

### Item 1A. Risk Factors

In evaluating our business, you should carefully consider the following risks, as well as the other information contained in this Annual Report on Form 10 K. These risk factors could cause our actual results to differ materially from those contained in forward looking statements we have made in this Annual Report on Form 10 K and those we may make from time to time. If any of the following risks actually occurs, our business, financial condition and operating results could be harmed. The risks and uncertainties described below are not the only ones facing us. Additional risks and uncertainties not presently known to us, or that we currently see as immaterial, may also harm our business.

Our prospects are highly dependent on the successful commercialization of TAVALISSE® (fostamatinib disodium hexahydrate), which received approval in April 2018 from the FDA for patients with chronic ITP who have had an insufficient response to a previous treatment. To the extent that TAVALISSE is not commercially successful, our business, financial condition and results of operations may be materially adversely affected and the price of our common stock may decline.

TAVALISSE is our only drug that has been approved for sale and it has only been approved in the United States for patients with chronic ITP who have had an insufficient response to a previous treatment. We are focusing a significant portion of our activities and resources on fostamatinib, and we believe our prospects are highly dependent on, and a significant portion of the value of our Company relates to, our ability to successfully commercialize TAVALISSE in



the United States.

Successful commercialization of TAVALISSE is subject to many risks. We have never, as an organization, launched or commercialized a product, and there is no guarantee that we will be able to do so successfully with fostamatinib for its approved indication. There are numerous examples of unsuccessful product launches and failures to meet high expectations of market potential, including by pharmaceutical companies with more experience and resources than us.

Market acceptance of fostamatinib and any of our or collaborative partners' future product candidates that may receive approval, will depend on a number of factors, including:

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- the efficacy and safety as demonstrated in clinical trials;
- the timing of market introduction of the product as well as competitive products;
- the clinical indications for which the product is approved;
- acceptance by physicians, the medical community and patients of the product as a safe and effective treatment;
- the ability to distinguish safety and efficacy from existing, less expensive generic alternative therapies, if any;
- the convenience of prescribing, administering and initiating patients on the product and the length of time the patient is on the product;
- the potential and perceived advantages of the product over alternative treatments;
- the potential and perceived value of the product over alternative treatments;
- the cost of treatment in relation to alternative treatments, including any similar generic treatments;
- the availability of coverage and adequate reimbursement and pricing by third-party payors and government authorities;
- the prevalence and severity of adverse side effects; and
- the effectiveness of sales and marketing efforts.

Even if we are successful in building out our commercial team, there are many factors that could cause the launch and commercialization of TAVALISSE to be unsuccessful, including a number of factors that are outside our control. The commercial success of TAVALISSE depends on the extent to which patients and physicians accept and adopt TAVALISSE for patients with chronic ITP who have had an insufficient response to a previous treatment. We also do not know how physicians, patients and payors will respond to the price increases of fostamatinib.

Physicians may not prescribe TAVALISSE and patients may be unwilling to use TAVALISSE if coverage is not provided or reimbursement is inadequate to cover a significant portion of the cost. Additionally, any negative development for fostamatinib in clinical development in additional indications, may adversely impact the commercial

results and potential of fostamatinib. Thus, significant uncertainty remains regarding the commercial potential of fostamatinib.

If the launch or commercialization of TAVALISSE is unsuccessful or perceived as disappointing, our stock price could decline significantly and the long-term success of the product and our company could be harmed.

We also may not be successful entering into arrangements with third parties to sell and market one or more of our product 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, including Kissei's development and commercialization of fostamatinib in all indications in Japan, China, Taiwan, and the Republic of Korea, and any of them may fail to devote the necessary resources and attention to sell and market one or more of our product candidates effectively, which could damage our reputation. If we do not establish sales and marketing capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our product candidates.

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Even if we, or any of our collaborative partners, are able to continue to commercialize TAVALISSE or any product candidate that we, or they, develop, the product may become subject to unfavorable pricing regulations, third-party payor reimbursement practices or labeling restrictions, any of which could harm our business.

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

There is significant uncertainty related to third-party payor coverage and reimbursement of newly approved drugs. Marketing approvals, pricing and reimbursement for new drug products vary widely from country to country. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we, or any of our collaborative partners, might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay commercial launch of the product, possibly for lengthy time periods, which may negatively impact the revenues we are able to generate from the sale of the product in that country. Adverse pricing limitations may hinder our ability or the ability of any future collaborators to recoup our or their investment in one or more product candidates, even if our product candidates obtain marketing approval.

Patients who are provided medical treatment for their conditions generally rely on third-party payors to reimburse all or part of the costs associated with their treatment. Therefore, our ability, and the ability of any of our collaborative partners, to successfully commercialize fostamatinib or any of our product candidates will depend in part on the extent to which coverage and adequate reimbursement for these products and related treatments will be available from third-party payors.

Additionally, the approved labeling ultimately approved for any of our product candidates for which we have or may obtain regulatory approval may include restrictions on their uses and may be subject to ongoing FDA or international regulatory authority requirements governing the labeling, packaging, storage, distribution, safety surveillance, advertising, promotion, record-keeping and reporting of safety and other post-market information. If we or any of our collaborative partners do not timely obtain or comply with the labeling approval by the FDA or international regulatory authorities on any of our product candidates, it may delay or inhibit our ability to successfully commercialize our products and generate revenues.

If we are unable to successfully launch TAVALISSE and retain experienced sales force, our business will be substantially harmed.

We currently have limited experience in marketing and selling pharmaceutical products. TAVALISSE is a newly-marketed drug and, therefore, none of the members of our sales force will have ever promoted TAVALISSE prior to its launch. As a result, we will be required to expend significant time and resources and to continuously to train our sales force to be credible, persuasive and compliant with applicable laws in marketing TAVALISSE for patients with chronic ITP who have had an insufficient response to a previous treatment. In addition, we must continually train our sales force to ensure that an appropriate and compliant message about TAVALISSE is being delivered. If we are unable to effectively train our sales force and equip them with compliant and effective materials, including medical and sales literature to help them appropriately inform and educate regarding its potential benefits and proper administration, our efforts to successfully commercialize TAVALISSE could be put in jeopardy, which would negatively impact our ability

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to generate product revenues.

We have only recently established our distribution and reimbursement capabilities, all of which will be necessary to successfully commercialize TAVALISSE. As a result, we will be required to expend significant time and resources to market, sell, and distribute TAVALISSE to hematologists and hematologists-oncologists. There is no guarantee that the marketing strategies, or the distribution and reimbursement capabilities, that we have developed will be successful. Particularly, we are dependent on third-party logistics, specialty pharmacies and distribution partners in the distribution of TAVALISSE. If they are unable to perform effectively or if they do not provide efficient distribution of the medicine to patients, our business may be harmed.

If the market opportunities for TAVALISSE and product candidates are smaller than we believe they are, our revenues may be adversely affected, and our business may suffer.

Certain of the diseases that TAVALISSE and our other product candidates being developed to address are in underserved and underdiagnosed populations. Our projections of both the number of people who have these diseases, as well as the subset of people with these diseases who will seek treatment utilizing our products or product candidates, may not be accurate. If our estimates of the prevalence or number of patients potentially on therapy prove to be inaccurate, the market opportunities for fostamatinib and our other product candidates may be smaller than we believe they are, our prospects for generating expected revenue may be adversely affected and our business may suffer.

We have recently increased, and will continue to increase, the size of our organization. We may encounter difficulties with managing our growth, which could adversely affect our results of operations.

As of December 31, 2018, we had approximately 158 full-time employees. Although we have substantially increased the size of our organization, we may need to add additional qualified personnel and resources, especially now that we have a commercial sales force. Our current infrastructure may be inadequate to support our development and commercialization efforts and expected growth. Future growth will impose significant added responsibilities on members of management, including the need to identify, recruit, maintain and integrate additional employees, and may take time away from running other aspects of our business, including development and commercialization of TAVALISSE and our other product candidates.

Our future financial performance and our ability to commercialize TAVALISSE and our other product candidates that may receive regulatory approval will depend, in part, on our ability to manage any future growth effectively. In particular, as we commercialize TAVALISSE, we will need to support the training and ongoing activities of our sales force and will likely need to continue to expand the size of our employee base for managerial, operational, financial and other resources. To that end, we must be able to successfully:

- manage our development efforts effectively;
- integrate additional management, administrative and manufacturing personnel;
- further develop our marketing and sales organization; and
- maintain sufficient administrative, accounting and management information systems and controls.

We may not be able to accomplish these tasks or successfully manage our operations and, accordingly, may not achieve our research, development, and commercialization goals. Our failure to accomplish any of these goals could materially and adversely affect our business and operations.

Regulatory approval for any approved product is limited by the FDA to those specific indications and conditions for which clinical safety and efficacy have been demonstrated, and we may incur significant liability if it is determined that we are promoting the “off-label” use of TAVALISSE or any of our future product candidates if approved.

Any regulatory approval is limited to those specific diseases, indications and patient populations for which a

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product is deemed to be safe and effective by the FDA. For example, the FDA-approved label for TAVALISSE is only approved for use in adults with ITP who have had an insufficient response to other treatments. In addition to the FDA approval required for new formulations, any new indication for an approved product also requires FDA approval. If we are not able to obtain FDA approval for any desired future indications for our products and product candidates, our ability to effectively market and sell our products may be reduced and our business may be adversely affected.

While physicians may choose to prescribe drugs for uses that are not described in the product's labeling and for uses that differ from those tested in clinical studies and approved by the regulatory authorities, our ability to promote the products is limited to those indications and patient populations that are specifically approved by the FDA. These "off-label" uses are common across medical specialties and may constitute an appropriate treatment for some patients in varied circumstances. We have implemented compliance and monitoring policies and procedures, including a process for internal review of promotional materials, to deter the promotion of TAVALISSE for off-label uses. We cannot guarantee that these compliance activities will prevent or timely detect off-label promotion by sales representatives or other personnel in their communications with health care professionals, patients and others, particularly if these activities are concealed from the Company. Regulatory authorities in the United States generally do not regulate the behavior of physicians in their choice of treatments. Regulatory authorities do, however, restrict communications by pharmaceutical companies on the subject of off-label use. If our promotional activities fail to comply with the FDA's regulations or guidelines, we may be subject to warnings from, or enforcement action by, these regulatory authorities. In addition, our failure to follow FDA rules and guidelines relating to promotion and advertising may cause the FDA to issue warning letters or untitled letters, suspend or withdraw an approved product from the market, require a recall or institute fines, which could result in the disgorgement of money, operating restrictions, injunctions or civil or criminal enforcement, and other consequences, any of which could harm our business.

Notwithstanding the regulatory restrictions on off-label promotion, the FDA and other regulatory authorities allow companies to engage in truthful, non-misleading and non-promotional scientific exchange concerning their products. We engage in medical education activities and communicate with investigators and potential investigators regarding our clinical trials. If the FDA or other regulatory or enforcement authorities determine that our communications regarding our marketed product are not in compliance with the relevant regulatory requirements and that we have improperly promoted off-label uses, or that our communications regarding our investigational products are not in compliance with the relevant regulatory requirements and that we have improperly engaged in pre-approval promotion, we may be subject to significant liability, including civil and administrative remedies as well as criminal sanctions.

Enacted or future legislation, including potentially unfavorable pricing regulations or other healthcare reform initiatives, may increase the difficulty and cost for us to obtain regulatory approval of our product candidates and/or commercialize fostamatinib or our product candidates, once approved, and affect the prices we may set or obtain.

The regulations that govern, among other things, regulatory approvals, coverage, pricing and reimbursement for new drug products vary widely from country to country. In the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could



prevent or delay regulatory approval of our product candidates, restrict or regulate post-approval activities and affect our ability to successfully sell fostamatinib or any product candidates for which we obtain regulatory approval in the future. In particular, in March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, collectively, the Affordable Care Act, was enacted, which substantially changes the way health care is financed by both governmental and private insurers, and significantly impacts the U.S. pharmaceutical industry. The Affordable Care Act and its implementing regulations, among other things, addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for certain drugs and biologics, including our approved product and product candidates, that are inhaled, infused, instilled, implanted or injected, increased the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program, extended the Medicaid Drug Rebate Program to utilization of prescriptions of individuals enrolled in Medicaid managed care organizations, subjected manufacturers to new annual fees and taxes for certain branded prescription drugs, provided incentives to programs that increase the federal government's comparative effectiveness research and established a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 70% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap

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period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D.

Other legislative changes have been proposed and adopted in the United States since the Affordable Care Act was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least \$1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of 2% per fiscal year, which went into effect in April 2013, and, due to subsequent legislative amendments, will remain in effect through 2027, unless additional Congressional action is taken. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, or the ATRA, which, among other things, further reduced Medicare payments to several providers, including hospitals and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

There have been, and likely will continue to be, legislative and regulatory proposals at the foreign, federal and state levels directed at broadening the availability of healthcare and containing or lowering the cost of healthcare. We cannot predict the initiatives that may be adopted in the future. The continuing efforts of the government, insurance companies, managed care organizations and other payors of healthcare services to contain or reduce costs of healthcare and/or impose price controls may adversely affect:

- the demand for fostamatinib or our product candidates, if we obtain regulatory approval;
- our ability to set a price that we believe is fair for our products;
- our ability to generate revenue and achieve or maintain profitability;
- the level of taxes that we are required to pay; and
- the availability of capital.

Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors, which may adversely affect our future profitability.

Since its enactment, there have been judicial and Congressional challenges to numerous provisions of the Affordable Care Act, as well as recent efforts by the Trump administration to repeal or replace certain aspects of the Affordable Care Act. Since January 2017, President Trump has signed two Executive Orders designed to delay the

implementation of certain provisions of the Affordable Care Act or otherwise circumvent some of the requirements for health insurance mandated by the Affordable Care Act. Concurrently, Congress has considered legislation that would repeal or repeal and replace all or part of the Affordable Care Act. While Congress has not passed comprehensive repeal legislation, two bills affecting the implementation of certain taxes under the Affordable Care Act have been enacted. More recently, in July 2018, the Centers for Medicare and Medicaid Services, or CMS, published a final rule permitting further collections and payments to and from certain Affordable Care Act qualified health plans and health insurance issuers under the Affordable Care Act risk adjustment program in response to the outcome of federal district court litigation regarding the method CMS uses to determine this risk adjustment. On December 14, 2018, a U.S. District Court Judge in the Northern District of Texas ruled that the individual mandate is a critical and inseverable feature of the Affordable Care Act, and because it was repealed as part of the Tax Cuts and Jobs Act of 2017, the remaining provisions of the Affordable Care Act are invalid as well. While neither the Texas District Court Judge, Trump administration nor CMS have stated that the ruling will have an immediate effect, it is unclear how this decision, subsequent appeals, if any, and other efforts will impact the Affordable Care Act. Additional policy changes, including potential modification or repeal of all or parts of the Affordable Care Act or the implementation of new health care legislation could result in significant changes to the health care system, which could have a material adverse effect on our business, results of operations and financial condition.

Legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. We cannot be sure whether additional legislative changes will be

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enacted, or whether the FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the regulatory approvals of our product candidates, if any, may be.

In the United States, the European Union and other potentially significant markets for our current and future products, 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 has resulted in lower average selling prices. For example, in the United States, there have been several recent Congressional inquiries and proposed federal 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, the Trump administration's budget proposal for fiscal year 2019 contains further drug price control measures that could be enacted during the 2019 budget process or in other future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain drugs under Medicare Part B, to allow some states to negotiate drug prices under Medicaid, and to eliminate cost sharing for generic drugs for low-income patients. Further, the Trump administration released a "Blueprint", or plan, to lower drug prices and reduce out of pocket costs of drugs that contains additional proposals to increase drug manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products, and reduce the out of pocket costs of drug products paid by consumers. The United States Department of Health and Human Services has already started the process of soliciting feedback on some of these measures while concurrently implementing others under its existing authority. For example, in September 2018, CMS announced that it will allow Medicare Advantage Plans the option to use step therapy for Part B drugs beginning January 1, 2019, and in October 2018, CMS proposed a new rule that would require direct-to-consumer television advertisements of prescription drugs and biological products, for which payment is available through or under Medicare or Medicaid, to include in the advertisement the Wholesale Acquisition Cost, or list price, of that drug or biological product. On January 31, 2019, the HHS Office of Inspector General proposed modifications to federal Anti-Kickback Statute safe harbors which, among other things, may affect rebates paid by manufacturers to Medicare Part D plans, the purpose of which is to further reduce the cost of drug products to consumers. While some proposed measures will require authorization through additional legislation to become effective, 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 have increasingly passed legislation and implemented 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, to encourage importation from other countries and bulk purchasing. Furthermore, the increased emphasis on managed healthcare in the United States and on country and regional pricing and reimbursement controls in the E.U. will put additional pressure on product pricing, reimbursement and usage, which may adversely affect our sales and results of operations. These pressures can arise from rules and practices of managed care groups, judicial decisions and governmental laws and regulations related to Medicare, Medicaid and healthcare reform, pharmaceutical reimbursement policies and pricing in general.

We may be subject, directly or indirectly, to federal and state healthcare fraud and abuse laws, false claims laws and other federal and state healthcare laws, and the failure to comply with such laws could result in substantial penalties. Our employees, independent contractors, consultants, principal investigators, CROs, commercial partners and vendors may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements.

Our business operations and current and future arrangements with investigators, healthcare professionals, consultants, third-party payers and customers, may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations. These laws may constrain the business or financial arrangements and relationships through which we conduct our operations, including how we research, market, sell and distribute any product for which we have obtained regulatory approval, or for which we obtain regulatory approval in the future. In particular, the promotion, sales and marketing of healthcare items and services, as well as certain business arrangements in the healthcare industry, are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, including off-label uses of our products, structuring and commission(s), certain customer incentive programs and other business arrangements generally. Activities subject to these laws also involve the improper use or misrepresentation of information obtained in the course of patient recruitment for clinical trials, creating fraudulent data

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in our preclinical studies or clinical trials or illegal misappropriation of drug product, which could result in regulatory sanctions and cause serious harm to our reputation. The laws that may affect our ability to operate include, but are not limited to:

- the Federal Anti-Kickback Statute, which prohibits, among other things, individuals and entities from knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe, or rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce, or in return for, either the referral of an individual for, or the purchase, lease, order or recommendation of, any good, facility, item or service for which payment may be made, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs. A person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;
- federal civil and criminal false claims laws and civil monetary penalty laws, including the federal civil False Claims Act, which impose criminal and civil penalties, through government or civil whistleblower, or qui tam, actions, on individuals and entities for, among other things, knowingly presenting, or causing to be presented, claims for payment or approval from the federal government, including federal healthcare programs, such as Medicare, Medicaid that are false, fictitious or fraudulent, or knowingly making, using or causing to be made or used, a false statement to avoid, decrease or conceal an obligation to pay money to the federal government. Entities can be held liable under the federal civil False Claims Act if they are deemed to “cause” the submission of false or fraudulent claims by, for example, providing inaccurate billing or coding information to customers, promoting a product off label, or for providing medically unnecessary services or items. In addition, the government may assert that a claim including items and services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act;
- the Federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which imposes criminal and civil liability for, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud or to obtain any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e.g., public or private), willfully obstructing a criminal investigation of a healthcare offense, and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false, fictitious or fraudulent statements in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters. Similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the healthcare fraud statute implemented under HIPAA or specific intent to violate it in order to have committed a violation;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, and their respective implementing regulations, which impose requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses, as well as their respective business associates that perform services for them that involve the creation, use, maintenance or disclosure of, individually identifiable health information, relating to the privacy, security and transmission of individually identifiable health information without appropriate authorization;
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the federal physician payment transparency requirements, sometimes referred to as the Physician Payments Sunshine Act, created under the Affordable Care Act, and its implementing regulations, which require 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 certain exceptions) to report annually to CMS, information related to payments or other transfers of value made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members;

- the U.S. Federal Food, Drug and Cosmetic Act, or FDCA, which prohibits, among other things, the adulteration or misbranding of drugs and medical devices; and

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- federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers.

Additionally, we are subject to state and foreign equivalents of each of the healthcare fraud and abuse laws described above, among others, some of which may be broader in scope and may apply regardless of the payor. 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 government; state and local laws that restrict payments that may be made to healthcare providers; state and local laws that require pharmaceutical manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers and entities, or marketing expenditures; state and local laws that require the registration of pharmaceutical sales representatives; state laws that require information to be reported related to drug pricing; and equivalent foreign laws and regulations. Further, we may be subject to state and foreign laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

We are also exposed to the risk of fraud, misconduct or other illegal activity by our employees, independent contractors, consultants, principal investigators, CROs, commercial partners and vendors. Misconduct by these parties could include intentional, reckless and/or negligent conduct that fails to: comply with the laws of the FDA and other similar foreign regulatory bodies; provide true, complete and accurate information to the FDA and other similar foreign regulatory bodies; comply with manufacturing standards we have established; comply with federal and state data privacy, security, fraud and abuse and other healthcare laws and regulations in the United States and similar foreign fraudulent misconduct laws; or report financial information or data accurately or to disclose unauthorized activities to us. It is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent inappropriate conduct may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations.

We are also subject to the risk that a person or government could allege such fraud or other misconduct, even if none occurred. Efforts to ensure that our business arrangements will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental and enforcement authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law interpreting applicable fraud and abuse or other healthcare laws and regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of civil, criminal and administrative penalties, damages, disgorgement, monetary fines, individual imprisonment, additional reporting obligations and oversight if we become subject to a corporate integrity agreement or other agreement to resolve allegations of non-compliance with these laws, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, and curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. In addition, the approval and commercialization of any of our product candidates outside the United States will also likely subject us to foreign equivalents of the healthcare laws mentioned above, among other foreign laws.



If manufacturers obtain approval for generic versions of TAVALISSE, or of products with which we compete, our business may be harmed.

Under the U.S. Food, Drug and Cosmetic Act, or FDCA, the FDA can approve an Abbreviated New Drug Application, or ANDA, for a generic version of a branded drug without the ANDA applicant undertaking the clinical testing necessary to obtain approval to market a new drug. Generally, in place of such clinical studies, an ANDA applicant usually needs only to submit data demonstrating that its product has the same active ingredient(s), strength, dosage form, route of administration and that it is bioequivalent to the branded product.

The FDCA requires that an applicant for approval of a generic form of a branded drug certify either that its generic product does not infringe any of the patents listed by the owner of the branded drug in the Orange Book or that those patents are not enforceable. This process is known as a paragraph IV challenge. Upon notice of a paragraph IV

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challenge, a patent owner has 45 days to bring a patent infringement suit in federal district court against the company seeking ANDA approval of a product covered by one of the owner's patents. If this type of suit is commenced, the FDCA provides a 30-month stay on the FDA's approval of the competitor's application. If the litigation is resolved in favor of the ANDA applicant or the challenged patent expires during the 30-month stay period, the stay is lifted and the FDA may thereafter approve the application based on the standards for approval of ANDAs. Once an ANDA is approved by the FDA, the generic manufacturer may market and sell the generic form of the branded drug in competition with the branded medicine.

The ANDA process can result in generic competition if the patents at issue are not upheld or if the generic competitor is found not to infringe the owner's patents. If this were to occur with respect to TAVALISSE or products with which it competes, our business would be materially harmed. We have a number of patents listed in the Orange Book, the last of which is expected to expire in July 2032.

Unforeseen safety issues could emerge with TAVALISSE that could require us to change the prescribing information to add warnings, limit use of the product, and/or result in litigation. Any of these events could have a negative impact on our business.

Discovery of unforeseen safety problems or increased focus on a known problem could impact our ability to commercialize TAVALISSE and could result in restrictions on its permissible uses, including withdrawal of the medicine from the market.

If we or others identify additional undesirable side effects caused by TAVALISSE after approval:

- regulatory authorities may require the addition of labeling statements, specific warnings, contraindications, or field alerts to physicians and pharmacies;
- regulatory authorities may withdraw their approval of the product and require us to take our approved drugs off the market;
- we may be required to change the way the product is administered, conduct additional clinical trials, change the labeling of the product, or implement a Risk Evaluation and Mitigation Strategy, or REMS;
- we may have limitations on how we promote our drugs;
- third-party payers may limit coverage or reimbursement for TAVALISSE;

- sales of TAVALISSE may decrease significantly;
- we may be subject to litigation or product liability claims; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of TAVALISSE and could substantially increase our operating costs and expenses, which in turn could delay or prevent us from generating significant revenue from sale of TAVALISSE.

If a safety issue emerges post-approval, we may become subject to costly product liability litigation by our customers, their patients or payers. Product liability claims could divert management's attention from our core business, be expensive to defend, and result in sizable damage awards against us that may not be covered by insurance. If we cannot successfully defend ourselves against claims that TAVALISSE caused injuries, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

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- decreased demand for any product candidates or products that we may develop;
- the inability to commercialize any products that we may develop;
- injury to our reputation and significant negative media attention;
- withdrawal of patients from clinical studies or cancellation of studies;
- significant costs to defend the related litigation;
- substantial monetary awards to patients; and
- loss of revenue.

We currently hold \$10.0 million in product liability insurance coverage, which may not be adequate to cover all liabilities that we may incur. Insurance coverage is increasingly expensive. We may not be able to obtain insurance coverage at a reasonable cost or in amounts adequate to satisfy any liability or associated costs that may arise in the future. These events could harm our business and results of operations and cause our stock price to decline.

If we fail to comply with our reporting and payment obligations under the Medicaid Drug Rebate Program or other governmental pricing programs in the United States, we could be subject to additional reimbursement requirements, fines, sanctions and exposure under other laws which could have a material adverse effect on our business, results of operations and financial condition.

We participate in the Medicaid Drug Rebate Program, as administered by the CMS, and other federal and state government pricing programs in the United States, and we may participate in additional government pricing programs in the future. These programs generally require us to pay rebates or otherwise provide discounts to government payers in connection with drugs that are dispensed to beneficiaries/recipients of these programs. In some cases, such as with the Medicaid Drug Rebate Program, the rebates are based on pricing that we report on a monthly and quarterly basis to the government agencies that administer the programs. Pricing requirements and rebate/discount calculations are complex, vary among products and programs, and are often subject to interpretation by governmental or regulatory agencies and the courts. The requirements of these programs, including, by way of example, their respective terms and scope, change frequently. Responding to current and future changes may increase our costs, and the complexity of compliance will be time consuming. Invoicing for rebates is provided in arrears, and there is frequently a time lag of up to several months between the sales to which rebate notices relate and our receipt of those notices, which further complicates our ability to accurately estimate and accrue for rebates related to the Medicaid program as implemented by individual states. Thus, there can be no assurance that we will be able to identify all factors that may cause our discount and rebate payment obligations to vary from period to period, and our actual results may differ significantly from our estimated allowances for discounts and rebates. Changes in estimates and assumptions may have a material adverse effect on our business, results of operations and financial condition.

In addition, the Office of Inspector General of the Department of Health and Human Services and other Congressional enforcement and administrative bodies have recently increased their focus on pricing requirements for products, including, but not limited to the methodologies used by manufacturers to calculate average manufacturer price, or AMP, and best price, or BP, for compliance with reporting requirements under the Medicaid Drug Rebate Program. We are liable for errors associated with our submission of pricing data and for any overcharging of government payers. Failure to make necessary disclosures and/or to identify overpayments could result in allegations against us under the Federal False Claims Act and other laws and regulations. Any required refunds to the U.S. government or responding to a government investigation or enforcement action would be expensive and time consuming and could have a material adverse effect on our business, results of operations and financial condition. In addition, in the event that CMS were to terminate our rebate agreement, no federal payments would be available under Medicaid or Medicare for our covered outpatient drugs.

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Even for those product candidates that have or may receive regulatory approval, they may fail to achieve the degree of market acceptance by physicians, patients, healthcare payors and others in the medical community necessary for commercial success, in which case we may not generate significant revenues or become profitable.

For our product candidates that have or may receive regulatory approval, they may nonetheless fail to gain sufficient market acceptance by physicians, hospital administrators, patients, healthcare payors and others in the medical community. The degree of market acceptance of our product candidates, if approved for commercial sale, will depend on a number of factors, including the following:

- relative convenience and ease of administration;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the willingness of physicians to change their current treatment practices;
- the willingness of hospitals and hospital systems to include our product candidates as treatment options;
- demonstration of efficacy and safety in clinical trials;
- the prevalence and severity of any side effects;
- the ability to offer product candidates for sale at competitive prices;
- the price we charge for our product candidates;
- the strength of marketing and distribution support; and