ARENA PHARMACEUTICALS INC
Form 10-K
February 28, 2019

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2018

or

TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the transition period from to

COMMISSION FILE NUMBER 000-31161

ARENA PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

Delaware	23-2908305
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)
6154 Nancy Ridge Drive, San Diego, CA	92121
(Address of principal executive offices)	(Zip Code)

858.453.7200

(Registrant’s telephone number, including area code)

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

Title of each class	Name of each exchange on which registered
Common Stock, par value $0.0001 per share	The Nasdaq Global Select Market

Securities registered pursuant to 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.

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

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

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

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant was approximately $1.9 billion as of June 29, 2018, based on the last sale price of the registrant's common stock as reported on the Nasdaq Global Select Market on such date. For purposes of this calculation, shares of the registrant's common stock held by directors and executive officers have been excluded. This number is provided only for purposes of this Annual Report on Form 10-K and does not represent an admission that any particular person or entity is an affiliate of the registrant.

As of February 22, 2019, there were 49,462,849 shares of the registrant's common stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Certain information required by Part III of this Annual Report on Form 10-K is incorporated by reference from the Registrant's Definitive Proxy Statement for the Annual Meeting of Stockholders to be held in June 2019, which will be filed with the Securities and Exchange Commission on or before April 30, 2019.

ARENA PHARMACEUTICALS, INC.

FORM 10-K – ANNUAL REPORT

For the Fiscal Year Ended December 31, 2018

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INFORMATION RELATING TO FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K, or Annual Report, includes forward-looking statements, which involve a number of risks and uncertainties. These forward-looking statements can generally be identified as such because the context of the statement will include words such as “may,” “will,” “intend,” “plan,” “believe,” “anticipate,” “expect,” “estimate,” “predict “potential,” “continue,” “likely,” or “opportunity,” the negative of these words or other similar words. Similarly, statements that describe our future plans, strategies, intentions, expectations, objectives, goals or prospects and other statements that are not historical facts are also forward-looking statements. Discussions containing these forward-looking statements may be found, among other places, in “Business” and “Management’s Discussion and Analysis of Financial Condition and Results of Operations” in this Annual Report. For such statements, we claim the protection of the Private Securities Litigation Reform Act of 1995. Readers of this Annual Report are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the time this Annual Report was filed with the Securities and Exchange Commission, or SEC. These forward-looking statements are based largely on our expectations and projections about future events and future trends affecting our business and are subject to risks and uncertainties that could cause actual results to differ materially from those anticipated in the forward-looking statements. These risks and uncertainties include, without limitation, those discussed in “Business”, “Risk Factors” and “Management’s Discussion and Analysis of Financial Condition and Results of Operations” of this Annual Report. In addition, past financial or operating performance is not necessarily a reliable indicator of future performance, and you should not use our historical performance to anticipate results or future period trends. We can give no assurances that any of the events anticipated by the forward-looking statements will occur or, if any of them do, what impact they will have on our results of operations and financial condition. In addition, statements that “we believe” and similar statements reflect our beliefs and opinions on the relevant subject. These statements are based upon information available to us as of the date of this Annual Report, and while we believe such information forms a reasonable basis for such statements, such information may be limited or incomplete, and our statements should not be read to indicate that we have conducted an exhaustive inquiry into, or review of, all potentially available relevant information. These statements are inherently uncertain and you are cautioned not to unduly rely upon these statements. Except as required by law, we undertake no obligation to update publicly or revise our forward-looking statements to reflect events or circumstances that arise after the filing of this Annual Report or documents incorporated by reference herein that include forward-looking statements.

TRADEMARKS AND CERTAIN TERMS

Arena Pharmaceuticals ® and Arena ® are registered service marks of Arena. Any other brand names or trademarks appearing in this Annual Report are the property of their respective holders.

In this Annual Report, “Arena Pharmaceuticals,” “Arena,” “we,” “us” and “our” refer to Arena Pharmaceuticals, Inc., and our wholly owned subsidiaries on a consolidated basis, unless the context otherwise provides. “APD” is an abbreviation for Arena Pharmaceuticals Development.

PART I

Item 1. Business.

Overview

We are a biopharmaceutical company focused on delivering novel, transformational medicines with optimized pharmacology and pharmacokinetics to patients globally. Our proprietary, internally-developed pipeline includes multiple potentially first- or best-in-class assets with broad clinical utility.

Our most advanced investigational clinical programs are: etrasimod (APD334), which we are evaluating in late-stage clinical programs in ulcerative colitis, and Crohn's disease, as well as progressing programs for atopic dermatitis and other indications; olorinab (APD371) for a broad range of visceral pain conditions associated with inflammatory bowel diseases and irritable bowel syndrome, and which we are evaluating in a Phase 2 trial for treatment of gastrointestinal pain; and ralinepag (APD811), which we have licensed to United Therapeutics Corporation, or United Therapeutics, and is being evaluated by United Therapeutics in a Phase 3 program for pulmonary arterial hypertension. We continue to assess other earlier research and development stage drug candidates, including APD418, a potential first-in-class calcium-independent myofilament derepressor, which we are studying in a preclinical program for the treatment of decompensated heart failure.

We have license agreements or collaborations with various companies, including United Therapeutics (ralinepag), Everest Medicines Limited (etrasimod in Greater China and select countries in Asia), Boehringer Ingelheim International GmbH (undisclosed orphan GPCR program for central nervous system – preclinical), Outpost Medicine, LLC (undisclosed program with potential utility in treating genitourinary disorders – preclinical) and Eisai Co., Ltd. and Eisai Inc., collectively, Eisai (BELVIQ®/BELVIQ XR® – marketed products).

Our Strategy

The primary elements of our focus are to:

- Develop etrasimod – a modulator of the sphingosine 1-phosphate, or S1P, receptor intended for the treatment of a broad range of immune and inflammatory conditions including inflammatory bowel diseases and dermatologic diseases
- Develop olorinab – an agonist of the cannabinoid receptor type 2, or CB2, intended for the treatment of a range of visceral gastrointestinal pain
- Develop APD418 – a calcium-independent myofilament derepressor for the treatment of decompensated heart failure
- Develop our pipeline by efficiently managing our cash and development timelines, which may include entering strategic agreements for certain clinical and preclinical programs
- Progress additional pipeline programs over time in select therapeutic areas
- Build a streamlined, high-performing and high-energy organization

Arena Pharmaceuticals, Inc. was incorporated in the state of Delaware in April 1997, and is located in San Diego, California. Our operations are located in San Diego, California; Boston, Massachusetts; and Zug, Switzerland.

Pipeline of Development Programs and Commercial Products

Below is a summary of our internally developed, proprietary portfolio:

We also own and have rights to other clinical and preclinical stage compounds that were internally discovered by us.

Etrasimod Program

Etrasimod is a next-generation, oral, selective sphingosine 1 phosphate (S1P) receptor modulator, discovered by Arena, designed to provide systemic and local cell modulation by selectively targeting S1P receptor subtypes 1, 4 and 5. Etrasimod has therapeutic potential in immune and inflammatory-mediated diseases such as ulcerative colitis, Crohn's disease, and atopic dermatitis. S1P receptors have been demonstrated to be involved in the modulation of several biological responses, including lymphocyte trafficking from lymph nodes to the peripheral blood. By isolating subpopulations of lymphocytes in lymph nodes, fewer immune cells are available in the circulating blood to effect tissue damage.

Inflammatory Bowel Diseases

Inflammatory bowel diseases, or IBD, like ulcerative colitis, or UC, and Crohn's disease, or CD, are chronic inflammatory conditions of the gastrointestinal tract that affect approximately 3.1 million patients in the US alone. The prevalence of UC and CD in the US are currently estimated at 1.8 million and 1.3 million patients, respectively. The prevalence of IBD in European Union, or EU, is estimated at 3.0 million with 1.7 million patients with UC and 1.3 million patients with CD. Both conditions have a significant impact on the patient's quality of life and can in many cases be very aggressive and disabling.

UC is characterized by mucosal inflammation limited to the colon which involves the rectum in approximately 95% of cases and may extend to involve parts or all of the large intestine. In contrast, CD is characterized by full thickness inflammation that can occur anywhere in the gastrointestinal, or GI, tract but most typically involves the terminal ileum and colon; and causes fistulation and scarring. Symptoms for UC and CD can vary, depending on the location and severity of inflammation, but some of the most common are diarrhea, abdominal cramps, and rectal bleeding.

Important goals of therapy for IBD are to induce and maintain remission while improving the patient's quality of life. Currently available treatment options have limitations in terms of long-term efficacy and side effects, have complicated administration regimens, and often fail to induce or maintain remission. Therefore, we believe a significant unmet need remains for differentiated oral agents that are efficacious for induction and maintenance therapy with a favorable side effect profile. We believe that the oral once-daily dosing, selectivity, mechanism of action, and emerging clinical profile of etrasimod may represent a significant opportunity to provide patients with an effective treatment for IBD with an improved safety and dosing profile over current therapies.

Atopic Dermatitis

Atopic Dermatitis, or AD, is a chronic, inflammatory skin disorder characterized by dry skin, pruritus, and relapsing lesions. AD has a severe impact on quality of life, including potential occupational, social, and psychological impairments. The adult prevalence is approximately 18 million patients in the US and 22 million patients in the EU.

A survey published in 2016 showed that 86% of patients were not satisfied with current treatment options. Two new therapies have been marketed since 2016, however these treatments have less desirable administration routes and are not effective in all patients. Long-term efficacy of these therapies also remains relatively unknown. Therefore, we believe a significant unmet need remains for differentiated, safe, oral agents that are effective and have a favorable side effect profile.

AD pathology is driven by a combination of impaired skin epithelial barriers, altered microbiota, and aberrant inflammation driven by activated immune cells, including skin-infiltrating T cells and dendritic cells, or DCs. Etrasimod may have the potential to reduce DC migration/activation (S1P receptor subtypes 1 and 4 mediated) and T cell infiltration (S1P receptor subtype 1 mediated) in the skin. These effects could reduce the T cell-mediated inflammation in the skin that underlies atopic dermatitis pathogenesis.

Etrasimod Development

Inflammatory Bowel Disease

We are currently preparing for a Phase 3 program in UC and a Phase 2b/3 program in CD.

In 2019, we announced positive results from a 34-week open-label extension, or OLE, of the Phase 2 OASIS trial of etrasimod for the treatment of ulcerative colitis. The trial enrolled 118 patients (84% of OASIS study completers), of which 22 completers also received 2 mg in OASIS, for a total of 46 weeks of treatment with etrasimod. Overall, etrasimod demonstrated durable, long-term clinical remission and was generally safe and well tolerated in this trial. Adverse events in the OLE study were generally mild to moderate in severity and no new safety findings were noted. Impact on heart rate and atrioventricular, or AV, conduction was minimal throughout the study with no discontinuations from study related to bradycardia or AV block.

In 2018, we announced topline results from OASIS, a dose finding 12-week randomized, double-blind, placebo-controlled multinational Phase 2 clinical trial of etrasimod in moderate to severe UC. The aim of the trial was to investigate a clear dose response and establish a clinically meaningful signal for the active arm(s) from placebo.

The trial evaluated the effects of etrasimod at 1mg and 2mg versus placebo on multiple efficacy measures including a three-component partial Mayo Clinic Score, clinical remission, clinical response, and endoscopic improvement in 156 patients. Etrasimod demonstrated a clear dose response and statistically significant improvements versus placebo in the primary, all secondary, and clinical remission endpoints at the 2 mg dose. There were fewer patients with serious adverse events, or SAEs, compared to placebo (0% in 2 mg, 5.8% in 1 mg and 11.1% in placebo). Impact on heart rate and atrioventricular, or AV, conduction was low throughout the study with no discontinuations from study related to bradycardia or AV block. There were no increases in liver function tests compared to placebo and no reports of macular edema or pulmonary function test abnormalities. In this trial, etrasimod was well tolerated and safety results support a potential best-in-class profile.

Δ = % difference from placebo estimated using Mantel-Haenszel method adjusted with current oral corticosteroid use and prior exposure to TNFa antagonists.

Atopic Dermatitis

We are currently preparing for a Phase 2 program in atopic dermatitis.

In 2018, we evaluated data from relevant patients with dermatological conditions in etrasimod trials. We believe the data we have, although limited, support ongoing investigation of etrasimod in skin disorders.

Prior Development

Starting in 2017, we initiated exploratory Phase 2, proof-of-concept, open-label studies to evaluate the efficacy and safety of etrasimod in patients with pyoderma gangrenosum, primary biliary cholangitis and active dermatologic extraintestinal manifestations of IBD. We decided to conclude these studies based on our strategic focus on IBD and atopic dermatitis.

In January 2015, we announced top-line results from a Phase 1b multiple-ascending dose clinical trial for etrasimod. In the trial, etrasimod demonstrated a dose-dependent effect on lymphocyte count lowering in blood, with mean decreases from baseline of up to 69%. Lymphocyte counts, on average, recovered to baseline within one week of conclusion of dosing. There was a modest impact on heart rate, but none of the changes were classified by the investigator as clinically significant. There were also no findings with respect to pulmonary function or liver enzyme tests that were classified by the investigator as clinically significant. The most common treatment-emergent adverse events were mild or moderate contact dermatitis, headache, constipation and diarrhea, with none being clearly drug related. There were no discontinuations for adverse events, and no serious adverse events were observed.

The randomized, double-blind, placebo-controlled Phase 1b clinical trial evaluated the safety, tolerability, pharmacodynamics and pharmacokinetics of multiple-ascending doses of etrasimod. In five different dosing cohorts, 50 healthy volunteers received etrasimod and 10 healthy volunteers received placebo for 21 days.

Prior to commencing the Phase 1b multiple-ascending dose clinical trial for etrasimod, we completed a Phase 1 single-ascending dose clinical trial of the compound. This randomized, double-blind and placebo-controlled trial evaluated the safety, tolerability and pharmacokinetics of single-ascending doses of etrasimod in 40 healthy adult volunteers. In the trial, etrasimod demonstrated favorable pharmacokinetic and pharmacodynamic effects, a dose-responsive reduction in blood lymphocyte count and a slowing of heart rate that appears comparable to other S1P receptor modulators. The terminal half-life was approximately 35 hours.

Etrasimod Intellectual Property

As of February 15, 2019, we owned issued patents that cover compositions of matter for etrasimod and related compounds, methods of treatment utilizing etrasimod and related compounds, and various salts of etrasimod and crystalline forms thereof in 61 jurisdictions, including the United States, China, Japan, Germany, France, Italy, the United Kingdom, Spain, Canada, India, Russia, South Korea and Australia, and had an application pending in one other jurisdiction (Brazil). Patents on etrasimod issued by the US Patent and Trademark Office include serial numbers US 8,580,841, US 9,126,932, and US 9,522,133 while the corresponding patent granted by the European Patent Office has serial number EP 2326621 B2. We also own issued patents and/or pending applications directed to solid-state

forms of etrasimod, dosage regimens for etrasimod, synthetic routes and intermediates useful in the manufacturing of etrasimod, and other methods of treatment utilizing etrasimod. The earliest priority date for the patents on etrasimod is 2008. The terms of these patents are capable of continuing into 2029 in most jurisdictions without taking into account any patent term adjustment or extension regimes of any country or any additional term of exclusivity we might obtain by virtue of the later filed patent applications.

Olorinab Program

Olorinab, a potentially first-in-class, orally available, potent, peripherally restricted, highly selective, full agonist of the CB2 receptor, is an internally discovered investigational drug candidate we are exploring for the treatment of visceral pain, specifically pain associated with the gastrointestinal system, such as IBD and irritable bowel syndrome, or IBS.

Visceral pain is defined as pain that originates within muscle, pleura, connective tissue, nervous system or solid organs within the abdomen or peritoneum. It is distinct from somatic or neuropathic pain, and is perceived as stretching, pulling and distention, rather than by cutting, crushing, or burning more commonly associated with neuropathic pain. Visceral pain is one of the most common types of pain. For example, abdominal pain affects approximately 20% of the general population. Visceral pain may be caused by a diverse set of organic causes, such as inflammation (e.g., IBD, including CD and UC, pancreatitis, prostatitis, and vaginitis), obstruction (e.g., bowel obstruction, and nephrolithiasis), ischemia, and malignancy, among others. Visceral pain may also be caused by functional disorders such as interstitial cystitis, dyspepsia, IBS, and vulvodynia.

There are approximately 3.1 million patients in the US with IBD, with 90% experiencing abdominal pain or cramps. There are approximately 24 million patients in the US with IBS, with 78% reporting frequently recurring or continuous abdominal pain. Common treatments for visceral pain range from non-invasive, conservative approaches (e.g., physical therapy or acupuncture), to pharmacologic (e.g., tricyclic antidepressants acting as neurotransmitter reuptake inhibitors), and invasive interventions (e.g., bowel resection). Potent analgesics, such as opioids, can adversely affect GI function. Other commonly prescribed analgesics are often not potent enough and may lead to other GI side effects such as bleeding. Except for linaclotide and lubiprostone, prescribed for IBS, no visceral-specific analgesics are currently available. Approximately one in eight CD patients is chronically treated with opioids.

The CB2 receptor is expressed in the GI nervous system, and in many tissues and organs of the abdomen. CB2 receptors are found peripherally on immune cells but also on microglia, terminal neurons, dorsal root ganglia, and on visceral sensory neurons. We believe selectively targeting the CB2 receptor may provide therapeutic benefit for visceral pain without the potential for dependence, abuse, and GI and cardiovascular side effects associated with opiates or nonsteroidal anti-inflammatory drugs, or NSAIDs, which are among the most common pain relievers. In addition to analgesic effects, olorinab may have anti-inflammatory properties.

Olorinab is designed to be a peripherally restricted and selective CB2 receptor agonist and is intended to provide pain relief without the unwanted side effects associated with CB1 receptor activation.

Olorinab Development

In 2018, we announced positive topline results from our Phase 2a trial of olorinab in development for the treatment of pain associated with CD. This exploratory study was an open label investigation to evaluate safety and tolerability of olorinab in this patient population and to gain initial insights into its efficacy via a pain visual analog scale, or VAS. Fourteen patients were enrolled into two cohorts at 25 mg and 100 mg administered three times daily for up to eight weeks. Reductions in pain were seen within the first week of treatment and statistically significant improvement from baseline in Average Abdominal Pain Score, or AAPS, at weeks four and eight. In this trial, olorinab appeared safe and generally well tolerated with no clinically significant changes in heart rate or blood pressure, no psychotropic effects, and no discontinuations due to adverse events.

In April 2016, we announced favorable results from a Phase 1b multiple-ascending dose clinical trial of olorinab. This randomized, double-blind, placebo-controlled Phase 1b clinical trial enrolled 36 healthy adults to evaluate the safety, tolerability and pharmacokinetics of multiple-ascending doses of olorinab. Cohorts of 12 subjects (9 active, 3 placebo) were administered doses of 50 mg, 100 mg, or 200 mg of olorinab or placebo three times daily for 10 days and, in connection with the pharmacokinetic evaluation, one time on the 11th day. The most common adverse events were headache and nausea. All adverse events were classified as mild, and there were no serious adverse events reported. There was one discontinuation in the high-dose group due to an adverse event of mild thirst and somnolence. Reductions in blood pressure and heart rate were observed, but none were symptomatic or resulted in an adverse event. Drug levels at all doses tested in the trial, including the lowest dose, were well above those believed to be needed to stimulate the CB2 receptor.

In April 2015, we announced favorable top-line results from a Phase 1 single-ascending dose clinical trial of olorinab. The randomized, double-blind and placebo-controlled trial enrolled 56 healthy adults to evaluate the safety, tolerability and pharmacokinetics of single-ascending doses of olorinab. Dose-responsive exposure was observed over the explored dose range of 10-400 mg with good tolerability at all doses administered.

Olorinab Intellectual Property

As of February 15, 2019, we owned issued patents covering compositions of matter for olorinab and related compounds, and methods of treatment utilizing olorinab and related compounds, in 21 jurisdictions, including the United States, China, Japan, Canada, Russia, South Korea and Australia, and we had applications pending in 10 other jurisdictions, of which the ones with the largest pharmaceutical markets were Europe, Venezuela, Brazil and India. Patents on olorinab issued by the US Patent and Trademark Office include serial numbers US 8,778,950 and US 9,944,606. We also own issued patents and/or pending applications directed to various solid-state forms of olorinab, and other methods of treatment utilizing olorinab. The earliest priority date for the patents on olorinab is 2009. The terms of these patents are capable of continuing into 2030 in most jurisdictions without taking into account any patent term adjustment or extension regimes of any country or any additional term of exclusivity we might obtain by virtue of the later filed patent applications.

APD418 Program

APD418 is a potential first-in-class calcium-independent myofilament derepressor, or CMD, in development for the treatment of decompensated heart failure, or DHF.

DHF is a clinical syndrome of new or worsening signs and symptoms of chronic heart failure, often leading to hospitalization or a visit to the emergency department. DHF is an area of high unmet medical need affecting a heterogeneous population with high post-discharge readmission rates and significant morbidity and mortality. Projections of decompensated heart failure forecast 9.5 million hospitalizations annually by 2025 in major markets worldwide. Approximately 70% of patients are readmitted within one year of the first treatment and patients experience a 20% increased mortality with each rehospitalization. The current in-hospital standard of care for DHF aims to improve hemodynamic status with drugs that increase cardiac contractility (inotropes) via modulation of the myocardial beta-adrenergic receptor, or AdrR, pathway. However, treatment with currently approved inotropes targeting beta1/beta2 adrenergic pathways has been associated with adverse effects on blood pressure and heart rate and result in increased long-term mortality.

APD418 is a beta3 AdrR antagonist, with no action on beta1/beta2 AdrRs. Beta3 AdrR upregulation and activation in DHF has been shown to decrease cardiac contractility, thus inhibition of beta3 with APD418 potentially represents a novel mechanism to improve contractility without the adverse hemodynamic and chronotropic changes associated with current inotropes that put stress on the heart. We are currently preparing an investigational new drug, or IND,

application enabling package.

Additional Internal Preclinical and Clinical Programs

We have additional clinical and preclinical assets, including temanogrel and APD597, which we are evaluating for future development. We are also evaluating additional delivery forms of the products in our pipeline to extend clinical utility or improve the product profile.

Collaborations and License Agreements

In addition to our primary focus on developing our proprietary, unencumbered clinical pipeline, we have strategic collaborations and licenses with pharmaceutical companies, including United Therapeutics, Everest Medicines Limited, or Everest, Boehringer Ingelheim International GmbH, or Boehringer Ingelheim, Outpost Medicine, LLC, or Outpost Medicine, Beacon Discovery, Inc., or Beacon, and Eisai.

United Therapeutics License Agreement

In November 2018, we entered into a collaboration and license agreement with United Therapeutics. Under the United Therapeutics Agreement, we granted United Therapeutics an exclusive, worldwide, royalty-bearing license to develop, manufacture and commercialize ralinepag. This transaction was completed on January 24, 2019. At the closing of the transaction, we transferred to United Therapeutics certain other assets relating to ralinepag, including, among others, related domain names and trademarks, permits, certain contracts, inventory, regulatory documentation, IND, and non-clinical, pre-clinical and clinical trial data. United Therapeutics has agreed to assume certain limited liabilities, including, among others, all post-closing obligations under assumed contracts and the IND. United Therapeutics is responsible for all development, manufacture and commercialization of the licensed products globally.

Upon the closing of this transaction, in January 2019, we received an upfront payment of $800.0 million. We are eligible to receive a payment of $150.0 million upon first marketing approval of ralinepag in a major non-US market, and a payment of $250.0 million upon US marketing approval of an inhaled formulation of ralinepag. In addition, we are entitled to receive low double-digit, tiered royalties on net sales of ralinepag products, subject to certain adjustments for third party license payments.

The United Therapeutics Agreement contains various representations and warranties of Arena and United Therapeutics, and various covenants of the parties, including covenants to cooperate in seeking regulatory approvals, as well as our agreement not to compete, during the period in which royalties are payable (or during the five-year period following the closing if we are subject to a change of control transaction) in the development of a prostacyclin to treat pulmonary arterial hypertension, or PAH.

Ralinepag Program

Ralinepag is a next-generation potent, highly selective oral IP receptor agonist intended for the treatment of PAH. Ralinepag was designed by us to deliver intravenous prostacyclin-like potency and pharmacokinetics in an oral tablet. In non-clinical experiments, ralinepag demonstrated potentially best-in-class activation of the IP receptor resulting in vasodilation, inhibition of smooth muscle cell proliferation and inhibition of platelet aggregation. Additionally, early stage studies of ralinepag pharmacokinetics in humans revealed an approximately 24-hour half-life and a low peak-to-trough ratio supporting therapeutic blood levels with once daily dosing.

Ralinepag was granted orphan drug status for the treatment of PAH by the US Food and Drug Administration, or FDA, in September 2014, and by the European Medicines Agency in January 2019.

PAH is a progressive, life-threatening disorder characterized by increased pressure in the pulmonary arteries that carry blood from the heart to the lungs. PAH occurs when the pulmonary arteries thicken or grow rigid. This makes blood flow more difficult. The heart must work harder to push blood through the arteries, and the arteries are unable to carry adequate blood to the lungs. The increased pressure strains the heart, which can limit physical activity, result in heart failure and reduce life expectancy. PAH will continue to worsen over time, even with proper treatment. Based on data from the Registry to EValuate Early And Long-term PAH disease management, or REVEAL, of patients in the US, there is an estimated five-year survival rate of 57% from diagnosis.

PAH involves several interrelated mechanisms, with prostacyclin and thromboxane A2 playing a major role in maintaining pulmonary vascular tone through their balanced activity. Prostacyclin, released by endothelial cells, promotes vasodilation and inhibits platelet aggregation. Prostacyclin also has antiproliferative effects on vascular smooth muscle. Despite treatment guidelines, targeting the prostacyclin pathway has been primarily reserved for patients with advanced disease due to limitations of currently available options including parenteral prostacyclins which are the only PAH treatment that have demonstrated a mortality benefit.

Ralinepag Development

In 2018, we announced positive data from a planned interim analysis of the ongoing open-label extension of the Phase 2 trial of ralinepag in development for the treatment of pulmonary arterial hypertension.

In 2017, we announced topline results from a 22-week, randomized, double-blind, placebo-controlled Phase 2 trial evaluating the effectiveness in reducing pulmonary vascular resistance, or PVR, improving exercise capacity, tolerability and safety of ralinepag. In this trial, 40 patients with PAH received ralinepag and 21 received placebo. Topline results showed statistically significant improvement of both absolute and percentage change from baseline in PVR. Ralinepag also demonstrated numerical improvement in six-minute walk distance, or 6MWD, but as the study was not powered to show a difference in 6MWD from placebo, this was a not a statistically-significant finding. The safety and tolerability profiles were in line with other oral prostacyclins.

In 2013, we announced topline results from a multiple-dose, randomized, double-blind and placebo-controlled Phase 1 clinical trial evaluating multiple-ascending doses of ralinepag in healthy volunteers. In this trial, 40 healthy volunteers received ralinepag and 15 received placebo. The safety profile of ralinepag in this trial was characteristic of IP receptor agonists: the most frequent treatment-emergent adverse events were headache, nausea and jaw pain. One serious adverse event, transient atrial fibrillation, occurred in a single subject, and the study investigator considered it to be possibly treatment related. Further review revealed that the subject had multiple characteristics predisposing the patient to atrial fibrillation, including cardiac abnormalities prior to study start.

In 2011, we announced topline results of a Phase 1 clinical trial to evaluate the safety, tolerability and pharmacokinetics of single-ascending doses of ralinepag. The randomized, double-blind and placebo-controlled trial evaluated 32 healthy volunteers in four cohorts of eight participants each, with six randomized to ralinepag and two to placebo. Ralinepag was rapidly absorbed and demonstrated dose-proportional pharmacokinetic exposure over the tested dose range. Consistent with the expected pharmacology of ralinepag, the most common adverse events were headache, vomiting, nausea, jaw pain and flushing.

Everest Collaboration

In December 2017, we entered into a Collaboration and License Agreement, or the Everest Agreement, with Everest regarding the development and commercialization of ralinepag and etrasimod in China, Taiwan, Hong Kong, Macau and South Korea, or the Everest Territories. In January 2019, we and Everest amended the Everest Agreement by entering into two separate agreements, one for each of ralinepag and etrasimod, with the terms for each program that are substantially the same as in the original Everest Agreement. Under the United Therapeutics Agreement, we assigned the separate Everest Agreement related to ralinepag to United Therapeutics.

Under the separate Everest Agreement related to etrasimod, we granted Everest an exclusive, royalty-bearing license to develop, manufacture and commercialize etrasimod (in oral formulations only), in the Everest Territories.

Everest is responsible for all development, manufacture and commercialization of the licensed products in the Everest Territories, and may participate in the portion of our global clinical trials that is conducted in the Everest Territories.

In addition to an upfront payment of $12.0 million, we are eligible to receive development, regulatory and commercial milestone payments from Everest of up to $115.0 million, as well as tiered royalties on net sales ranging from the high single digits to low double digits. Following an initial royalty term, we are eligible to receive a lower trademark royalty if Everest continues to use our licensed product-related trademarks.

In the fourth quarter of 2018, the National Medical Products Administration of China, formerly known as the China Food and Drug Administration, or CFDA, accepted the initial clinical trial applications for an oral formulation of ralinepag and for etrasimod.

Boehringer Ingelheim Collaboration

In 2015, we entered into an exclusive agreement with Boehringer Ingelheim, to conduct joint research to identify drug candidates targeting a GPCR that belongs to a group of orphan central nervous system, or CNS, receptors. An “orphan receptor” is structurally related to a family of proteins that are known to act as functional cell-surface receptors but whose ligand has not yet been identified. In December 2018, Boehringer Ingelheim opted to start the preclinical development of the subject compound.

We contracted with Beacon to perform our research obligations under the Boehringer Ingelheim collaboration. In exchange, we agreed to share limited near-term milestones with Beacon as well as the full-time equivalent funding

paid to us by Boehringer Ingelheim. We have retained the longer-term success milestones and all royalties.

Outpost Medicine License Agreement

In 2017, we entered into a research study and option to license agreement with Outpost Medicine, LLC, or Outpost Medicine. In 2018, Outpost Medicine exercised its option to enter into a licensing agreement with us to advance an undisclosed, preclinical compound with potential utility in treating genitourinary disorders. We received an upfront fee comprised of cash and equity totaling $3.0 million and are eligible to receive $96.5 million in development and commercial milestone payments and up to low double-digit tiered royalties on annual net sales of the compound.

Beacon Discovery Agreements

In September 2016, we entered into a series of agreements with Beacon. Beacon was founded and is owned by several of our former employees.

We entered into a License and Collaboration Agreement with Beacon, pursuant to which we granted Beacon a non-exclusive, non-assignable and non-sublicensable license to certain database information relating to compounds, receptors and pharmacology, and transferred certain equipment to Beacon. Beacon will seek to engage global partners to facilitate discovery and development. Beacon has agreed to assign to us any intellectual property relating to our existing research and development programs developed in the course of performing research for us, and grant us a non-exclusive license to any intellectual property developed outside the course of performing work for us that is reasonably necessary or useful for developing or commercializing the products under our research and development programs. We are also entitled to rights of negotiation and rights of first refusal to potentially obtain licenses to certain compounds discovered and developed by Beacon. In addition, we are entitled to receive (i) a percentage of any revenue received by Beacon on or after the second anniversary of the effective date of the agreement from any third party pursuant to a third-party license, including upfront payments, milestone payments and royalties; (ii) single-digit royalties on the aggregate net sales of any related products sold by Beacon and its affiliates; and (iii) in the event that Beacon is sold, a percentage of the consideration for such sale transaction.

We also entered a Master Services Agreement with Beacon, pursuant to which Beacon performs certain research services for us relating to our proprietary pipeline, as well as a services agreement to support our research obligations under our collaboration with Boehringer Ingelheim.

BELVIQ (lorcaserin) Agreement

Lorcaserin is approved for marketing in the United States, South Korea, Brazil, Mexico, Israel, and Taiwan for the indication of weight management, and is being commercialized by Eisai or its distributors in the United States, South Korea, Israel, and Taiwan. BELVIQ was made available by prescription in the United States in June 2013 and in South Korea in February 2015. Eisai also has launched of a once-daily formulation of lorcaserin in the United States, which is marketed under the brand name BELVIQ XR. Lorcaserin has not yet been launched in Brazil or Mexico. In December 2016, we entered into a Transaction Agreement and a Supply Agreement with Eisai, which replaced our prior marketing and supply agreement with Eisai for lorcaserin. In 2018, Eisai reported positive top line results from CAMELLIA-TIMI61, a long-term cardiovascular outcome trial of lorcaserin.

Transaction Agreement

Pursuant to the Transaction Agreement, we granted Eisai an exclusive, royalty-bearing license, or transferred intellectual property, to develop, manufacture and commercialize lorcaserin in all countries and territories of the world. In consideration for the rights granted to Eisai under the Transaction Agreement, Eisai has agreed to make tiered royalty payments to us on the net sales of lorcaserin. The royalty rates range from 9.5% on annual global net sales less than or equal to $175.0 million, 13.5% on annual global net sales greater than $175.0 million but less than or equal to $500.0 million and 18.5% on annual global net sales greater than $500.0 million.

We are eligible to receive a milestone payment of $25.0 million upon the achievement of global net sales of lorcaserin for a calendar year first exceeding $250.0 million.

Eisai is solely responsible for all costs and expenses in connection with the development of lorcaserin. Eisai has the exclusive right and responsibility to plan and implement all research and development of lorcaserin at its own cost and expense, including conducting all regulatory activities and all clinical and development activities.

Eisai is solely responsible, and has the exclusive rights, for commercializing lorcaserin and is responsible for manufacturing lorcaserin. Eisai is responsible for using commercially reasonable efforts to commercialize lorcaserin products in the United States, as well as to develop, seek regulatory approval and commercialize lorcaserin products in the European Union, China and Japan.

We and Eisai will each bear 50% of losses arising from any alleged defective manufacturing of lorcaserin that was manufactured in the past by us, and Eisai will be solely responsible for any expenses and losses associated with other product liability claims.

Siegfried Transaction

On March 9, 2018, we entered into an Asset Purchase Agreement, or Sale Agreement, with Siegfried Pharma AG and Siegfried AG, collectively and individually, Siegfried. Under the Sale Agreement, we agreed to sell and assign to Siegfried, and Siegfried agreed to purchase and assume from our subsidiary Arena Pharmaceuticals GmbH, or Arena GmbH, certain drug product finishing facility assets and know-how, including fixtures, equipment, other personal property and real estate assets located in Zofingen, Switzerland and related contracts and certain related liabilities, or collectively, the Manufacturing Operations. We refer to this transaction as the Siegfried Transaction. The Siegfried Transaction was completed on March 31, 2018. In connection with the Siegfried Transaction, all of Arena GmbH's approximately 50 employees transferred to Siegfried.

Intellectual Property

Our success depends in large part on our ability to protect our compounds and information, and to operate without infringing the proprietary rights of third parties. We rely on a combination of patent, trade secret, copyright, and trademark laws, as well as confidentiality, licensing and other agreements, to establish and protect our proprietary rights. We seek patent protection for our key inventions, including drug candidates we identify, routes for chemical synthesis, pharmaceutical formulations and methods of treatment.

There is no assurance that any of our patent applications will issue, or that any of the patents will be enforceable or will cover a drug or other commercially significant product or method. In addition, we regularly review our patent portfolio to identify patents and patent applications for potential abandonment that we deem to have relatively low value to our ongoing business operations. There is also no assurance that we will correctly identify which of our patents and patent applications should be maintained and which should be abandoned. The term of most of our other current patents commenced, and most of our future patents, if any, will commence, on the date of issuance and terminate 20 years from the earliest effective filing date of the patent application. Because any marketing and regulatory approval for a drug often occurs several years after the related patent application is filed, the resulting market exclusivity afforded by any patent on our drug candidates will likely be substantially less than 20 years.

In the United States, patent term adjustment is available for certain delays in patent office proceedings. In addition, under the Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Act, the term of a patent that covers an FDA-approved drug may be eligible for patent term extension, or PTE. PTE permits patent term restoration of a US patent as compensation for the patent term lost during product development and the FDA regulatory review process. The Hatch-Waxman Act permits a PTE of up to five years beyond the expiration of the patent. This period is generally one-half the time between the effective date of an Investigational New Drug, or IND (falling after issuance of the patent), and the submission date of an NDA, plus the time between the submission date of an NDA and the approval of that application, provided the sponsor acted with diligence. A PTE cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval and only one patent applicable to an approved drug may be extended. The application for PTE is subject to approval by the PTO in conjunction with the FDA.

Outside of the United States, similar provisions may be available in the European Union, Japan, South Korea and some other jurisdictions to extend the term of a patent that covers an approved drug. The length of any such extension would vary by country. Our European patents may be eligible for supplemental protection certificates of up to five years in one or more countries.

Due to the specific requirements for obtaining these extensions, there is no assurance that our patents will be afforded extensions even if we encounter significant delays in patent office proceedings or marketing and regulatory approval.

In addition to patent protection, we rely on trade secrets, proprietary know-how and continuing technological advances to develop and maintain our competitive position. To maintain the confidentiality of our trade secrets and proprietary information, all of our employees are required to enter into and adhere to an employee confidentiality and invention assignment agreement, and invention disclosure procedures as a condition of employment. Additionally, our employee confidentiality and invention assignment agreements require that our employees not bring to us, or use without proper authorization, any third-party proprietary technology. We also generally require our consultants and collaborators that have access to proprietary property and information to execute confidentiality and invention rights agreements in our favor before beginning their relationship with us. While such arrangements are intended to enable us to better control the use and disclosure of our proprietary property and provide for our ownership of proprietary technology developed on our behalf, they may not provide us with meaningful protection for such property and technology in the event of unauthorized use or disclosure.

Competition

The biotechnology and pharmaceutical industries are highly competitive and are subject to rapid and significant change. We face significant competition from many organizations with drugs or drug candidates that do or may compete drug candidates we are developing. We may not be able to compete successfully against these organizations, which include many large, well-financed and experienced pharmaceutical and biotechnology companies, as well as academic and research institutions and government agencies. Developments by others may render our drug candidates obsolete or noncompetitive, and we or our collaborators may not be successful in developing either first or best in class drugs.

Many of our existing and potential competitors have substantially greater drug development capabilities and financial, scientific and marketing resources than we do. Additional consolidation in the pharmaceutical industry may result in even more resources being concentrated with our competitors. As a result, our competitors may be able to devote greater resources than we can to the research, development, marketing and promotion of therapeutic products or drug discovery techniques, or to adapt more readily to technological advances than we can. Accordingly, our competitors may succeed in obtaining patent protection, receiving regulatory approval or commercializing drugs before we do.

We expect to encounter significant competition in the therapeutic areas targeted by our principal drug candidates. Companies that complete clinical trials, obtain regulatory approvals and commence commercial sales of their drug candidates before us may achieve a significant competitive advantage. Furthermore, we may be competing against companies with substantially greater manufacturing, marketing, distribution and selling capabilities, and any drug candidate that we successfully develop may compete with existing therapies that have longer histories of safe and effective use.

We may rely on collaborators for support of development programs and for the manufacturing and marketing of drug candidates. Such collaborators may be conducting multiple drug development efforts within the same disease areas that are the subject of their agreements with us, which may negatively impact the development of drugs that are subject to our agreements. In addition, we face and will continue to face intense competition from other companies for such collaboration arrangements, and technological and other developments by others may make it more difficult for us to establish such relationships.

Government Regulation

We and our collaborators are subject to significant governmental regulation. The FDA and comparable regulatory agencies in state and local jurisdictions and in foreign countries impose substantial requirements upon the preclinical and clinical development, pre-market approval, manufacture, import, export, marketing and distribution of pharmaceutical products. These agencies and other regulatory agencies regulate research and development activities and the testing, approval, manufacture, quality control, safety, effectiveness, labeling, storage, tracking, recordkeeping, advertising, pricing and promotion of drug candidates and commercialized drugs. Failure to comply with applicable FDA or other regulatory requirements may result in inspectional notices of violation, warning letters, civil or criminal penalties, suspension or delays in clinical development, recall or seizure of products, partial or total suspension of production, withdrawal of a product from the market or other negative consequences.

In the United States

In the United States, the FDA regulates drug products under the Federal Food, Drug, and Cosmetic Act, or FD&C Act, and its implementing regulations. The process required by the FDA before drug candidates may be marketed in the United States generally involves the following:

- completion of extensive preclinical laboratory tests and preclinical animal studies, many of which are required to be performed in accordance with the FDA's Good Laboratory Practice, or GLP, regulations;
- submission to the FDA of an IND, which must become effective before human clinical trials may begin and be updated annually;
- performance of adequate and well-controlled human clinical trials to establish the safety and efficacy of the drug candidate for each proposed indication;
- submission to the FDA of a New Drug Application, or NDA, after completion of adequate and well-controlled human clinical trials, generally accompanied by payment of a substantial user fee to the FDA;
- a determination by the FDA within 60 days of its receipt of the NDA to file the NDA for review;
- satisfactory completion of an FDA pre-approval inspection of the manufacturing facilities at which the active pharmaceutical ingredient and finished drug product are produced and tested to assess compliance with Current Good Manufacturing Practices, or cGMP, regulations;

- FDA review and approval of the NDA prior to any commercial marketing or sale of the drug in the United States; and
- Prior to commercialization, centrally acting drugs may be subject to review and potential scheduling by the DEA.

The development and approval process requires substantial expertise, time, effort and financial resources, and we cannot be certain that any approvals for our drug candidates will be granted on a timely basis, if at all.

The results of preclinical tests (which include laboratory evaluation as well as GLP studies to evaluate toxicity in animals) for a particular drug candidate, together with related manufacturing information and analytical data, are submitted as part of an IND to the FDA. The initial IND becomes effective 30 days after receipt by the FDA, following its initial safety review. During the 30-day time period the FDA may require additional information. The FDA may institute a clinical hold at the 30-day time period if any questions are not fully addressed or because of other concerns about the conduct of the clinical trial, including concerns that human research subjects will be exposed to unreasonable health risks. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. The FDA may place an IND on partial or full clinical hold at any time during a product candidate's development. A separate submission to an existing IND must also be made for each successive clinical trial conducted during product development. Further, an independent institutional review board, or IRB, for each medical center proposing to conduct the clinical trial must review and approve the plan for any clinical trial before it commences at that center and it must monitor the study until completed. The FDA, the IRB or the sponsor may suspend a clinical trial at any time on various grounds, including a finding that the subjects or patients are being exposed to an unacceptable health risk. Clinical testing also must satisfy extensive Good Clinical Practice, or GCP, regulations and regulations for informed consent and privacy of individually identifiable information.

Clinical trials. For purposes of NDA submission and approval, clinical trials are typically conducted in the following sequential phases, which may overlap:

- Phase 1 clinical trials. Studies are initially conducted in a limited population to test the drug candidate for safety, dose tolerance, absorption, metabolism, distribution and excretion, typically in healthy volunteers, but in some cases in patients.
- Phase 2 clinical trials. Studies are generally conducted in a limited patient population to identify possible adverse effects and safety risks, explore the initial efficacy of the product for specific targeted indications and to determine dose range or pharmacodynamics. Multiple Phase 2 clinical trials may be conducted by the sponsor to obtain information prior to beginning larger and more expensive Phase 3 clinical trials.
- Phase 3 clinical trials. These are commonly referred to as pivotal studies or adequate and well-controlled studies. When Phase 2 evaluations demonstrate that a dose range of the product is effective and has an acceptable safety profile, Phase 3 clinical trials are undertaken in large patient populations to further evaluate dosage, provide substantial evidence of clinical efficacy and further test for safety in an expanded and diverse patient population at multiple, geographically dispersed clinical trial centers.
- Phase 4 clinical trials. The FDA may approve an NDA for a drug candidate but require that the sponsor conduct additional clinical trials to further assess the drug after NDA approval under a post-approval commitment. In addition, a sponsor may decide to conduct additional clinical trials after the FDA has approved an NDA. Post-approval trials are typically referred to as Phase 4 clinical trials.

New drug applications. The results of drug development, preclinical studies and clinical trials are submitted to the FDA as part of an NDA. NDAs also must contain extensive chemistry, manufacturing and control, or CMC, information. An NDA is usually accompanied by a significant user fee. The FDA reviews all NDAs submitted to ensure that they are sufficiently complete for substantive review before it accepts them for filing, which occurs, if at all, 60 days after submission by the NDA sponsor. Once the submission has been accepted for filing, the FDA's goal is to review applications within 10 months from its acceptance of the filing or, if the application relates to an unmet medical need in a serious or life-threatening indication, six months from its acceptance of the filing. The review process can be significantly extended by FDA requests for additional information or clarification. The FDA may refer

the application to an advisory committee for review, evaluation and recommendation as to whether the application should be approved. The FDA is not bound by the recommendation of an advisory committee. The FDA may deny approval of an NDA by issuing a Complete Response Letter, or CRL, if the applicable regulatory criteria are not satisfied. A CRL may require additional clinical data and/or an additional pivotal Phase 3 clinical trial(s), and/or other significant, expensive and time-consuming requirements related to clinical trials, preclinical studies or manufacturing. Data are not always conclusive, and the FDA may interpret data differently than we or our collaborators interpret data. Approval may occur with Risk Evaluation and Mitigation Strategies, or REMS, that may limit the labeling, distribution or promotion of a drug product. Once issued, the FDA may withdraw product approval if ongoing regulatory requirements are not met or if safety problems occur after the product reaches the market. In addition, the FDA may require testing, including Phase 4 clinical trials, and surveillance programs to monitor the safety effects of approved products which have been commercialized, and the FDA has the power to prevent or limit further marketing of a product based on the results of these postmarketing programs or other information.

Other US regulatory requirements. Products manufactured or distributed pursuant to FDA approvals are subject to continuing regulation by the FDA, including recordkeeping, annual product quality review and reporting requirements. Adverse event experience with the product must be reported to the FDA in a timely fashion and pharmacovigilance programs to proactively look for these adverse events are mandated by the FDA. Drug manufacturers and their subcontractors are required to register their establishments with the FDA and certain state agencies and are subject to periodic inspections (which may be unannounced) by the FDA and certain state agencies for compliance with ongoing regulatory requirements, including cGMP regulations, which impose certain procedural and documentation requirements upon us and our third-party manufacturers. Following such inspections, the FDA may issue notices on Form FDA 483 and warning letters that could cause us to modify certain activities. A Form FDA 483 notice, if issued at the conclusion of an FDA inspection or after the appropriate FDA office review of the Establishment Inspection Report prepared by the investigator, can list conditions the FDA believes may have violated cGMP or other FDA regulations. FDA guidelines specify that a warning letter be issued for violations of "regulatory significance," also known as Official Action Indicated, or OAI. Failure to adequately and promptly correct the observation(s) can result in regulatory action. In addition to Form FDA 483 notices and warning letters, failure to comply with the statutory and regulatory requirements can subject a manufacturer to possible legal or regulatory action, such as suspension of manufacturing, recall of product, seizure of product, injunctive action or possible civil or criminal penalties.

The FDA closely regulates the post-approval marketing and promotion of drugs, including standards and regulations for healthcare professional marketing activities and materials, direct-to-consumer advertising, dissemination of off-label information, industry-sponsored scientific and educational activities and promotional activities involving the Internet. Drugs may be marketed only for their approved indications and in accordance with the provisions of the confines of the pivotal studies and the approved label. Further, we may be required to develop additional data or conduct additional preclinical studies and clinical trials, and we may be required to submit and obtain FDA approval of a new or supplemental NDA for changes to, among other things, the indications, labeling, or manufacturing processes or facilities of a drug. Failure to comply with these requirements can subject a manufacturer to possible legal or regulatory action, such as warning letters, corrective advertising, suspension of manufacturing, seizure of product, injunctive action or potential civil and criminal penalties.

Physicians may prescribe legally available drugs for uses that are not described in the product's labeling and that differ from those tested by us and approved by the FDA, if in their professional medical judgment, the physicians deem such use to be appropriate. Such off-label uses are common across certain medical specialties. The FDA does not regulate the behavior of physicians in their choice of treatments. The FDA does, however, impose stringent restrictions on manufacturers' communications regarding off-label use.

To distribute products commercially, we or our collaborators, as applicable, must comply with state laws that require the registration of manufacturers and wholesale distributors of pharmaceutical products in a state, including, in certain states, manufacturers and distributors who ship products into the state even if such manufacturers or distributors have no place of business within the state. Some states also impose requirements on manufacturers and distributors to establish the pedigree of product in the chain of distribution.

Drug Enforcement Administration regulation. The DEA regulates drugs that are controlled substances. Controlled substances are those drugs that appear on one of the five schedules promulgated and administered by the DEA under the Controlled Substances Act, or CSA. The CSA governs, among other things, the inventory, distribution, recordkeeping, handling, security and disposal of controlled substances. Any drug that acts on the central nervous system has the potential to become a controlled substance based on an evaluation of its abuse potential, and scheduling by the DEA is a separate process that may delay the commercial launch of a drug even after FDA approval of the NDA. Companies with a scheduled drug are subject to periodic and ongoing inspections by the DEA and similar state drug enforcement authorities to assess ongoing compliance with the DEA's regulations. Any failure to

comply with these regulations could lead to a variety of sanctions, including the revocation or a denial of renewal of any DEA registration, injunctions, or civil or criminal penalties.

Hatch-Waxman Exclusivity. Market exclusivity provisions of the Hatch-Waxman Act can delay the submission or approval of applications seeking to rely upon the FDA's findings of safety and effectiveness for a previously approved NDA. A new chemical entity, or NCE, subject to an NDA is entitled to a five-year period of non-patent marketing exclusivity in the United States. A drug is an NCE if the FDA has not previously approved any other new drug containing the same active moiety, which is the molecule or ion responsible for the action of the drug substance. During the exclusivity period, the FDA may not accept for review an abbreviated new drug application, or ANDA, or a 505(b)(2) NDA submitted by another company for another version of such drug where the applicant does not own or have a legal right of reference to all the data required for approval. However, such an application may be submitted after four years if it contains a certification of patent invalidity or non-infringement of patents listed with the FDA by the NDA holder. The Hatch-Waxman Act also provides three years of marketing exclusivity for an NDA, or supplement to an existing NDA, if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are deemed by the FDA to be essential to the approval of the application. This three-year exclusivity covers only the conditions of use associated with the new clinical investigations and does not prohibit the FDA from approving ANDAs for drugs containing the original active ingredient. Five-

year and three-year exclusivity will not delay the submission or approval of a full NDA. However, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the preclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness.

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

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

Outside of the United States

Outside of the United States, the ability to market a product is contingent upon obtaining marketing authorization from the appropriate regulatory authorities. The requirements governing marketing authorization, pricing and reimbursement vary widely from country to country. Whether or not we obtain FDA approval for a product candidate, we must obtain the requisite approvals from regulatory authorities in foreign jurisdictions prior to the commencement of clinical studies or marketing and sale of the product in those countries. Approval in the United States does not guarantee approval in other countries and vice-versa.

Prescription drug reimbursement. In the United States and markets in other countries, sales of prescription drug products depend in part on the availability of reimbursement from third-party payers. Third-party payers include government health administrative authorities, managed care organizations, private health insurers and other organizations. The process for determining whether a payer will provide coverage for a drug product may be separate from the process for setting the price or reimbursement rate that the payer will pay for the drug product. Third-party payers may limit coverage to specific drug products on an approved list, or formulary, which might not include all of the FDA-approved drug products for a particular indication. Third-party payers are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. We may need to conduct expensive pharmacoeconomic studies to demonstrate the cost-effectiveness of our products. A payer's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development. Patients who are prescribed medications for the treatment of their conditions, and their prescribing physicians, generally rely on third-party payers to reimburse all or part of the costs associated with their prescription drugs. Patients are less likely to use our products unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of our products. Therefore, coverage and adequate reimbursement are important to new product acceptance.

If a drug is reimbursed by Medicare or Medicaid, pricing and rebate programs must comply with, as applicable, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 as well as the Medicaid rebate requirements of the Omnibus Budget Reconciliation Act of 1990 and the Veterans Health Care Act of 1992, or VHCA, each as amended. If products are made available to authorized users of the Federal Supply Schedule of the General Services Administration, additional laws and requirements apply. Under the VHCA, drug companies are required to offer certain drugs at a reduced price to a number of federal agencies including US Department of Veterans Affairs and US Department of Defense, the Public Health Service and certain private Public Health Service designated entities in order to participate in other federal funding programs including Medicare and Medicaid. Participation under the VHCA requires submission of pricing data and calculation of discounts and rebates pursuant to complex statutory formulas, as well as entry into government procurement contracts governed by the Federal Acquisition Regulations.

The containment of healthcare costs has become a priority of federal, state and foreign governments, and the prices of drugs have been a focus in this effort, which has resulted in several recent congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for products. In addition, emphasis on managed care in the United States has increased and we expect will continue to increase the pressure on drug pricing. Coverage

policies, third-party reimbursement rates and drug pricing regulation may change at any time. In particular, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the ACA, was enacted in the United States in March 2010 and contains provisions that may reduce the profitability of drug products, including, for example, increased rebates for drugs sold to Medicaid programs, extension of Medicaid rebates to Medicaid managed care plans, mandatory discounts for certain Medicare Part D beneficiaries and annual fees based on pharmaceutical companies' share of sales to federal healthcare programs. There have been judicial and Congressional challenges to certain aspects of the ACA. For example, since January 2017, President Trump has signed two Executive Orders and other directives designed to delay the implementation of certain provisions of the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. Concurrently, Congress has considered legislation that would repeal or repeal and replace all or part of the ACA. While Congress has not passed comprehensive repeal legislation, two bills affecting the implementation of certain taxes under the ACA have been signed into law. The Tax Cuts and Jobs Act of 2017, or TCJA, includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate". Additionally, on January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain ACA-mandated fees, including the so-called "Cadillac" tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device excise tax on non-exempt medical devices. Further, the Bipartisan Budget Act of 2018, or the BBA, among other things, amended the ACA, effective January 1, 2019, to increase from 50 percent to 70 percent the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole". In July 2018, the United States Department of Health and Human Services' Centers for Medicare & Medicaid Services, or CMS, published a final rule permitting further collections and payments to and from certain ACA qualified health plans and health insurance issuers under the ACA 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 Texas U.S. District Court Judge ruled that the ACA is unconstitutional in its entirety because the "individual mandate" was repealed by Congress as part of the TCJA. While the Texas U.S. District Court Judge, as well as the Trump administration and CMS, have stated that the ruling will have no immediate effect pending appeal of the decision, it is unclear how this decision, subsequent appeals, and other efforts to repeal and replace the ACA will impact the ACA and our business. Even if favorable coverage and reimbursement status is attained for our products, less favorable coverage policies and reimbursement rates may be implemented in the future. In the case of BELVIQ, Medicare explicitly excludes coverage of drugs for weight loss.

In countries outside the United States, pricing of pharmaceutical products may be subject to governmental control. Evaluation criteria used by many government agencies for the purposes of pricing and reimbursement typically focus on a product's degree of innovation and its ability to meet a clinical need unfulfilled by currently available therapies. Some countries operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical trials that compare the cost-effectiveness of a particular drug candidate to currently available therapies. Other countries allow companies to fix their own prices for medicines but monitor and control company profits. In addition, in some countries, cross-border imports from low-priced markets exert a commercial pressure on pricing within a country. There can be no assurance that any country that has price controls or reimbursement limitations for drug products will allow favorable reimbursement and pricing arrangements for any of our products.

Healthcare fraud and abuse. Pharmaceutical companies are subject to various federal and state laws pertaining to healthcare fraud and abuse, including, but not limited to, anti-kickback and false claims laws.

The Federal Anti-Kickback Statute makes it illegal for any person or entity, including a prescription drug manufacturer, or a party acting on its behalf, to knowingly and willfully solicit, offer, receive or provide any remuneration, directly or indirectly, in exchange for, or to induce, the referral of business, including the purchase, order, lease of any good, facility, service or item, including the prescription of a particular drug, for which payment may be made under federal healthcare programs such as Medicare and Medicaid. Some of the state prohibitions are broader in scope and apply to referral of patients for healthcare services reimbursed by any source, not only the Medicare and Medicaid programs.

In the course of practicing medicine, physicians may legally prescribe FDA-approved drugs for an indication that has not been approved by the FDA and which, therefore, is not described in the product's approved labeling, so-called "off-label use" or "the practice of medicine," if deemed appropriate in the physicians' professional medical judgment. The FDA does not ordinarily regulate the behavior of physicians in their choice of treatments. The FDA and other government agencies do, however, restrict communications on the subject of off-label use by a manufacturer or those acting on behalf of a manufacturer. Companies may not promote FDA-approved drugs for off-label uses. The FDA and other governmental agencies do permit a manufacturer (and those acting on its behalf) to engage in some limited, non-misleading, non-promotional exchanges of scientific information regarding unapproved indications.

There are numerous federal false claims laws and civil monetary penalty laws that forbid, among other things, anyone from knowingly presenting, or causing to be presented for payment to third-party payers (including Medicare and Medicaid) claims for

reimbursed drugs or services that are false or fraudulent, claims for items or services not provided as claimed or claims for medically unnecessary items or services.

Violations of fraud and abuse laws may be punishable by criminal, civil and/or administrative sanctions, including individual imprisonment, disgorgement, criminal fines and civil monetary penalties, possible exclusion from federal healthcare programs (including Medicare and Medicaid), and integrity oversight and reporting obligations to resolve allegations of non-compliance with these laws. In addition, under certain healthcare fraud and abuse laws, there is an ability for private individuals to bring similar actions. Additionally, many states have analogous fraud and abuse laws, some of which may be broader in scope. Further, there are an increasing number of state laws that require pharmaceutical companies to establish marketing compliance programs, file periodic reports with the state, make periodic public disclosures on sales, marketing, pricing, clinical trials and other activities, or register their sales representatives, as well as prohibiting certain other sales and marketing practices. The federal transparency requirements under the ACA require certain manufacturers of drugs, devices, biologics and medical supplies to annually report to the Department of Health and Human Services information related to payments and other transfers of value to physicians and teaching hospitals and physician ownership and investment interests. Additionally, recent federal legislation imposes additional obligations on certain pharmaceutical manufacturers, among others, regarding drug product tracking and tracing.

Our activities are also potentially subject to federal and state consumer protection and unfair competition laws. We are also subject to the US Foreign Corrupt Practices Act, or the FCPA, which prohibits companies and individuals from engaging in specified activities to obtain or retain business or to influence a person working in an official capacity. Under the FCPA, it is illegal to pay, offer to pay, or authorize the payment of anything of value to any foreign government official, governmental staff members, political party or political candidate in an attempt to obtain or retain business or to otherwise influence a person working in an official capacity.

Healthcare privacy and security laws. The Health Insurance Portability and Accountability Act of 1996, or HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information. In addition, many state laws apply to the use and disclosure of health information. We may be subject to, or our collaborators' marketing activities may be limited by, HIPAA and its implementing regulations. In addition, the European Union has established its own data security and privacy legal framework, including but not limited to Directive 95/46/EC, or the Data Protection Directive. The Data Protection Directive will be replaced starting in May 2018 with the recently adopted European General Data Protection Regulation, or GDPR, which contains new provisions specifically directed at the processing of health information, higher sanctions and extra-territoriality measures intended to bring non-EU companies under the regulation. We may in the future expand our business operations to include additional operations in the EU, including potentially conducting preclinical and clinical trials. With such expansion, we would be subject to increased governmental regulation, including the GDPR, in the EU countries in which operate.

Additionally, California recently enacted legislation that has been dubbed the first "GDPR-like" law in the United States. Known as the California Consumer Privacy Act, or CCPA, it creates new individual privacy rights for consumers (as that word is broadly defined in the law) and places increased privacy and security obligations on entities handling personal data of consumers or households. When it goes into effect on January 1, 2020, the CCPA will require covered companies to provide new disclosures to California consumers, provide such consumers new ways to opt-out of certain sales of personal information, and allow for a new cause of action for data breaches. Legislators have stated that amendments will be proposed to the CCPA before it goes into effect, but it remains unclear what, if any, modifications will be made to this legislation or how it will be interpreted. As currently written, the CCPA will likely impact (possibly significantly) our business activities and exemplifies the vulnerability of our business to the evolving regulatory environment related to personal data and protected health information.

Manufacturing, Revenues from External Customers, and Sources and Availability of Materials

Our revenues of $18.0 million for the year ended December 31, 2018, included $6.6 million from Eisai, $4.4 million from Boehringer Ingelheim, $2.8 million from Outpost Medicine, $2.2 million from Axovant, and $2.0 million from Everest. Our revenues of $21.3 million for the year ended December 31, 2017, included $12.0 million from Everest, $5.1 million from Boehringer Ingelheim and $1.7 million from Eisai. Our revenues of $92.2 million for the year ended December 31, 2016, included $78.4 million from Eisai, $5.1 million from Boehringer Ingelheim and $4.2 million from Ildong. This information excludes revenue activity reported within discontinued operations. See Note 5 and Note 8 to our consolidated financial statements included in this Annual Report for additional information. We do not currently engage in manufacturing activities and we are not dependent on availability of materials for our core business operations.

Compliance with Environmental Regulations

Our business involves the controlled use of hazardous materials, chemicals, biological materials and various radioactive compounds. In the United States, we are subject to regulation under the Occupational Safety and Health Act, the Environmental Protection Act, the US Environmental Protection Agency, the California Environmental Protection Agency, the Toxic Substances Control Act, the Resource Conservation and Recovery Act, the CSA and other federal, state or local regulations.

We may be subject to further such regulations in the future. Although we believe that our operations comply in all material respects with the applicable environmental laws and regulations, the risk of accidental contamination or injury from these materials cannot be eliminated. In the event of such an accident, we could be held liable for any damages that result, and the extent of that liability could exceed our resources. Our compliance with these laws and regulations has not had, and is not expected to have, a material effect upon our capital expenditures, results of operations or competitive position.

Employees

As of February 15, 2019, we had a total of 194 employees, including 138 in research and development and 56 in administration, which includes finance, legal, facilities, information technology and other general support areas.

Available Information

Our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and all amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, or the Exchange Act, are available free of charge on our website (www.arenapharm.com) as soon as reasonably practicable after they are electronically filed with, or furnished to, the SEC.

Item 1A. Risk Factors.

Investment in our stock involves a high degree of risk. You should consider carefully the risks described below, together with other information in this Annual Report on Form 10-K and other public filings, before making investment decisions regarding our stock. If any of the following events actually occur, our business, operating results, prospects or financial condition could be materially and adversely affected. This could cause the trading price of our common stock to decline and you may lose all or part of your investment. Moreover, the risks described below are not the only ones that we face. Additional risks not presently known to us or that we currently deem immaterial may also affect our business, operating results, prospects or financial condition.

Risks Relating to Our Business

Drug development programs are expensive, time consuming, uncertain and susceptible to change, interruption, delay or termination.

Drug development programs are very expensive, time consuming and difficult to design and implement. Our drug candidates are in various stages of clinical and preclinical development and are prone to the risks of failure inherent in research and development. Clinical trials and preclinical studies are needed to demonstrate that drug candidates are

safe and effective to the satisfaction of the FDA, and similar non-US regulatory authorities, and the FDA or other regulatory authority may require us to, or we or others may decide to, conduct additional research and development even after a drug is approved. The commencement or completion of our clinical trials or preclinical studies could be substantially delayed or prevented by several factors, including the following:

- limited number of, and competition for, suitable patients required for enrollment in our clinical trials or animals to conduct our preclinical studies;
- limited number of, and competition for, suitable sites to conduct our clinical trials or preclinical studies;
- delay or failure to obtain a meeting, approval or agreement from the applicable regulatory authority to commence a clinical trial or approval of a study protocol;
- delay or failure to obtain sufficient supplies of drug candidates, drugs or other materials for the trial or study;
- delay or failure to reach agreement on acceptable agreement terms or protocols; and
- delay or failure to obtain institutional review board, or IRB, approval to conduct a clinical trial at a prospective site.

For example, recruitment for the indications in our ongoing and planned clinical studies is competitive and challenging, and it is difficult to predict when such trials will be fully enrolled or when data will be available.

In addition, the FDA, other regulatory authorities, collaborators, or we may suspend, delay or terminate our development programs at any time for various reasons, including those listed above affecting the commencement or completion of trials and the following:

- side effects experienced by study participants or other safety issues;
- lack of effectiveness of any drug candidate during clinical trials;
- slower than expected rates of patient recruitment and enrollment or lower than expected patient retention rates;
- inadequacy of or changes in our manufacturing process or compound formulation;
- delays in obtaining regulatory approvals to commence a study, or "clinical holds," or delays requiring suspension or termination of a study by a regulatory authority, such as the FDA, after a study is commenced;
- changes in applicable regulatory policies and regulations;
- delays in identifying and reaching agreement on acceptable terms with prospective clinical trial sites;
- uncertainty regarding proper dosing;
- unfavorable results from ongoing clinical trials or preclinical studies;
- failure of our clinical research organizations to comply with all regulatory and contractual requirements or otherwise perform their services in a timely or acceptable manner;
- scheduling conflicts with participating clinicians and clinical institutions;
- failure to design appropriate clinical trial protocols;
- insufficient data to support regulatory approval;
- termination of clinical trials at one or more clinical trial sites;
- inability or unwillingness of medical investigators to follow our clinical protocols;
- difficulty in maintaining contact with subjects during or after treatment, which may result in incomplete data;
- lack of sufficient funding to continue clinical trials or preclinical studies; or
- changes in business priorities or perceptions of the value of the program.

There is typically a high rate of attrition from the failure of drug candidates proceeding through clinical trials, and many companies have experienced significant setbacks in advanced development programs even after promising results in earlier studies or trials. We have experienced setbacks in our internal and partnered development programs and expect to experience additional setbacks from time to time in the future. In addition, even if the earlier-stage results of our development programs are favorable, these programs may take significantly longer than expected to complete or may not be completed at all. If we or our collaborators abandon or are delayed in our development efforts related to any drug or drug candidate, we may not be able to generate sufficient revenues to continue our operations at the current or planned level or be profitable, our reputation in the industry and in the investment community would likely be significantly damaged, additional funding may not be available to us or may not be available on terms we or others believe are favorable, and our stock price may decrease significantly.

We may not be successful in initiating, enrolling patients in, or completing our studies or trials or advancing our programs on our projected timetable, if at all. Any failure to initiate or delays in our studies, trials or development programs, or unfavorable results or decisions or negative perceptions regarding any of our programs, could cause our stock price to decline significantly. This is particularly the case with respect to our clinical programs.

We will need to obtain additional funds or enter into collaboration agreements to execute on our corporate strategy, and we may not be able to do so at all or on terms you view as favorable; your ownership may be substantially diluted if we do obtain additional funds; you may not agree with the manner in which we allocate our available resources; and we may not be profitable.

It takes many years and potentially hundreds of millions of dollars to successfully develop a compound into a marketed drug. We have accumulated a large deficit that has primarily resulted from the significant expenditures we have made in research and development since our inception. We expect that our losses and operating expenses will continue to be substantial.

All of our internal programs are in the development stage, and we may not have adequate funds to develop all of our compounds into marketed drugs.

We may seek to obtain additional funding through the capital markets or other financing sources. Additional funding may not be available to us or may not be available on terms we or others believe are favorable. Our ability to obtain additional funding may depend on many factors, including those outside our control. Should we obtain additional funding, your ownership interest may be diluted or otherwise negatively impacted.

We may enter into collaboration or other agreements with other entities to continue to develop and, if successful, commercialize one or more of our drug candidates. We may not be able to enter into any such agreements on terms that we or third parties, including investors or analysts, view as favorable, if at all. Our ability to enter into any such agreement for any of our programs or drug candidates depends on many factors, potentially including the outcomes of additional testing (including clinical trial results) or regulatory applications for marketing approval, and we do not control these outcomes.

We may allocate our resources in ways that do not improve our results of operations or enhance the value of our assets, and our stockholders and others may also not agree with the manner in which we choose to allocate our resources or obtain additional funding. We may also eliminate, scale back or delay some or all of our research and development programs, and any such reductions or failure to apply our resources effectively or to obtain additional funding could narrow, slow or otherwise adversely impact the development and commercialization of one or more of our drug candidates, which could reduce our opportunities for success and have a material adverse effect on our business, our prospects and the market price of our common stock.

In addition, we cannot assure you that we will be profitable or, if we are profitable for any particular time period, that we will be profitable in the future.

Our business may be negatively impacted based on the clinical trials and preclinical studies of, and decisions affecting, one or more of our drug candidates.

The results and timing of clinical trials and preclinical studies, as well as related decisions by us, collaborators and regulators, can affect our stock price. Results of clinical trials and preclinical studies are uncertain and subject to different interpretations by regulatory agencies, us or others. The design of these trials and studies (which may change significantly and be more expensive than anticipated depending on results and regulatory decisions), as well as related analyses of such results, including adverse effects, may not be viewed favorably by us or third parties, including investors, analysts, current or potential collaborators, the academic and medical communities, and regulators, which could adversely impact the development and opportunities for regulatory approval of drug candidates and commercialization (and even result in withdrawal from the market) of approved drugs. The same may be true of decisions regarding the focus and prioritization of our research and development efforts. Stock prices of companies in our industry have declined significantly when such results and decisions were unfavorable or perceived negatively or when a drug candidate or product did not otherwise meet expectations.

The development, approval or commercialization of any of our drug candidates could be negatively affected by circumstances related to other drug candidates or approved products.

Information on our drug candidates in clinical development is preliminary and incomplete, and for such drug candidates, particularly in the earlier stages of development, information on approved products in the same or related drug classes may indicate potential risks related to the development of our drug candidates. For example, etrasimod is an orally available modulator of the S1P receptors. An approved drug that is also an orally available modulator of the S1P receptors, Gilenya, is associated with risks such as adverse cardiovascular effects, including lowering of the heart rate and heart blocks, infection, macular edema, respiratory effects, fetal risk, a rare brain infection, and elevations in liver enzymes. These adverse reactions and risks may be associated with S1P receptor modulation and could be found to be associated with the use of etrasimod. Such adverse reactions and risks, either actual or perceived, could

negatively impact its development, approval or commercialization, or our ability to enter into a collaboration on acceptable terms.

Topline data may not accurately reflect the complete results of a particular study or trial.

We may publicly disclose topline or interim data from time to time, which are based on a preliminary analysis of then-available efficacy and safety data, and the results and related findings and conclusions are subject to change following a more comprehensive review of the data related to the particular study or trial.

We also make assumptions, estimations, calculations and conclusions as part of our analyses of data, and others, including regulatory agencies, may not accept or agree with our assumptions, estimations, calculations, conclusions or analyses or may interpret or weigh the importance of data differently, which could impact the value of the particular program, the approvability or commercialization of the particular drug candidate or drug and our company in general. In addition, the information we may publicly disclose regarding a particular study or clinical trial is based on what is typically extensive information, and you or others may not agree with what we determine is the material or otherwise appropriate information to include in our disclosure, and any information we determine not to disclose may ultimately be deemed significant with respect to future decisions, conclusions, views, activities or otherwise regarding a particular drug, drug candidate or our business.

Our hypothesis that selectively targeting receptors can lead to more efficacious or safer drugs may not be correct.

In general, we have designed and optimized the drug candidates that we or our collaborators and licensees are developing (including etrasimod, ralinepag and olorinab) to selectively target certain receptors found on cells in humans. Our hypothesis is that selectivity may allow our drug candidates to address diseases more efficaciously or without some of the negative effects associated with less selective drugs. In certain cases, we believe early research and, if available, early clinical testing, provides preliminary support for our hypothesis. However, our hypothesis may not be correct, early research and early phase clinical testing may not be predictive of efficacy or safety in later trials, and our drug candidates may not be approved or, if approved, have the desired efficacy or safety profile.

It is generally our strategy to develop drug candidates that we believe will be first-in-class, best-in-class, or similar descriptions, or otherwise have broad clinical utility, optimized pharmacology or optimized pharmacokinetics. Some or all of our drug candidates may not achieve these goals. For example, failure to complete enrollment in clinical trials on schedule or at all could prevent a drug candidate from being first-in-class. Similarly, comparing data from different trials, or making predictions based on preclinical data, may not allow us to correctly determine whether our drug candidates are superior to competitive drugs or drug candidates in the same way that comparisons can be made from conducting trials in which our and a competitive drug is tested “head to head” in the same trial. The failure of our drugs or drug candidates to be first-in-class, best-in-class, or similar descriptions, or have broad clinical utility, optimized pharmacology, or optimized pharmacokinetics, could adversely affect development, regulatory approval, third-party payor support, or market adoption, which would have a material adverse impact on our business.

The results of preclinical studies and completed clinical trials are not necessarily predictive of future results, and our current drug candidates or any approved drugs may not be further developed or have favorable results in later studies or trials.

Preclinical studies and Phase 1 and Phase 2 clinical trials are not primarily designed to test the efficacy of a drug candidate, but rather to test safety, to study pharmacokinetics and pharmacodynamics, and to understand the drug candidate’s side effects at various doses and schedules. Favorable results in early studies or trials may not be confirmed in later studies or trials, including preclinical studies that continue or that are initiated after earlier clinical trials and large-scale clinical trials, and our drug candidates or drugs in subsequent trials or studies may fail to show desired safety and efficacy despite having progressed through earlier-stage trials. For example, we have announced positive topline Phase 2 results for etrasimod in patients with ulcerative colitis, but these results may not be confirmed in any subsequent Phase 3 study. By way of another example, the impact of etrasimod on heart rate that was observed in completed clinical trials may not be observed in subsequent trials, and it could be viewed negatively by the FDA or other regulatory agencies.

Unfavorable results from clinical trials or preclinical studies could result in delays, modifications or abandonment of ongoing or future clinical trials, or abandonment of a program. Clinical and preclinical results are frequently susceptible to varying interpretations that may delay, limit or prevent regulatory approvals or commercialization.

Negative or inconclusive results or adverse medical events during such trials or studies could cause a clinical trial to be delayed, repeated or terminated; a program to be abandoned; or negatively impact a related marketed drug, which could have a material adverse effect on our business, financial condition and results of operations.

Drug discovery and development is intensely competitive in the therapeutic areas on which we focus. If the number of our competitors increase or they develop treatments that are approved faster, marketed better, less expensive or demonstrated to be more effective or safer than our drugs or drug candidates, our commercial opportunities will be reduced or eliminated.

Many of the drugs we or our collaborators are attempting or may attempt to discover and develop may compete with existing therapies in the United States and other territories. In addition, many companies are pursuing the development of new drugs that target the same diseases and conditions that we target. For example, with regard to etrasimod, there are other drugs that have a similar mechanism of action that entered Phase 3 clinical development before etrasimod for the same indications that we are pursuing, such as ulcerative colitis.

Our competitors, particularly large pharmaceutical companies, may have substantially greater research, development and marketing and sales capabilities and greater financial, scientific and human resources than we do. Companies that complete clinical trials, obtain required regulatory agency approvals and commence commercial sale of their drugs before we do for the same indication may achieve a significant competitive advantage, including certain patent and marketing exclusivity rights. In addition, our competitors' drugs may have fewer side effects, more desirable characteristics (such as efficacy, route of administration or frequency of dosing), or be viewed more favorably by patients, healthcare providers, healthcare payers, the medical community, the media or others than our drug candidates or drugs, if any, for the same indication. Our competitors may also market generic or other drugs that compete with our drugs at a lower price than our drugs, which may negatively impact our drug sales, if any. Any results from our research and development efforts, or from our joint efforts with our existing or any future collaborators, may not compete successfully with existing or newly discovered products or therapies.

Our revenues in the future will be substantially dependent on the success of our or our collaborators' and licensees' marketing of drugs we have discovered or developed. To the extent such drugs are 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.

We believe our revenues will be substantially dependent on the success of the drugs we or our collaborators and licensees successfully develop. We do not know whether or when such drug candidates will be approved by regulatory authorities for sale or commercialized. Even if approved and commercialization begins, we do not know if such commercialization will be successful or otherwise meet our, your, analysts' or others' expectations, and the market price of our common stock could decline significantly. For example, sales of lorcaserin to date have been less than we and others initially anticipated. Lorcaserin is the only approved and marketed drug in which we have a financial interest. Our future revenue for the near-term is substantially dependent on our license and partnership agreements.

We cannot guarantee future product sales or achievement of milestones under our collaborations and license agreements. For example, our license agreement with United Therapeutics for ralinepag does not contain a covenant obligating United Therapeutics to use any particular efforts to develop or commercialize any product, and we may never receive any milestone or royalty payments under this license agreement. In addition, our Transaction Agreement with Eisai for lorcaserin, and our other collaborations, may be terminated early in certain circumstances, which may result in us not receiving additional milestone or other payments under the terminated agreement.

The degree of market acceptance and commercial success of a drug will depend on a number of factors, including the following, as well as risks identified in other risk factors: