ANNUAL REPORT
2018

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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-K

(Mark One)

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

For the fiscal year ended December 31, 2018

or

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

For the transition period from ____ to ____ .

Commission File Number 001-33451

Albireo Pharma, Inc.

(Exact Name of Registrant as Specified in Its Charter)

Delaware	**90-0136863**
(State or Other Jurisdiction of Incorporation or Organization)	**(I.R.S. Employer Identification No.)**
10 Post Office Square, Suite 502 South Boston, MA	**02109**
(Address of Principal Executive Offices)	**(Zip Code)**

Registrant's telephone number, including area code
(857) 254-5555

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

Title of Each Class	**Name of Each Exchange on Which Registered**
Common Stock, par value $0.01 per share	**The Nasdaq Capital Market**

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

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

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 common stock of the registrant held by non-affiliates was approximately $421.1 million based on the price at which the common stock was last sold on The Nasdaq Capital Market on June 30, 2018.

The number of shares of the registrant's common stock outstanding as of March 1, 2019, was 12,026,025.

Documents Incorporated by Reference

The following documents (or parts thereof) are incorporated by reference into the following parts of this Form 10-K: Certain information required in Part III of this Annual Report on Form 10-K is incorporated from the Registrant's Proxy Statement for its 2019 Annual Meeting of Stockholders.

INDEX TO ANNUAL REPORT ON FORM 10-K

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K includes forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, which we refer to as the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, which we refer to as the Exchange Act, that relate to future events or to our future operating or financial performance. Any forward-looking statement involves known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to differ materially from any future results, levels of activity, performance or achievements expressed or implied by such forward-looking statement. Forward-looking statements include statements, other than statements of historical fact, about, among other things:

- the progress, number, scope, cost, duration or results of our development activities, nonclinical studies and clinical trials of A4250, elobixibat, A3384 or any of our other product candidates or programs, such as the target indication(s) for development or approval, the size, design, population, conduct, cost, objective or endpoints of any clinical trial, or the timing for initiation or completion of or availability of results from any clinical trial (including PEDFIC 1, our Phase 3 clinical trial of A4250 in patients with progressive familial intrahepatic cholestasis, or PFIC), for submission or approval of any regulatory filing, or for meeting with regulatory authorities;

- the potential benefits that may be derived from any of our product candidates;

- the timing of and our ability to obtain and maintain regulatory approval of our existing product candidates, any product candidates that we may develop, and any related restrictions, limitations, or warnings in the label of any approved product candidates;

- any payment that HealthCare Royalty Partners III, L.P., or HCR, or EA Pharma Co., Ltd., or EA Pharma, may make to us or any other action or decision that EA Pharma may make concerning elobixibat or our business relationship;

- our future operations, financial position, revenues, costs, expenses, uses of cash, capital requirements, our need for additional financing or the period for which our existing cash resources will be sufficient to meet our operating requirements; or

- our strategies, prospects, plans, expectations, forecasts or objectives.

Words such as, but not limited to, “believe,” “expect,” “anticipate,” “estimate,” “forecast,” “intend,” “may,” “plan,” “potential,” “predict,” “project,” “targets,” “likely,” “will,” “would,” “could,” “should,” “continue,” “scheduled” and similar expressions or phrases, or the negative of those expressions or phrases, are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Although we believe that we have a reasonable basis for each forward-looking statement contained in this report, we caution you that these statements are based on our estimates and projections of the future that are subject to known and unknown risks and uncertainties and other important factors that may cause our actual results, level of activity, performance or achievements to differ materially from those expressed or implied by any forward-looking statement. The description of our Business set forth in Item 1, the Risk Factors set forth in Item 1A and our Management’s Discussion and Analysis of Financial Condition and Results of Operations set forth in Item 7, as well as other sections in this report, discuss some of the factors that could contribute to these differences.

Actual results, performance or experience may differ materially from those expressed or implied by any forward-looking statement as a result of various important factors, including our critical accounting policies and risks and uncertainties relating, among other things, to:

- the design, size, duration and endpoints for, and results from, PEDFIC 1, our Phase 3 clinical trial of A4250 in patients with PFIC or our related extension study, or any other trials that will be required to obtain marketing approval for A4250 to treat patients with PFIC or any other pediatric cholestatic liver disease, for

elobixibat to treat nonalcoholic steatohepatitis, or NASH, or for A3384 to treat bile acid malabsorption, or BAM;

- whether favorable findings from clinical trials of A4250 to date, including findings in indications other than PFIC, will be predictive of results from future clinical trials, including the trials comprising our Phase 3 PFIC program for A4250;

- whether either or both of the U.S. Food and Drug Administration, or FDA, and European Medicines Agency, or EMA, will determine that the primary endpoint and treatment duration of the double blind Phase 3 trial in patients with PFIC are sufficient, even if such primary endpoint is met with statistical significance, to support approval of A4250 in the United States or the European Union, to treat PFIC, a symptom of PFIC, a specific PFIC subtype(s) or otherwise;

- the outcome and interpretation by regulatory authorities of an ongoing third-party study pooling and analyzing long-term PFIC patient data;

- the timing for initiation or completion of, or for availability of data from, the trials comprising the Phase 3 PFIC program for A4250, and the outcomes of such trials;

- delays or other challenges in the recruitment of patients for the double blind Phase 3 trial of A4250;

- whether A4250 will meet the criteria to receive a rare pediatric disease priority review voucher from the FDA when applicable, whether a rare pediatric disease priority review voucher that we may receive in the future for A4250, if any, will be valuable to us, and, if necessary, whether the rare pediatric disease priority review voucher program will be renewed beyond 2020;

- the competitive environment and commercial opportunity for a potential treatment for PFIC and other orphan pediatric cholestatic liver diseases;

- the conduct and results of clinical trials and nonclinical studies and assessments of A4250, elobixibat, A3384 or any of our other product candidates and programs, including the performance of third parties engaged to execute them and difficulties or delays in patient enrollment and data analysis;

- the medical benefit that may be derived from A4250, elobixibat, A3384 or any of our other product candidates;

- the extent to which our agreements with HCR and EA Pharma for elobixibat generate nondilutive income for us;

- the timing and success of submission, acceptance and approval of regulatory filings and any related restrictions, limitations or warnings in the label of any approved product candidates;

- the significant control or influence that EA Pharma has over the commercialization of elobixibat in Japan and the development and commercialization of elobixibat in EA Pharma's other licensed territories;

- whether we elect to seek and, if so, our ability to establish a license or other partnering transaction with a third party for elobixibat in the United States or Europe;

- whether findings from nonclinical studies and clinical trials of IBAT inhibitors will be predictive of future clinical success for a product candidate of ours in the treatment of NASH;

- the accuracy of our estimates regarding expenses, costs, future revenues, uses of cash and capital requirements;
- our ability to obtain additional financing on reasonable terms, or at all;
- our ability to establish additional licensing, collaboration or similar arrangements on favorable terms and our ability to attract collaborators with development, regulatory and commercialization expertise;
- the success of competing third-party products or product candidates;
- our ability to successfully commercialize any approved product candidates, including their rate and degree of market acceptance;
- our ability to expand and protect our intellectual property estate;
- regulatory developments in the United States and other countries;
- our ability to fully remediate our identified internal control material weaknesses;
- the performance of our third-party suppliers, manufacturers and contract research organizations and our ability to obtain alternative sources of raw materials;
- our ability to attract and retain key personnel; and
- our ability to comply with regulatory requirements relating to our business, and the costs of compliance with those requirements, including those on data privacy and security.

These and other risks and uncertainties are described in greater detail under the caption "Risk Factors" in Item 1A of Part I of this report and in other filings that we make with the Securities and Exchange Commission, or SEC. As a result of the risks and uncertainties, the results or events indicated by the forward-looking statements may not occur. We caution you not to place undue reliance on any forward-looking statement.

In addition, any forward-looking statement in this Annual Report on Form 10-K represents our views only as of the date of this annual report and should not be relied upon as representing our views as of any subsequent date. We anticipate that subsequent events and developments may cause our views to change. Although we may elect to update these forward-looking statements publicly at some point in the future, we specifically disclaim any obligation to do so, except as required by applicable law. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments we may make.

PART I

All brand names or trademarks appearing in this report are the property of their respective holders. Use or display by us of other parties' trademarks, trade dress, or products in this report is not intended to, and does not, imply a relationship with, or endorsements or sponsorship of, us by the trademark or trade dress owners. Unless the context requires otherwise, references in this report to "we," "us," and "our" refer to Albireo Pharma, Inc. and its direct and indirect subsidiaries.

Item 1. BUSINESS

Overview

We are a biopharmaceutical company focused on the development and commercialization of novel bile acid modulators to treat orphan pediatric liver diseases and other liver or gastrointestinal, or GI, diseases and disorders. The initial target indication for our lead product candidate, A4250, is progressive familial intrahepatic cholestasis, or PFIC, a rare, life-threatening genetic disorder affecting young children for which there is currently no approved drug treatment. We completed a Phase 2 clinical trial of A4250 in children with chronic cholestasis and pruritus, and in May of 2018 we enrolled the first patient in our Phase 3 clinical trial for A4250 in patients with PFIC, which we refer to as PEDFIC 1. In June of 2018, the FDA granted a rare pediatric disease designation to A4250 for the treatment of PFIC, which affirms our eligibility to apply for a rare pediatric disease priority review voucher upon submission of a new drug application for A4250. In September of 2018, the FDA granted fast track designation to A4250 for the treatment of pruritus associated with PFIC. In October of 2018, the FDA granted orphan drug designation to A4250 for the treatment of Alagille syndrome, or ALGS, a rare, life-threatening disease that affects the liver and for which there is no approved pharmacologic treatment option. In December of 2018, the European Commission granted orphan designation to A4250 for the treatment of biliary atresia, another rare, life-threatening disease that affects the liver and for which there is no approved pharmacologic treatment option. In January of 2019, the FDA granted orphan drug designation to A4250 for the treatment of biliary atresia. In addition to PFIC, we plan to initiate a pivotal clinical trial for A4250 in biliary atresia, which we believe to be one of the most common rare pediatric liver diseases, in the second half of 2019. We also plan to conduct clinical development of A4250 in 2020 as a treatment for one or more other pediatric cholestatic liver diseases and disorders.

Our most advanced product candidates in addition to A4250 include elobixibat, which is approved in Japan for the treatment of chronic constipation and with which we anticipate initiating a global Phase 2 clinical trial of as a treatment for nonalcoholic fatty liver disease, or NAFLD and nonalcoholic steatohepatitis, or NASH, in the second quarter of 2019, and A3384, which is a product candidate to treat bile acid malabsorption, or BAM. In June 2018, the Company was granted a patent for a method of using elobixibat to treat NASH in both the U.S. and Europe. We also have a preclinical program in NASH.

Bile acids are a component of bile, a key digestive liquid made in the liver, that play a critical role in dietary absorption and the regulation of metabolic processes. Specifically, bile acids are recycled from the small intestine to the liver as part of a process known as enterohepatic circulation. When the flow of bile from the liver stops or is disrupted, a condition known as cholestasis, bile acids accumulate in the liver and in the serum, which is a component of blood. Elevated bile acids in the liver and serum often lead to severe liver damage and other consequences, including pruritus, or itching. A4250 partially inhibits a protein known as ileal sodium dependent bile acid transporter, or IBAT, which is responsible for initiating the recirculation of bile acids from the small intestine to the liver. As an IBAT inhibitor, A4250 is designed to reduce bile acids in the serum and liver and to increase bile acids being excreted through the colon. Elobixibat is also an IBAT inhibitor.

A4250 — our lead product candidate for PFIC and potentially other orphan pediatric liver diseases. A4250 is a novel, minimally absorbed, orally administered IBAT inhibitor. Our initial target indication for A4250 is PFIC. We completed an open label, dose finding Phase 2 clinical trial in children with chronic cholestasis and pruritus and we initiated PEDFIC 1, our Phase 3 clinical trial in patients with PFIC in May of 2018. The Phase 2 trial included children with chronic cholestasis caused by any of a number of different liver conditions, including PFIC, biliary atresia and ALGS. Data from the study showed a reduction in serum bile acids and improvement in pruritus in most patients,

particularly patients with PFIC. In addition, A4250 exhibited a favorable overall tolerability profile in the study, with all patients completing the four-week treatment period and no reports of diarrhea associated with repeated dose therapy.

- *A4250 as a treatment for PFIC*. We are conducting PEDFIC 1, a Phase 3 clinical trial of A4250 in patients with PFIC, as well as an extension study to evaluate long-term outcomes, which we refer to as PEDFIC 2. We initiated the PEDFIC 1 trial in May 2018. We have chosen PFIC as the lead indication for A4250 because we believe there is an especially strong scientific rationale for the use of an IBAT inhibitor to prevent progressive liver disease caused by PFIC.

The precise prevalence of PFIC is unknown, and we are not aware of any patient registries or other method of establishing with precision the actual number of patients with PFIC in any geography. PFIC has been estimated to affect between one in every 50,000 to 100,000 children born worldwide. Benign recurrent familial intrahepatic cholestasis, or BRIC, is a disease that is caused by the same genetic defect as PFIC, and patients who manifest the same symptoms as PFIC but their symptomatology tends to be episodic in nature. We estimate that BRIC affects between one in every 50,000 to 100,000 children born worldwide. Based on the published incidence, published regional populations, and estimated median life expectancies, we estimate the prevalence of PFIC together with BRIC to be approximately 8,000 to 10,000 patients in the U.S. and E.U. but we are not able to estimate the prevalence of PFIC or BRIC with precision. We estimate that there are approximately 3,000 to 4,000 PFIC patients in the U.S. and E.U. We also estimate that there are approximately 5,000 to 6,000 BRIC patients in the U.S. and E.U. We currently have not modeled other regional opportunities in Asia, the Middle East and Latin America. We are aware there may be higher prevalence of disease in some countries such as Saudi Arabia and Turkey. There are currently no drugs approved for the treatment of PFIC. First-line treatment for PFIC is typically off-label ursodeoxycholic acid, or UDCA, which is approved in the United States and elsewhere for the treatment of primary biliary cholangitis, or PBC. However, many PFIC patients do not respond well to UDCA, undergo partial external bile diversion, or PEBD, surgery and often require liver transplantation. PEBD surgery is a life-altering and undesirable procedure in which bile is drained outside the body to a stoma bag that must be worn by the patient 24 hours a day.

- *Other Indications Under Development.* We plan to initiate a pivotal clinical trial with A4250 in biliary atresia in the second half of 2019. We plan to conduct clinical development of A4250 in 2020 as a treatment for other pediatric cholestatic liver diseases and disorders as well, which may include ALGS and primary sclerosing cholangitis.

Biliary atresia is a partial or total blocking or absence of large bile ducts that causes cholestasis and resulting accumulation of bile that damages the liver. The estimated worldwide incidence of biliary atresia is between 4.5 and 8.5 for every 100,000 live births. There are currently no drugs approved for the treatment of biliary atresia. The current standard of care is a surgery known as the Kasai procedure, or hepatoportoenterostomy, in which the obstructed bile ducts are removed and a section of the small intestine is connected to the liver directly. However, only an estimated 25% of those initially undergoing the Kasai procedure will survive to their twenties without need for liver transplantation. The European Commission granted orphan designation to A4250 for the treatment of biliary atresia in December of 2018. In January of 2019, the FDA granted orphan drug designation to A4250 for the treatment of biliary atresia. We intend to initiate a pivotal clinical trial with A4250 for the treatment of biliary atresia in the second half of 2019.

ALGS is a genetic condition associated with liver, heart, eye, kidney and skeletal abnormalities. In particular, ALGS patients have fewer than normal bile ducts inside the liver, which leads to cholestasis and the accumulation of bile and causes scarring in the liver. ALGS is estimated to affect between one in every 30,000 to 70,000 children born worldwide. There are currently no drugs approved for the treatment of ALGS. Current treatment for ALGS is generally in line with current treatments for PFIC as described above. In October of 2018, the FDA granted orphan drug designation to A4250 for the treatment of ALGS.

Primary sclerosing cholangitis refers to swelling (inflammation), scarring, and destruction of bile ducts inside and outside of the liver. The first symptoms are typically fatigue, itching and jaundice, and many patients with sclerosing cholangitis also suffer from inflammatory bowel disease. The estimated incidence of primary sclerosing cholangitis is 6.3 cases per 100,000 people. There are currently no drugs approved for the treatment of sclerosing cholangitis. First-line

treatment is typically off-label UDCA, although UDCA has not been established to be safe and effective in patients with sclerosing cholangitis in well controlled clinical trials.

Elobixibat — approved in Japan for chronic constipation and our lead product candidate for NASH. Elobixibat is another novel, minimally absorbed, orally administered IBAT inhibitor.

- *Elobixibat as a treatment for chronic constipation.* We have granted commercial rights to elobixibat for the treatment of chronic constipation and other GI diseases in Japan and other select markets in Asia to EA Pharma Co., Ltd. (formerly known as Ajinomoto Pharmaceuticals Co., Ltd.), or EA Pharma, a company formed by a business combination between Ajinomoto Pharmaceuticals and the GI business of Eisai Co., Ltd., or Eisai. In January 2018, the Japanese Ministry of Health, Labour and Welfare, or MHLW, approved a new drug application filed by EA Pharma for elobixibat for the treatment of chronic constipation. EA Pharma co-markets elobixibat in Japan with Mochida Pharmaceutical Co., Ltd, or Mochida, and to co-promotes elobixibat in Japan with Eisai.

We have commercial rights to elobixibat in the United States, Europe, China and otherwise outside of the territories licensed to EA Pharma. We do not have any current plan to seek a license or other partnering transaction with a third party for elobixibat for chronic constipation in the United States or Europe. Whether or not we elect to seek such a transaction, we do not anticipate that we will conduct future clinical trials of elobixibat as a treatment for chronic constipation independently.

- *Elobixibat as a treatment for NASH*. NASH is a common, serious and sometimes fatal chronic liver disease that resembles alcoholic liver disease but occurs in people who drink little or no alcohol. Based on multiple epidemiological studies published by third parties in 2014 and 2015, we estimate that NASH affects 2 to 3.5% of adults, representing over 9 million people in the United States and 10 million people in the European Union. There are currently no drugs approved for the treatment of NASH. Lifestyle changes, including modification of diet and exercise to reduce body weight, as well as treatment of concomitant diabetes and dyslipidemia, are commonly accepted as the standard of care for NASH, but have not conclusively been shown to prevent disease progression. Based on findings on parameters relevant to NASH in clinical trials of elobixibat that we previously conducted in patients with chronic constipation and in patients with elevated cholesterol and findings on other parameters relevant to NASH from nonclinical studies that we previously conducted with elobixibat or a different IBAT inhibitor, we believe elobixibat has potential benefit in the treatment of NASH. We expect to initiate a Phase 2 clinical trial of elobixibat in NAFLD and NASH in the second quarter of 2019.

A3384 — a product candidate for the treatment of BAM. A3384 is a proprietary formulation of cholestyramine that is designed to release cholestyramine directly in the colon. We have formulation-related patents pending in various jurisdictions with respect to A3384. We are considering conducting either or both of a Phase 2 clinical trial of A3384 as a treatment for BAM if our pending formulation related patents issue in the United States, or a clinical trial in healthy volunteers to assess A3384's drug-drug interaction profile. If we elect to conduct a clinical trial of A3384 in BAM, we expect to initiate the trial in 2020.

BAM, which is sometimes also called bile acid diarrhea, occurs when bile acids are not sufficiently reabsorbed in the small intestine or are overproduced in the liver, causing elevated levels of bile acids to instead reach the colon and leading to chronic watery diarrhea. Based on a reported estimate of the prevalence of irritable bowel syndrome with diarrhea, or IBS-D, and published third-party studies that suggest approximately one-third of IBS-D patients have BAM, we estimate the prevalence of BAM in the United States and the European Union to be to be approximately 4 million people. There are currently no drugs approved in the United States for the treatment of BAM.

Cholestyramine, which is approved in some countries in Europe to treat diarrhea associated with certain GI conditions, is commonly prescribed off-label to treat BAM. Cholestyramine is a well characterized bile acid sequestrant, which is also known as a resin. The benefit of cholestyramine has historically been limited both because of poor tolerability and because of its negative effect on absorption of other medications and important fat soluble vitamins. We

believe that a better tolerated formulation that is capable of delaying the activity of cholestyramine until it reaches the colon has potential to provide therapeutic benefit for patients with BAM.

Preclinical Program in NASH

We have an ongoing preclinical program directed towards discovering and advancing to the clinic a novel compound that modulates bile acid levels to treat NASH. We hope to provide more details on the specific mechanism of action and our progress in the future. Some of the principal characteristics of NASH include high LDL cholesterol levels, resistance to insulin in the body, chronic inflammation in the liver and progressive scarring of tissue, known as fibrosis. We have generated favorable clinical or preclinical data on each of these measures with our IBAT inhibitors, either A4250 or elobixibat, supporting the potential of bile acid modulators generally, and IBAT inhibitors specifically, to become a new treatment option for NASH.

Our Corporate History

Prior to November 3, 2016, we were a specialty biopharmaceutical company known as Biodel Inc. that historically had been focused on the development and commercialization of innovative treatments for diabetes. Biodel was originally incorporated in the State of Delaware in December 2003 under the name "Global Positioning Group, Ltd." and subsequently changed its name to "Biodel Inc." Albireo Limited was formed in connection with a spinout transaction from AstraZeneca AB in 2008 in which AstraZeneca assigned to Albireo AB all of its rights in and to its portfolio of IBAT inhibitors, including elobixibat and A4250, as well as other programs that are currently at a preclinical stage.

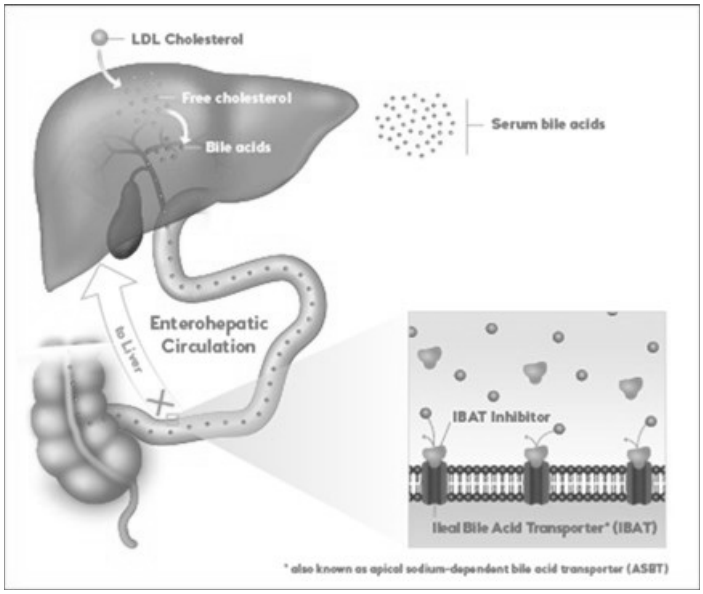
On November 3, 2016, we completed a share exchange transaction, or the Biodel Transaction, pursuant to an Amended and Restated Share Exchange Agreement dated July 13, 2016 that we entered into with Albireo Limited and the shareholders and noteholders of Albireo Limited. In the Biodel Transaction, each holder of Albireo Limited shares or notes convertible into Albireo Limited shares sold their shares of Albireo Limited for newly issued shares of our common stock. As a result, Albireo Limited became a wholly owned subsidiary of Biodel, Biodel's corporate name was changed to Albireo Pharma, Inc. and the business of Albireo Limited became our business.

The Role of Bile Acids and IBAT

The liver is responsible for many vital body functions, including the regulation of bile acid synthesis and metabolism. The liver uses cholesterol to produce bile acids, which are then transported to, and stored in, the gall bladder. In response to food ingestion, the gall bladder contracts and releases bile acids into the small intestine where they promote digestion and absorption of dietary fats and fat soluble vitamins A, D, E and K.

After completing digestion, bile acids bind to IBAT, which is sometimes referred to as the apical sodium bile acid transporter, or ASBT, at a location at the end of the small intestine known as the terminal ileum. As depicted below,

IBAT then initiates the transport of bile acids across the intestinal wall through the portal vein back to the liver in the enterohepatic circulation process.



In healthy persons, approximately 95% of bile acids recirculate back to the liver, with the remainder being excreted to the colon. The liver produces a small amount of new bile acids every day to make up for this loss.

In addition to their role in digestion, bile acids are important signaling molecules that help regulate a network of metabolic pathways throughout the GI system. Bile acids bind to receptors in the colon that promote the release of intestinal hormones, such as glucagon-like peptide-1, or GLP-1, that can stimulate insulin release from the pancreas and, over time, decrease levels of plasma hemoglobin A1c, or HbA1c, a measure of glucose. In the liver, bile acids bind to other receptors that regulate bile acid production from cholesterol. Under normal conditions, bile acids bind to these receptors and inhibit the synthesis of new bile acids. As bile acid levels are lowered, the liver produces needed bile acids from cholesterol, which requires increased uptake of cholesterol and results in the decrease of cholesterol levels in the liver and otherwise in circulation in the body.

Cholestatic liver disease results in the accumulation of elevated bile acids in the liver and in the serum. Elevated bile acid levels are linked with progressive liver disease. In addition, although a direct causative correlation has not been definitely established, there is substantial clinical support linking elevated serum bile acids to pruritus, a challenging symptom impacting patients with cholestatic liver disease.

Interruption of enterohepatic circulation in patients with PFIC or ALGS surgically via the partial external biliary diversion, or PEBD, procedure has been shown to lower serum bile acid levels, relieve pruritus, improve clinical outcomes and delay the progression of serious liver disease. A4250 is designed to treat PFIC and other cholestatic liver diseases pharmacologically by inhibiting IBAT to reduce bile acids in the liver and serum, while at the same time reducing pruritus. In addition to the beneficial effects that may be achievable through IBAT inhibition, A4250 is minimally absorbed into the bloodstream, resulting in minimal systemic exposure of the drug to the body.

Our Strategy

Our goal is to be a leader in the development and commercialization of novel therapeutics for orphan pediatric cholestatic liver diseases and disorders where there is high unmet medical need, while also leveraging our expertise in bile acid modulation to treat other liver and GI diseases and disorders. To achieve our goal, we intend to pursue the following strategies.

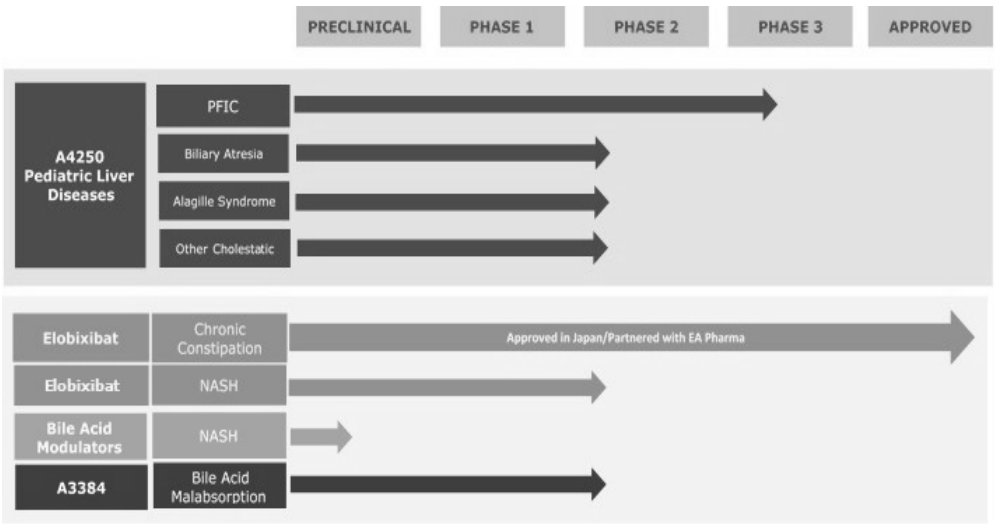
- ***Rapidly develop A4250 to regulatory approval to treat patients with PFIC***. We are conducting a single Phase 3 clinical trial in patients with PFIC, which we refer to as PEDFIC 1. It is our objective that PEDFIC 1, together with available data from PEDFIC 2, our long-term, open label extension study, forms the primary support for applications for marketing approval of A4250 in both the United States and European Union.

- ***Maximize the benefit and commercial potential of A4250 by expanding development to additional orphan pediatric cholestatic indications***. . Although we have chosen PFIC as our lead indication for A4250, we also believe A4250 can benefit children suffering from other cholestatic diseases and disorders. We plan to initiate a pivotal clinical trial with A4250 for the treatment of biliary atresia in the second half of 2019. We also plan to conduct clinical development of A4250 as a treatment for one or more other pediatric cholestatic liver diseases and disorders in 2020, which may include ALGS and primary sclerosing cholangitis, to help address these unmet medical needs and to maximize the commercial potential of A4250.

- ***Develop the capability to commercialize A4250 to treat orphan pediatric liver diseases, if approved, through a targeted sales force in the United States and Europe and collaborate selectively to commercialize A4250 outside of these regions***. If we receive marketing approval in the United States or Europe for A4250 to treat patients with PFIC or any other pediatric cholestatic liver disease or disorder, we plan to build the capabilities to effectively commercialize A4250 in the approved indication(s) in the applicable region. We believe that the required commercial organization would be modest in size and targeted to the relatively small number of specialists in the United States and Europe who treat children with cholestatic liver disease. If we receive marketing approval outside of the United States and Europe for A4250 to treat patients with PFIC or any other pediatric cholestatic liver disease or disorder, we plan to selectively utilize collaboration, distribution and other marketing arrangements with third parties to commercialize A4250 in the approved indication(s) in the regions outside the United States or Europe where we receive approval.

- ***Collaborate selectively to develop and commercialize product candidates targeting nonorphan indications, potentially including elobixibat, A3384 or any future product candidate to treat NASH.*** We intend to selectively seek alliances and collaborations to assist us in furthering the development or commercialization of product candidates targeting large primary care markets that must be served by large sales and marketing organizations. These product candidates may include any or all of elobixibat, A3384, and any potential future product candidate that arises from our preclinical program in NASH.

Our Pipeline



A4250

We completed a Phase 2 clinical trial of A4250 in children with chronic cholestasis and pruritus and we have advanced A4250 into a Phase 3 clinical trial in patients with PFIC, and an extension study to evaluate long-term outcomes. In addition to PFIC, we intend to initiate a pivotal clinical trial in biliary atresia in the second half of 2019. We also plan to conduct clinical development of A4250 in 2020 as a treatment for other pediatric cholestatic liver diseases and disorders as well, which may include ALGS and primary sclerosing cholangitis.

A4250 is a highly potent and selective inhibitor of IBAT that is designed to reduce bile acid reabsorption from the small intestine to the liver, and therefore reduce levels of bile acids in the serum and liver and increase excretion of bile acids via the colon. We believe that reducing liver and serum bile acid levels may reduce bile acid-related liver damage to improve liver function and alleviate symptoms of PFIC and other cholestatic liver diseases, including pruritus. Moreover, at therapeutic doses, A4250 has minimal systemic exposure, acts locally in the gut and, based on preclinical testing, appears to be excreted substantially intact in the feces, which may reduce the risk of systemic side effects and undesirable drug-drug interactions compared with drugs that have broad distribution in the body. A4250 has been granted orphan drug designation for PFIC, PBC, biliary atresia and ALGS in the United States and the European Union.

Lead Indication for A4250

PFIC. PFIC is our lead indication for A4250. PFIC is a rare genetic disorder that causes progressive, life-threatening liver disease, which may start early after birth or at a young age and rapidly progress to end-stage liver disease. PFIC is commonly associated with elevated serum bile acids. Prominent symptoms of PFIC include pruritus, which is associated with severe sleep disturbance and diminished overall quality of life, and poor growth. First-line treatment in PFIC is typically off-label UDCA. UDCA is itself a type of bile acid that is thought to act by diluting the toxic effects in the liver and bile ducts of a different type of bile acids, known as hydrophobic bile acids, which are often elevated in cholestatic liver disease. Third-party retrospective analyses published in 2009 and 2010 indicate that, following treatment with UDCA, many PFIC patients require PEBD surgery and PFIC patients will often ultimately require liver transplantation. Although success rates vary, published third-party studies have shown that PEBD surgery can slow and, in some cases, stop the progression of liver disease and lead to reduced pruritus and improved sleep. We believe these outcomes validate our approach of reducing liver and serum bile acids with an IBAT inhibitor such as A4250 to treat PFIC.

The precise prevalence of PFIC is unknown, and we are not aware of any patient registries or other method of establishing with precision the actual number of patients with PFIC in any geography. PFIC has been estimated to affect between one in every 50,000 to 100,000 children born worldwide. Based on the estimated incidence, published birth rates and estimates of the effect of pediatric liver transplant on life expectancy, we estimate that there are approximately 3,000 to 4,000 PFIC patients in the U.S. and E.U. but we are not able to estimate the prevalence of PFIC with precision. We currently have not modeled other regional opportunities in Asia, the Middle East and Latin America. We are aware there may be higher prevalence of disease in other countries such as Saudi Arabia and Turkey. Three alternative gene defects have been identified that correlate to three separate PFIC subtypes, known as types 1, 2 and 3.

- PFIC, type 1, which is sometimes referred to as “Byler disease” or “FIC1 deficiency,” is caused by impaired bile secretion due to mutations in the ATP8B1 gene that result in an imbalance of molecules known as phospholipids that is associated with cholestasis and elevated bile acids in the liver. Children affected by PFIC, type 1 usually develop cholestasis in the first months of life and, in the absence of surgical treatment, progress to cirrhosis and end-stage liver disease before the end of the first decade of life. PFIC, type 1 is especially common in the Old Order Amish population in the United States, as well as the Inuit population of Greenland.

- PFIC, type 2, which is sometimes referred to as “Byler syndrome” or “BSEP deficiency,” is caused by impaired bile salt secretion due to mutations in the ABCB11 gene that result in the buildup of bile salts in liver cells. Children with PFIC, type 2 often develop liver failure within the first few years of life and are at increased risk of developing hepatocellular carcinoma, the most common form of liver cancer.

- PFIC, type 3, which typically presents in the first years of childhood with progressive cholestasis, is caused by mutations in the ABCB4 gene. Mutations in the ABCB4 gene lead to a lack of phospholipids available to bind to bile acids, resulting in a buildup of bile acids that damages liver cells.

The TJP2 gene, NR1H4 gene or Myo5b gene mutations have also been proposed to be causes of PFIC. In addition, some patients with PFIC do not have a mutation in any of the ATP8B1, ABCB11, ABCB4, TJP2, NR1H4 or Myo5b genes. In these cases, the cause of the condition is unknown.

Potential Additional Target Indications for A4250

Biliary atresia. Biliary atresia is a partial or total blocking or absence of large bile ducts that irreversibly prevents bile flow from the liver to the small intestine, causing cholestasis and resulting accumulation of bile that damages the liver. The damage leads to scarring, loss of liver tissue and cirrhosis, which makes it difficult for the liver to remove toxins from the blood and deteriorates the liver. Biliary atresia is life threatening.

There are currently no drugs approved for the treatment of biliary atresia. The current standard of care is the Kasai procedure. The chance of a successful Kasai procedure is highest if performed before a patient is two months of age. However, even with early intervention, scarring of the liver can continue, resulting in cirrhosis and eventually the need for transplantation. Only an estimated 25% of those initially undergoing the Kasai procedure will survive to their twenties without need for liver transplantation.

The estimated worldwide incidence of biliary atresia is between 4.5 and 8.5 for every 100,000 live births . Of all biliary atresia patients, we believe A4250 will primarily benefit those who have undergone a Kasai procedure that has been sufficiently successful to obviate the need for liver transplant within the first year of life. We estimate the addressable biliary atresia patient population for A4250 to be approximately 3,500 patients in the United States and approximately 5,500 patients in the European Union.

The exact cause of biliary atresia is unknown, but it is thought to result from an event in the womb or around the time of birth. Possible triggers may include viral or bacterial infection, an immune system malfunction, a genetic mutation, a problem during liver or bile duct development or exposure to toxic substances. In January of 2019, the FDA granted orphan designation to A4250 for the treatment of biliary atresia. The European Commission granted orphan drug designation to A4250 for the treatment of biliary atresia in December of 2018. We plan to initiate a pivotal clinical trial biliary atresia in the second half of 2019.

ALGS. ALGS is a genetic condition associated with liver, heart, eye, kidney and skeletal abnormalities. In particular, ALGS patients have fewer than normal bile ducts inside the liver, which leads to cholestasis and the accumulation of bile and causes scarring in the liver. Symptoms include jaundice, pruritus, poor growth and specific facial features and typically develop in the first two years of life.

There are currently no drugs approved for the treatment of ALGS. Current treatments for ALGS are generally in line with current treatments for PFIC as described above, including off-label UDCA, PEBD surgery and, where liver disease is advanced, liver transplantation.

The prevalence of ALGS has been estimated to be one in 70,000 newborns. ALGS is predominately caused by mutations in a gene called Jagged1. In a small number of cases, ALGS results from mutations in a gene called Notch2. In October of 2018, the FDA granted orphan drug designation to A4250 for the treatment of ALGS.

Primary Sclerosing cholangitis. Primary sclerosing cholangitis refers to swelling (inflammation), scarring, and destruction of bile ducts inside and outside of the liver. The first symptoms are typically fatigue, itching and jaundice, and many patients with sclerosing cholangitis also suffer from inflammatory bowel disease. The estimated incidence of primary sclerosing cholangitis is 6.3 cases per 100,000 people. There are currently no drugs approved for the treatment of sclerosing cholangitis. First-line treatment is typically off-label UDCA, although UDCA has not been established to be safe and effective in patients with primary sclerosing cholangitis in well controlled clinical trials.

Development of A4250

Preclinical and Phase 1 Clinical Development

To assess the preclinical efficacy of A4250 to treat cholestasis, we studied A4250 in a mouse model in which select genes had been removed from the mice to induce cholestatic liver injury. In the model, A4250 significantly reduced serum levels of bile acids and normalized levels of alanine aminotransferase, or ALT, and alkaline phosphatase, or ALP, which are enzymes in the liver that are elevated in a diseased liver. A4250 also significantly inhibited the expression of proteins known to be associated with inflammation, including tumor necrosis factor alpha (Tnf- a), vascular cell adhesion molecule-1 (Vcam-1) and monocyte chemoattractant protein-1 (Mcp-1), and proteins known to be associated with fibrosis, including collagen, type 1 alpha1 (Col1a1) and collagen, type 1 alpha2 (Col1a2).

In addition, we completed a placebo controlled Phase 1 clinical trial of A4250 in healthy volunteers. The trial enrolled a total of 104 subjects and had three parts — a single ascending dose phase evaluating five different doses of A4250, a multiple ascending dose phase evaluating three different doses of A4250 (a 1 mg dose once daily, a 3 mg dose once daily and a 1.5 mg dose twice daily) over seven days, and a multiple ascending dose phase evaluating A4250 in combination with a bile acid sequestrant over seven days.

A4250 was generally well tolerated in all dose groups in the trial. In addition, A4250 was associated with a variety of biological effects, including a dose-related reduction in serum bile acids, decreased levels of the protein Fibroblast Growth Factor 19, or FGF19, and increased levels of the bile acid intermediate 7 a -hydroxy-4-cholesten-3-one, or C4. The effects on FGF19 and C4 levels are consistent with the IBAT inhibition mechanism, as IBAT inhibition reduces levels of bile acids in cells in the distal small intestine, which leads to decreased FGF19 production. There were no treatment-related serious adverse events, or SAEs, and the most commonly reported adverse event was diarrhea. Based on the results of the trial, we determined to include doses up to 3 mg daily in our next clinical trials.

Completed Phase 2 Clinical Trial in PBC

A4250 was previously evaluated in an investigator-initiated Phase 2 clinical trial for the treatment of PBC. We facilitated the trial, which was completed in the fourth quarter of 2016, primarily to provide additional learning on the effects of A4250 in patients with cholestatic liver disease to guide future development and to address feedback received from the FDA at a pre-investigational new drug, or IND, meeting regarding the need to generate data in adults with cholestatic liver disease prior to initiating clinical development in children in the United States. PBC is a chronic disease of the liver in which the bile ducts become inflamed and are slowly destroyed. When bile ducts are damaged, bile acids can build up in the liver, leading to irreversible cirrhosis. As cirrhosis progresses and the amount of scar tissue in the liver increases, the liver loses its ability to function. Cirrhosis also prevents blood from the intestines from returning to the heart.

The trial was an open label, crossover study designed to evaluate the safety and tolerability of A4250, the efficacy of A4250 in relieving pruritus and the effects of A4250 on liver biochemistry and bile acid metabolism in patients with PBC and cholestatic pruritus. The investigator conducted the trial at two sites in Sweden. The trial design provided for enrollment of adult patients who had not responded adequately to at least six months of treatment with UDCA and who met specified criteria for elevated serum levels of ALP and for itching.

In the trial, patients initially continued their existing regimen of either cholestyramine or colestipol for four weeks. After a two-week washout period, patients in the first cohort received a 1.5 mg once daily oral dose of A4250 for one week and a 3 mg once daily oral dose of A4250 for the succeeding three weeks. A4250 was administered in a powder formulation in a capsule, and patients who did not tolerate the higher dose could revert to the lower dose at the discretion of the investigator. After another two-week washout period beginning at the end of the four-week A4250 treatment period, patients again returned to their initial dosing regimen of either cholestyramine or colestipol for four weeks.

Following completion of the first cohort, the investigator began to enroll a second cohort of six patients into the trial to receive a lower daily dose of A4250 than patients in the first cohort received. However, the investigator

experienced recruitment delays for the second cohort and determined to conclude the study prior to completion of the second cohort, citing GI side effects.

The primary endpoint of the trial was the incidence of treatment-emergent SAEs during the treatment period. The VAS-itch, a commonly used tool to assess pruritus based on a linear 10-point scale, was one of the exploratory efficacy endpoints in the trial.

Based on data from the trial that we received from the investigator, eight patients received A4250 and all of them reported a substantial reduction in pruritus, assessed by the VAS-itch scale, at the time of the first assessment (one week). The reduction in pruritus was sustained throughout the remaining period of participation in the trial with dosing with A4250, and pruritus levels returned to pre-A4250 levels when dosing was stopped.

Two of the five patients in the first cohort dropped out of the trial due to diarrhea, an effect consistent with the IBAT inhibition mechanism. Three of the four patients in the abbreviated second cohort of the trial dropped out prior to completion of the four-week dosing period due to GI side effects, including diarrhea, abdominal pain and, in one case, bleeding.

Completed Phase 2 Clinical Trial in Children with Chronic Cholestasis and Pruritus

Our completed Phase 2 clinical trial of A4250 in children with chronic cholestasis and pruritus was an open label, dose finding trial designed to evaluate the safety and efficacy of A4250. The chronic cholestasis was caused by one of a number of different conditions, including PFIC, biliary atresia or ALGS. We conducted the trial at six enrolling sites in Denmark, France, Germany and Sweden.

The trial enrolled 20 patients between one and 17 years of age who met specified criteria for elevated serum bile acids and itching. Four of the 20 patients reenrolled to participate in a different dose group, resulting in a total of 24 datasets. Ten of the 20 patients had PFIC. Following screening, patients received a single oral dose of A4250 on the first day of the trial. If pharmacokinetic assessments met objective criteria for minimal systemic exposure of A4250 and, at a follow-up visit between 10 and 14 days later, there were no safety concerns, patients then received oral doses of A4250 once daily for four weeks. The term “pharmacokinetic” refers to how a drug moves within the body, including its absorption, distribution, metabolism and excretion. The trial design initially provided for six dose groups, ranging from 0.01 mg/kg to 0.3 mg/kg. An independent data safety and monitoring board, or DSMB, determined whether to initiate each successive dose group based on evaluation of safety, tolerability and pharmacokinetic data from the preceding dose group. A4250 was administered in the trial as pellets contained in a gelatin capsule that could be either swallowed whole or opened, enabling the pellets to be sprinkled on and mixed in food such as yogurt. This pellet formulation was different from the powder formulation used in the investigator-initiated clinical trial in PBC and prior clinical trials described above.

The primary efficacy endpoint of the trial was change from baseline in total serum bile acids at the end of the four-week treatment period. Secondary efficacy endpoints included change from baseline on various patient or caretaker-reported assessments of change in itching, including VAS-itch, the partial PO-SCORAD scale and the Whitington itching score, and evaluation of liver biochemistry. The PO-SCORAD is a 10-point scale that assesses itching and sleep disturbance. The Whitington itching score assesses the severity of itching based on specified alternative descriptions of effect on the skin. For each of the efficacy endpoints, “baseline” referred to the most recent assessment of the applicable measure taken prior to the beginning of the four-week treatment period, which varied among endpoints. The primary safety endpoint of the trial was the incidence of treatment-emergent SAEs during the treatment period.

The data from the trial showed a reduction in serum bile acids in a substantial majority of patients. The mean reduction in serum bile acids among dose groups ranged from 31% +/- 23% (standard error of the mean, or SEM) to 63% +/- SEM 12%, with some patients experiencing reductions in excess of 90%. The subpopulation of PFIC patients (n = 10, including three patients who participated in two different dose groups) in the trial had a greater mean reduction in serum bile acids than patients in the trial with other cholestatic liver diseases. Overall, the reductions in serum bile acids

exhibited high variability which is due to the wide range of doses and to the various diseases and disorders represented and variability in baseline serum bile acid levels within and across dose groups in the trial.

The data from the trial also showed improvement in pruritus across multiple assessment scales for most patients, with a significant correlation between reduction in serum bile acids and reduction in pruritus. The various liver biochemistry measures assessed in the trial showed high patient variability. There were some increased liver transaminases, which were assessed as mild, transient and either unrelated to A4250 or with an unclear relationship. In the trial's fifth dose group (0.2 mg/kg A4250 dosing), a patient with ALGS whose ALT and aspartate aminotransferase, or AST, had begun increasing prior to enrollment in the trial showed elevated transaminases during the trial that had not come down at the trial's follow-up visit two weeks following completion of dosing. These elevations were not accompanied by any increase in bilirubin levels, and there are reports in the medical literature of ALGS patients having increased ALT and AST levels after undergoing PEBD surgery, which, like A4250, is designed to reduce bile acids in the liver. After review and analysis, the independent DSMB approved continued dosing in the sixth and final cohort in the trial at an A4250 dose not to exceed 0.2 mg/kg.

There were no patient dropouts in the trial, and A4250 exhibited a favorable overall tolerability profile. In particular, all patients completed the trial and there was only one incidence of diarrhea, which occurred prior to the four-week treatment period and was characterized by the applicable clinical investigator as mild. There were two treatment-emergent SAEs reported in the trial, both of which were determined by the applicable clinical investigator to be not related to A4250.

Phase 3 Clinical Program in Patients with PFIC

Our Phase 3 clinical trial of A4250 in patients with PFIC is a randomized, double blind, placebo controlled, multicenter, study designed to enroll approximately 60 patients with PFIC (type 1 or 2). Patients will be assigned to receive either 40 μg/kg/day or 120 μg/kg/day of A4250, or placebo, for 24 weeks. The primary endpoint for FDA evaluation, and a key secondary endpoint for EMA evaluation, will be an assessment of change in pruritus using a caregiver-reported outcome instrument that we have developed taking into account input from PFIC patients and their caregivers. The primary endpoint for EMA evaluation, and a key secondary endpoint for FDA evaluation, will be serum bile acid responder rate where a responder is a patient who achieves either a reduction in serum bile acid levels of 70% or more from baseline or a reduction of serum bile acid levels at least to an absolute level that is specified in between 50 and 100 μmol/l. As designed, the trial provides at least 80% power to detect a positive outcome on both the change in pruritus endpoint and the serum bile acid responder rate endpoint, with a positive outcome currently defined as superiority for either the 40 μg/kg/day A4250 dose group or the 120 μg/kg/day A4250 dose group compared to the placebo dose group at a significance level of $p \leq 0.025$. We are in discussions with the FDA regarding our statistical analysis for measuring change in pruritis and demonstrating a clinically meaningful change. The trial will also have several additional secondary endpoints. Patients in the double-blind trial will have the opportunity to participate in the open label extension study to assess long-term safety and durability of response.

We initiated the double-blind Phase 3 trial in May 2018 and expect data from the trial to be available by the end of 2019 or early 2020.

Elobixibat

Our product candidate elobixibat is licensed for the treatment of chronic constipation and other functional diseases in Japan and other select markets in Asia to EA Pharma. In January 2018, the MHLW approved a new drug application filed by EA Pharma for elobixibat for the treatment of chronic constipation in Japan. EA Pharma co-markets elobixibat in Japan with another company, Mochida, and co-promotes elobixibat with Eisai in Japan under the trade name GOOFICE®.

We have commercial rights to elobixibat in the United States, Europe and all other territories not licensed to EA Pharma. We do not have any current plan to seek a license or other partnering transaction with a third party for elobixibat for chronic constipation in the United States and Europe. Whether or not we elect to seek such a transaction,

we do not anticipate that we will conduct future clinical trials of elobixibat as a treatment for chronic constipation independently.

Elobixibat is, like A4250, an IBAT inhibitor. Based on findings on parameters relevant to NASH in clinical trials of elobixibat that we previously conducted in patients with chronic constipation or elevated cholesterol and findings on other parameters relevant to NASH from nonclinical studies that we previously conducted with elobixibat or A4250 (see "— Preclinical Program in NASH," below), we believe elobixibat has potential benefit in the treatment of NASH. We have a method of use patent pending in various jurisdictions with respect to the use of elobixibat to treat NASH. We expect to initiate a Phase 2 clinical trial of elobixibat in NAFLD and NASH in the second quarter of 2019.

Chronic (Idiopathic) Constipation

Though occasional constipation is very common, some people experience chronic constipation that can interfere with their ability to go about their daily tasks. Pursuant to applicable Rome III diagnostic criteria, two or more of the following symptoms must be present: straining during at least 25% of defecations, lumpy or hard stools in at least 25% of defecations, sensation of incomplete evacuation for at least 25% of defecations, sensation of rectal obstruction or blockage for at least 25% of defecations, use of fingers or other manual maneuvers to facilitate at least 25% of defecations, and passing fewer than three stools per week. In order to support a diagnosis of constipation, the patient must rarely have loose stools without the use of laxatives. Further, in order for constipation to be considered chronic, these criteria must be present for at least three months, with symptom onset at least six months prior to diagnosis. The Rome III diagnostic criteria are established diagnostic measures for various GI disorders set forth by the Rome Foundation, a not-for-profit organization based in the United States. The term "idiopathic" indicates that the cause of the chronic constipation is unknown and not due to any underlying illness or medication.

The current standard of care for constipation is over-the-counter, or OTC, laxatives, which may improve symptoms of constipation but often exacerbate pain and bloating. Marketed products in Japan that may be prescribed for chronic constipation include Amitiza (lubiprostone) and Linzess (linaclotide), although linaclotide is approved in Japan for the treatment of IBS-C.

Preclinical and Early Clinical Development of Elobixibat

Prior to Albireo Limited's inception in 2008, elobixibat was evaluated by its predecessor owner, AstraZeneca, in various preclinical studies and Phase 1 single ascending dose and multiple ascending dose clinical trials. In Phase 1 clinical development, elobixibat was generally well tolerated in healthy volunteers and showed minimal systemic exposure. Subsequently, we conducted a two-year nonclinical carcinogenicity toxicology study that did not result in any findings of concern and we or our former licensee conducted various additional Phase 1 and early Phase 2 clinical trials to assess the pharmacokinetics and various effects of elobixibat. Findings from these studies indicated, among other things, favorable effects of elobixibat on colonic transit and on low-density lipoprotein, or LDL or "bad" cholesterol.

Completed Phase 2b Clinical Trial in the United States

We completed a multicenter, double blind, placebo controlled Phase 2b clinical trial of elobixibat as a treatment for chronic idiopathic constipation, or CIC, in 2010. We conducted the trial at 45 sites in the United States. Enrollment criteria included a diagnosis of CIC and meeting specified thresholds for numbers of complete spontaneous bowel movements, or CSBMs, per week during the two weeks prior to randomization. A spontaneous bowel movement, or SBM, was defined in the trial as a bowel movement occurring without a laxative, enema or suppository usage in the past 24 hours. A CSBM was defined in the trial as an SBM accompanied by a self-report of complete evacuation.

After a screening period during which patients were taken off laxatives and other excluded medications, patients in the trial entered a two-week baseline period. Following the baseline period, 190 patients were randomized to receive a once daily oral tablet dose of one of three doses of elobixibat (5, 10 or 15 mg), or placebo, for eight weeks. Of the randomized patients, 161 patients completed the trial.

The primary endpoint of the trial was change in number of weekly SBMs from baseline to the first treatment week for patients who received elobixibat compared with patients who received a placebo. The results demonstrated a dose response in favor of elobixibat among all three dose groups and were statistically significant in the 10 mg ($p < 0.002$) and 15 mg ($p < 0.001$) dose groups. A clinical trial result is statistically significant if it is unlikely to have occurred by chance. The statistical significance of a clinical trial result, such as an observed difference between two treatment groups or cohorts, is determined by a widely used statistical method that establishes the "p"-value of the result. A p-value of 0.05 (or less) indicates that there is a 1-in-20 (or less) statistical probability that the clinical trial result occurred by chance and typically represents statistical significance. If a p-value is above 0.05, the result is generally not considered statistically significant. The p-value of < 0.002 for the 10 mg elobixibat dose group indicates that there is a less than 1-in-500 statistical probability that the difference compared with placebo occurred by chance, and the p-value of < 0.001 for the 15 mg elobixibat dose group indicates that there is a less than 1-in-1,000 statistical probability that the difference compared with placebo occurred by chance.

Secondary efficacy endpoints of the trial included evaluations of changes in mean weekly number of SBMs and CSBMs, time to first SBM or CSBM, overall constipation response and reduction in C4 and LDL cholesterol levels. The 10 mg and 15 mg elobixibat doses met all of these secondary endpoints with statistical significance.

All doses of elobixibat were generally well tolerated in the clinical trial. The most frequently reported adverse events in the trial were abdominal pain and diarrhea, which occurred most often in the highest elobixibat dose group (abdominal pain: 10.4%, 5 mg elobixibat; 10.6%, 10 mg elobixibat; and 27.1%, 15 mg elobixibat; versus 0% placebo; and diarrhea: 8.3%, 5 mg elobixibat; 6.4%, 10 mg elobixibat; and 12.5%, 15 mg elobixibat; versus 2.2% placebo). None of the three SAEs reported in the trial (bleeding colonic diverticulum two weeks after the end of treatment in the 5 mg elobixibat dose group, breast carcinoma in the 10 mg elobixibat dose group, and shoulder pain in the placebo group) was considered by the applicable investigator to be related to study drug.

Completed Phase 2b Clinical Trial Conducted by EA Pharma in Japan

Our licensee, EA Pharma, completed a multicenter, double blind, placebo controlled Phase 2b clinical trial of elobixibat as a treatment for chronic constipation in 2015. Patients in the trial entered the two-week baseline period during which they were taken off excluded medications. Following the baseline period, patients were randomized to receive a once daily oral dose of either a low, mid or high dose of elobixibat for two weeks. During the baseline period and the treatment period, patients reported daily bowel and abdominal symptoms. Of the randomized patients, 154 patients completed the trial.

The primary endpoint of the trial was change in number of weekly SBMs from baseline to the first treatment week for patients who received elobixibat compared with patients who received a placebo. In the trial, both the mid and high dose groups of elobixibat showed a highly statistically significant advantage on change from baseline in weekly SBM frequency compared with placebo ($p < 0.001$). The findings in favor of elobixibat were substantially the same on a secondary endpoint of the trial assessing change from baseline in weekly CSBM frequency.

All doses of elobixibat were generally well tolerated in the trial, and no SAEs were reported. As in our completed Phase 2b clinical trial, the most frequently reported adverse events in the trial were abdominal pain and diarrhea, which were both assessed by EA Pharma to be typically mild.

Completed Phase 3 Clinical Trial and Long-Term Safety Trial Conducted by EA Pharma in Japan

In October 2016, we announced positive results from a Phase 3 clinical trial of elobixibat as a treatment for chronic constipation conducted by EA Pharma in Japan. The trial was a multicenter, double blind, placebo controlled trial in which patients with chronic constipation received a fixed dose of elobixibat or placebo once daily for two weeks. In the trial, elobixibat met the primary endpoint, which was change in the number of weekly SBMs from baseline to the first treatment week compared with placebo, with high statistical significance. Elobixibat also met all secondary efficacy endpoints in the trial assessed statistically, including assessments of change in frequency of CSBMs, time to first SBM, severity of constipation and stool consistency, with high statistical significance.

There were no SAEs reported in the trial. Consistent with prior clinical trials of elobixibat, the most common adverse events were abdominal pain (18.8%) and diarrhea (13.0%), all of which were characterized as mild or, in one case, moderate in severity.

EA Pharma also completed a clinical trial designed to evaluate the long-term safety of elobixibat in Japanese patients with chronic constipation over 52 weeks. The long-term safety trial was a multicenter, open label trial in which patients with chronic constipation received once daily dosing of elobixibat. In the trial, elobixibat showed a safety and tolerability profile consistent overall with prior clinical trials of elobixibat in Japan.

Phase 3 Clinical Trials Conducted by a Former Licensee

Two Phase 3 clinical trials conducted by a former licensee of ours to evaluate the efficacy and safety of elobixibat as a treatment for CIC, known as Echo 1 and Echo 2, ended in 2014. Our former licensee stopped Echo 1 and Echo 2 early citing an issue related to the distribution of study drug to study sites that was unrelated to the performance of elobixibat. Subsequent analysis by our former licensee determined the issue to have affected only Echo 2 and a small number of patients. As a result of the early termination of the trials, each of Echo 1 and Echo 2 enrolled substantially fewer than the number of patients contemplated by the trial's statistical plan. A third Phase 3 clinical trial conducted by our former licensee to evaluate the long-term safety of elobixibat, known as Echo 3, ended in 2015.

Echo 1. Echo 1 was a multicenter, double blind, placebo controlled Phase 3 clinical trial of elobixibat as a treatment for CIC conducted at 71 sites in the United States, Belgium, Canada, Czech Republic, Germany, Israel, the United Kingdom, Poland and South Africa. SBM and CSBM were defined in the trial in the same manner as our completed Phase 2b trial of elobixibat in CIC discussed above. The statistical plan for the trial contemplated that 840 patients would be enrolled.

After a screening period, patients in the trial entered a two-week baseline period. Following the baseline period, patients were randomized in a 1:1:1 ratio to receive a once daily oral dose of 5 mg of elobixibat, 10 mg of elobixibat or placebo, in tablet form, for 26 weeks. During the baseline period and the treatment period, patients reported daily bowel and abdominal symptoms. At the time the trial was stopped, 376 patients had been randomized into the trial, of which 312 patients had completed 12 weeks of treatment and 146 patients had completed 26 weeks of treatment.

The primary endpoint of the trial was the overall CSBM response. CSBM response refers to a patient having at least three CSBMs per week and an increase of at least one CSBM per week from baseline, in each case for at least nine of the first 12 weeks of the treatment period and at least three of the weeks from week 9 to week 12. The 5 mg elobixibat dose met the primary endpoint, and the result was statistically significant based on the study's predefined statistical methodology ($p = 0.029$). There was a trend in favor of the 10 mg elobixibat dose on the primary endpoint, but the result did not achieve statistical significance using the same methodology. Subsequently, at a meeting with the FDA held in 2014, the FDA advised us that, based on the unplanned stopping of the study, the FDA would apply a different statistical methodology than had been predefined and utilized for the study. Using the FDA's chosen statistical methodology, neither the 5 mg nor the 10 mg dose of elobixibat achieved statistical significance on the primary endpoint in Echo 1.

All doses of elobixibat were generally well tolerated in the trial. The rate of discontinuation due to adverse events was dose related (7%, 5 mg elobixibat and 9%, 10 mg elobixibat, versus 2% placebo). There were dose-related incidences of treatment-emergent abdominal pain and diarrhea considered a reasonable possibility to be treatment related (abdominal pain: 4%, 5 mg elobixibat and 12%, 10 mg elobixibat, versus 2% placebo; diarrhea: 6%, 5 mg elobixibat and 6%, 10 mg elobixibat, versus 2% placebo). None of the three SAEs reported in the 5 mg elobixibat dose group, two SAEs reported in the 10 mg elobixibat dose group and one SAE reported in the placebo group were considered by the applicable investigator to be related to study drug. The reported SAEs were: in the 5 mg elobixibat dose group, inflammation of the gallbladder, developmental bone growth disease and carpal tunnel syndrome; in the 10 mg elobixibat dose group, glaucoma and back pain worsening; and in the placebo group, hemorrhoids.

Echo 2. Echo 2 was a multicenter, double blind, placebo controlled Phase 3 clinical trial of elobixibat as a treatment for CIC. The trial was conducted at 79 sites in the United States, Canada, Czech Republic, Germany, Hungary,

Poland, Slovakia, Sweden, South Africa and the United Kingdom. Enrollment criteria, primary and key secondary endpoints and trial design were substantially the same as for Echo 1, except that Echo 2 from the outset provided for a 12-week treatment period and included a four-week post-treatment withdrawal period. The statistical plan for the trial contemplated that 840 patients would be enrolled.

Following the screening and baseline periods, patients were randomized in a 1:1:1 ratio to receive a once daily oral dose of 5 mg of elobixibat, 10 mg of elobixibat or placebo, in tablet form. During the baseline period and the treatment period, patients reported daily bowel and abdominal symptoms. At the time the trial was stopped, 314 patients had been randomized into the trial, of which 219 patients completed the trial including the withdrawal period.

In the trial, there were trends in favor of both the 5 mg and 10 mg elobixibat doses compared with placebo on the primary endpoint, but the result did not reach statistical significance. There were no signs of rebound during the four-week withdrawal period after the treatment period.

All doses of elobixibat were generally well tolerated in the trial. The rate of discontinuation due to adverse events was the same in the 5 mg elobixibat and placebo dose groups (2%) and greater in the 10 mg elobixibat dose group (6%). There were dose-related incidences of abdominal pain and diarrhea considered a reasonable possibility to be treatment related (abdominal pain: 2%, 5 mg elobixibat and 8%, 10 mg elobixibat, versus 2% placebo; diarrhea (7%, 5 mg elobixibat and 9%, 10 mg elobixibat, versus <1% placebo). There was one SAE reported in the 5 mg elobixibat dose group compared with five SAEs in the placebo group. The reported SAE in the 5 mg elobixibat dose group (basal cell carcinoma on the lip) occurred during the withdrawal period and was not considered by the applicable investigator to be related to study drug. The SAEs reported in the placebo group were tonsillitis, abnormal uterine bleeding, noncancerous uterine tumor, hysterectomy and exacerbation of hypertension.

Long-Term Safety. The long-term safety trial was a multicenter, open label, Phase 3 extension clinical trial of elobixibat as a treatment for CIC. The trial was conducted at 62 sites in the United States, Belgium, Canada, Czech Republic, Hungary, Poland, Slovakia, South Africa, Sweden and the United Kingdom. Enrollment criteria included completion of at least 12 weeks of double blind treatment in either Echo 1 or Echo 2. The trial enrolled 411 patients. Patients received a 10 mg dose of elobixibat in tablet form once daily, subject to reduction to 5 mg in the discretion of the applicable investigator, for up to 52 weeks. Of these patients, 282 patients completed 52 weeks of treatment with elobixibat and 316 patients completed at least 24 weeks of treatment with elobixibat.

There were several co-primary endpoints in the trial, all related to safety. In the trial, elobixibat was generally well tolerated, with a safety profile similar to Echo 1 and Echo 2. In particular, there was only one treatment-emergent SAE reported (constipation) that was considered by the applicable investigator to be related to study drug. Treatment-emergent adverse events leading to discontinuation occurred in 6.1% of patients, and the majority of treatment-emergent adverse events overall were classified as mild or moderate. Most adverse events were classified as GI.

A3384

A3384, a product candidate for the treatment of BAM, is a proprietary formulation of cholestyramine that is designed to release cholestyramine directly in the colon. BAM, which is sometimes also called bile acid diarrhea, occurs when bile acids are not sufficiently reabsorbed in the small intestine or are overproduced in the liver, causing elevated levels of bile acids to instead reach the colon and leading to chronic watery diarrhea.

There are no drugs currently approved in the United States for the treatment of BAM. Cholestyramine, which is approved in some countries in Europe to treat diarrhea associated with certain GI conditions, is commonly prescribed off label to treat BAM. However, cholestyramine is typically taken as a powder that does not dissolve in water and has been described as “drinking sand.” Because of poor tolerability and because of its negative effect on absorption of other medications and important fat soluble vitamins, the benefit of cholestyramine in the treatment of BAM has been limited. We believe that a formulation that has a more favorable tolerability profile than conventional cholestyramine can benefit patients with BAM.

We have completed a Phase 2 clinical trial of a prior formulation of A3384 in BAM. A subsequent pharmaceutical development program yielded two alternative optimized formulations of A3384 capable of selectively delivering a greater amount of cholestyramine to the colon. Each of these formulations constitutes a coating surrounding pellets of cholestyramine that travel through the body intact until the coating is dissolved in the colon to permit bile acids to bind to the cholestyramine.

We have formulation-related patents pending in various jurisdictions with respect to A3384. We are considering conducting either or both of a Phase 2 clinical trial of A3384 as a treatment for BAM, if our pending formulation-related patents for A3384 issue in the United States, or a clinical trial in healthy volunteers to assess A3384's drug-drug interaction profile. If we elect to conduct a clinical trial of A3384 in BAM, we expect to initiate the trial in 2020.

Bile Acid Malabsorption

BAM is a common cause of chronic watery diarrhea, with affected individuals having their bowels open several times a day. When bile acids are secreted into the colon, bacteria in the colon acts to convert the bile acids into different bile acids known as deoxycholate and lithocholate. These secondary bile acids play a key role in stimulating electrolyte and water secretion, which increases colonic motility and shortens colonic transit time. Highly elevated levels of these secondary bile acids can produce watery diarrhea, as well as other GI symptoms such as bloating, urgency and fecal incontinence.

We estimate the prevalence of BAM in the United States and the European Union to be approximately 4 million people. The approach to treating BAM currently depends on binding excess bile acids to reduce their secretory actions, using a bile acid sequestrant such as cholestyramine or a variant such as colestipol or colesevelam. However, many patients cannot tolerate these medications because of the texture or taste, because they worsen the diarrhea, cause intolerable nausea, heartburn, wind or bloating or because they negatively impact the absorption of important fat soluble vitamins or other medications. A third-party analysis of patients given a bile acid sequestrant to lower cholesterol showed that over half discontinued treatment within one year, and similar discontinuation was seen in a separate published study that followed treated patients with BAM.

Completed Phase 2 Clinical Trial of a Prior Formulation of A3384 in BAM

We completed a multicenter, double blind, placebo controlled Phase 2 clinical trial of a prior formulation of A3384 as a treatment for BAM in 2014. The discussion of the completed clinical trial that follows refers to the prior formulation as A3384. There were 19 patients enrolled in the trial based on a diagnosis of BAM or bile acid diarrhea and meeting specified criteria for numbers of bowel movements and liquid or soft stools per day. We had initially planned to enroll 36 patients in the trial. However, due to slower than expected patient enrollment and the fact that subjects in a Phase 1 clinical trial of A4250 in combination with A3384 that we were conducting in parallel had experienced diarrhea, we elected to discontinue enrollment in our BAM trial. As a result, the trial was not sufficiently powered to be able to detect statistically significant superiority of A3384 compared with placebo.

Patients in the trial continued their current treatment with conventional cholestyramine or another conventional bile acid resin for one week (referred to as baseline period 1), following which the bile acid resin was withdrawn for two weeks (referred to as baseline period 2). At that point, patients were randomized to receive twice daily oral doses of 250 mg of A3384, 1000 mg of A3384 or placebo for two weeks. The primary efficacy endpoint of the trial was change in mean daily number of bowel movements from baseline period 2 to the second treatment week for patients who received A3384 compared with patients who received a placebo.

In the trial, patients who received either dose of A3384 showed a numerically greater mean reduction in the number of mean daily bowel movements compared with placebo, but the result did not reach statistical significance. A secondary endpoint comparing severity of diarrhea from baseline period 2 to the second treatment week favored each dose of A3384 evaluated compared with placebo and reached statistical significance in the combined A3384 dose dataset ($p < 0.05$) and, using one of two different statistical methods employed, the 250 mg A3384 dataset ($p < 0.05$). There were some numerical advantages in favor of one or both A3384 dose groups or in the combined A3384 dose dataset on

other secondary endpoints, including assessments of abdominal discomfort, bloating and global symptom relief, but none approached statistical significance.

Both doses of A3384 were generally well tolerated in the clinical trial, with no adverse events leading to discontinuation in either A3384 dose group. The only SAE reported in the trial, metastasis with unknown primary tumor, was considered by the investigator to be not related to study drug.

Preclinical Program in NASH

We have an ongoing preclinical program directed towards discovering and advancing to the clinic a novel compound that modulates bile acid levels to treat NASH. We hope to provide more details on the specific mechanism of action and our progress in the future. NASH is a common, serious and sometimes fatal chronic liver disease that resembles alcoholic liver disease but occurs in people who drink little or no alcohol. Based on multiple epidemiological studies published by third parties in 2014 and 2015, we estimate that NASH affects 2 to 3.5% of adults, representing over 9 million people in the United States and 10 million people in the European Union. There are currently no drugs approved for the treatment of NASH. Lifestyle changes, including modification of diet and exercise to reduce body weight, as well as treatment of concomitant diabetes and dyslipidemia, are commonly accepted as the standard of care for NASH, but have not conclusively been shown to prevent disease progression.

Some of the principal characteristics of NASH include high LDL cholesterol levels, resistance to insulin in the body, chronic inflammation in the liver and progressive scarring of tissue, known as fibrosis. We have generated favorable clinical or preclinical data on each of these measures with our IBAT inhibitors, either A4250 or elobixibat, supporting the potential of bile acid modulators generally, and IBAT inhibitors specifically, to become a new treatment option for NASH.

In particular, the reduction in the reuptake of bile acids triggered by IBAT inhibition signals to the liver to make more bile acids to ensure the presence of a sufficient supply. The liver makes these bile acids from cholesterol, which has the effect of reducing levels of LDL cholesterol in the plasma. Also, increased bile acids in the colon resulting from IBAT inhibition stimulates the secretion of GLP-1 (glucagon-like peptide-1), which regulates insulin release from the pancreas and has been shown to decrease insulin resistance. Data from our clinical trials of elobixibat in patients with CIC or abnormal lipid levels demonstrated both of these effects. In addition, as discussed above under "A4250 — Development of A4250 — Preclinical and Phase 1 Clinical Development," in a preclinical mouse model of cholestatic liver injury, A4250 significantly inhibited the expression of different proteins known to be associated with inflammation and fibrosis. Moreover, in preclinical studies conducted by us or third parties, compounds that inhibit the IBAT have been reported to reduce liver concentrations of certain bile acids and cholesterol believed to play a role in the progression of NASH.

The results of a nonclinical study of A4250 conducted in an established model of NASH in mice known as the STAM™ model provide further support for the promise of IBAT inhibition mechanism to treat NASH. In the study, NASH conditions were simulated by injecting the mice with the drug streptozotocin soon after birth and providing a high fat diet beginning at four weeks. Baseline was established at week six, following which three cohorts of mice received 0.5 mg/kg of A4250, 10 mg/kg of A4250 or vehicle only once daily for 21 days. In the study, compared with the vehicle group, the 10 mg/kg A4250 dose group showed significant improvement ($p < 0.05$) on the nonalcoholic fatty liver disease activity score, or NAS, near significant improvement on a fibrosis measure ($p = 0.06$) and numerical improvement on plasma ALT levels and triglycerides. The 0.5 mg/kg A4250 dose group showed incremental advantages on some of these measures. We believe that NAS results with 10 mg/kg A4250 are competitive with NAS results previously presented from the same model for obeticholic acid, which is marketed as Ocaliva in combination with UDCA, or as a monotherapy for patients unable to tolerate UDCA, to treat PBC by Intercept Pharmaceuticals, Inc., or Intercept, and is currently in Phase 3 development as a treatment for NASH.

License and Royalty Monetization Agreements

Agreement with EA Pharma

Albireo AB, a wholly owned indirect subsidiary of ours, entered into a license agreement with EA Pharma (formerly known as Ajinomoto Pharmaceuticals Co., Ltd.) for the development and commercialization of elobixibat in specified countries in Asia in April 2012. Albireo AB subsequently transferred the agreement to its wholly owned subsidiary, Elobix AB, and the agreement was amended in January 2015, April 2016 and December 2017. For the remainder of this discussion of the agreement, "we" and the like refer to either or both of Albireo AB or Elobix AB, as the context requires.

Pursuant to the agreement, we granted EA Pharma an exclusive license under patents and other technology owned or licensed by us to develop and commercialize elobixibat in Japan, Indonesia, Korea, Myanmar, Taiwan, Thailand and Vietnam for all prophylactic or therapeutic uses of a pharmaceutical product for specified GI diseases and disorders, symptoms of constipation of all causes, or postoperative ileus or for use in colonoscopy cleansing procedures. The agreement also provides that the scope of the license may be expanded to include specified liver diseases, if we or an affiliate or licensee takes specified development actions outside of EA Pharma's licensed territory with elobixibat in that specified liver disease, or files an application for regulatory approval of elobixibat outside of EA Pharma's licensed territory for that specified liver disease, or otherwise approves that EA Pharma conduct a clinical trial in that specified liver disease.

Payment Terms. As of March 1, 2019, we have received $45.4 million in upfront and milestone payments from EA Pharma under the agreement. We are eligible to receive additional amounts of up to $4.9 million if a specified regulatory event is achieved for elobixibat. In addition, subject to the terms of the royalty interest acquisition agreement, or RIAA, with HealthCare Royalty Partners III, L.P., or HCR, described below, we may become eligible under the license agreement to receive up to $31.9 million if specified sales milestones are achieved for elobixibat and stepped royalties beginning in the high single digits on any future net sales of elobixibat.

EA Pharma's obligation under the license agreement to pay royalties for elobixibat expires on a country-by-country basis on the later of expiration of the patent rights in a country that have a specified scope and that we either licensed to EA Pharma or, subject to a specified term limit, are developed by EA Pharma, alone or together with us, in the course of its activities under the agreement or expiration of regulatory exclusivity for elobixibat in that country. The Japanese patent rights with respect to elobixibat that we licensed to EA Pharma expire between 2026 and 2029. In addition, we have two pending patent applications on specific crystal polymorphs of elobixibat that, if issued in Japan, will expire in 2034 and 2035, respectively. Royalty rates are subject to reduction under the agreement in specified circumstances, including in any country if elobixibat is subject to generic competition that exceeds a specified level, if the bulk price for unformulated elobixibat purchased from us for use in Japan exceeds a specified threshold or if EA Pharma licenses patent rights from any third party under circumstances where it is legally required to do so to commercialize elobixibat in its licensed field in a particular country in its licensed territory.

Development and Commercialization. EA Pharma is responsible for funding and using commercially reasonable efforts to execute the development and commercialization of elobixibat in its licensed field and licensed territory pursuant to agreed territory development and commercialization plans that are updated from time to time. In Japan, EA Pharma co-markets elobixibat with Mochida pursuant to a sublicense agreement and co-promotes elobixibat with Eisai. A joint development committee and a joint commercialization committee, each comprising representatives of each company, oversees activities under the agreement.

EA Pharma is responsible for commercial manufacture and supply of elobixibat in its licensed territory.

Restrictions. EA Pharma is not permitted to conduct clinical development or commercialize elobixibat outside of its licensed field of use or licensed territory. We are not permitted to commercialize elobixibat for any field of use in EA Pharma's licensed territory. In addition, if we determine to develop elobixibat in a liver disease outside of EA Pharma's licensed territory, our development is subject to specified restrictions on clinical trial design. After the first commercial

sale of elobixibat in any country in EA Pharma's licensed field, neither we nor EA Pharma may commercialize a different product for the treatment of chronic constipation or IBS-C in that country, subject to specified exceptions.

Term and Termination. Either we or EA Pharma can terminate the agreement in its entirety or on a country-by-country basis if the other party materially breaches the agreement and the breach is not cured within a specified period. Also, either we or EA Pharma can terminate the agreement in its entirety if a specified bankruptcy-related event with regard to the other party occurs. EA Pharma also has the right to terminate the agreement in its entirety or on a country-by-country basis (except for Japan) for any reason upon 180 days' notice. The rights and obligations of the parties that survive termination of the agreement vary depending on the basis for the termination.

Royalty Monetization Agreement with HCR

In December 2017, we entered into an RIAA with HCR. Pursuant to the RIAA, HCR paid us $45 million, net of certain transaction expenses, and we are eligible for an additional $15 million if a specified sales milestone is achieved for elobixibat in Japan. Under the RIAA, we sold in return our right to receive all royalties for elobixibat in Japan, and sales milestones for elobixibat in Japan or other countries in the licensed territories that may become payable by EA Pharma pursuant to our license agreement with EA Pharma, up to a specified maximum amount, or the Cap Amount, equal to 175% of the amount paid by HCR to us under the RIAA plus certain patent-related expenses (if such patent-related expenses become payable by HCR). The RIAA provides that, if the Cap Amount is reached, we will again become eligible to receive royalties and sales milestones for elobixibat from EA Pharma under the terms of the license agreement. We also have the right, but not the obligation, to pay to HCR at any time an amount that, when added to all royalties and sales milestones for elobixibat theretofore received by HCR under the RIAA, equals the Cap Amount, in which case we will again become eligible to receive royalties and sales milestones for elobixibat under the terms of the license agreement.

The RIAA requires us to take certain actions with respect to the elobixibat royalties and sales milestones and with respect to our license agreement with EA Pharma and contains certain representations and warranties, covenants, indemnification obligations and other provisions that are customary for a royalty monetization transaction. In addition, for protective purposes only, we (specifically, Albireo Pharma, Inc., Albireo AB and Elobix AB) have agreed to grant HCR a precautionary security interest in specified assets related to elobixibat, but only in the event that, notwithstanding the parties' intentions, the transfer contemplated by the RIAA is held by a court of competent jurisdiction not to be a true sale.

Terminated License Agreement with Ferring International Center S.A.

We entered into a license agreement with Ferring International Center S.A., or Ferring, for the development and commercialization of elobixibat outside of the territories licensed to EA Pharma in July 2012, following completion of our Phase 2b clinical trial of elobixibat to treat CIC. Pursuant to the agreement, Ferring commenced a Phase 3 clinical program of elobixibat to treat CIC. In May 2014, Ferring stopped two Phase 3 clinical trials of elobixibat that Ferring had been conducting due to an issue related to the distribution of study drug to study sites that was unrelated to the performance of elobixibat. Subsequently, in March 2015, Ferring terminated the agreement, effective in September 2015. As a result of the termination of the agreement, all licenses that we granted to Ferring under the license agreement terminated and commercial rights to elobixibat in Ferring's licensed territory reverted to us. In addition, Ferring was required, among other things, to assign to us all rights to all regulatory submissions and approvals controlled by Ferring pertaining to elobixibat in the licensed territory and to grant to us an exclusive right of reference to data, and specified licenses to data and technology, related to elobixibat for the development and commercialization of elobixibat in its licensed field. Notwithstanding the termination of the license agreement, Ferring may be entitled to low single-digit royalty payments on net sales of elobixibat on a country-by-country and product-by-product basis in specified circumstances.

Patents and Proprietary Rights

We actively seek to protect the proprietary technology that we consider important to our business, including compositions and forms and their methods of use in the United States, Europe and other jurisdictions internationally that we consider key pharmaceutical markets. We also rely upon trade secrets and contracts to protect our proprietary information.

As of March 1, 2019, our patent estate included 13 issued patents and 23 pending patent applications in the United States and approximately 360 counterpart patents and patent applications in other jurisdictions, including eight European regional issued patents and two Patent Cooperation Treaty, or PCT, applications which allow us to seek corresponding patent protection worldwide. The actual protection afforded by a patent varies from country to country and depends upon many factors, including the type of patent, the scope of its coverage and the availability of legal remedies in a particular jurisdiction.

We consider the following United States, European (EP) and, in the case of elobixibat, Japanese (JP) patents to be particularly important to the protection of our clinical-stage product candidates.

Product Candidate	Summary Description	Expiration Date
A4250	Composition of matter of A4250	September 2022
	Method of using certain IBAT inhibitor(s) to treat certain liver diseases	November 2031
	Method of using certain IBAT inhibitor(s) in combination with a bile acid binder to treat certain liver diseases	November 2031 (EP) (pending in US)
	Crystal modifications of A4250	June 2039 (priority pending)
	Formulations of A4250	June 2039 (priority pending)
Elobixibat	Composition of matter of elobixibat	December 2021 (EP, JP); August 2022 (US)
	Method of using an IBAT inhibitor to treat Chronic Idiopathic Constipation or Irritable Bowel Syndrome with Constipation	April 2024
	Crystal modifications of elobixibat	April 2034
	Crystal modifications of elobixibat	October 2035 (US, pending in EP, JP)
	Method of using certain IBAT inhibitor(s) to treat NASH	November 2031
A3384	Pharmaceutical formulations comprising cholestyramine	February 2037 (pending in US EP), August 2038 (PCT pending in US)

We also have issued patents and pending patent applications with equivalent or substantially comparable protection for our product candidates in jurisdictions internationally that we consider key pharmaceutical markets.

The patent expiration dates referenced above do not reflect any potential patent term extension that we may receive for the United States under The United States Drug Price Competition and Patent Term Restoration Act of 1984, known as the Hatch-Waxman Act, or similar patent term extension legislation in Europe and Japan. The Hatch-Waxman Act generally permits a patent extension term of up to five years as compensation for patent term lost during the FDA regulatory review process. Patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of FDA approval. The patent term restoration period is generally one-half of the time between the effective

date of an investigational new drug application, or IND, and the submission date of a new drug application, or NDA, plus the time between the submission date and approval date of an NDA. Typically, only one patent applicable to an approved drug is eligible for an extension, and, with limited exceptions, the extension must be applied for prior to expiration of the patent. The United States Patent and Trademark Office, in consultation with the FDA, reviews and approves applications for patent term extension.

In the European Economic Area (EEA; the European Union member countries plus Iceland, Liechtenstein and Norway), Regulation (EC) No 469/2009 generally permits an extension of the patent term for a drug as compensation for the patent term lost during the regulatory review process by the European Medicines Agency, or EMA or the national drug agencies. The term of a supplementary protection certificate, or SPC, corresponds to the period between the filing date of the patent and the date of the first Marketing Authorization in the EEA, reduced by a period of 5 years. An SPC may extend the patent term for an approved drug up to five years, but the remaining patent term may not exceed 15 years from the date of the first Marketing Authorization. Only one patent that covers the approved drug is eligible for an SPC. Applications for an SPC are reviewed and approved by the national patent offices of the EEA countries, and must be lodged within six months of the authorization date for the drug in each EEA country (or within six months of the grant of the patent, in case the Marketing Authorization is granted first).

In Japan, the Japanese Pharmaceutical Affairs Law generally permits the extension of the patent term for a drug as compensation for patent term lost during the regulatory review process by the Japanese PMDA. The patent term extension corresponds to the period from the date of the start of clinical trials or the date of patent registration, whichever is later, until one day prior to the date of approval for the drug. The term of a patent can be extended for up to five years, irrespective of the remaining natural term of the patent as of the date of approval. Each patent that covers the active ingredient in the approved drug, or a method of using the approved drug in the approved indication, is eligible for the extension, which means that, for any particular drug, multiple patents may be extended. The extension must be applied for prior to expiration of the patent and within three months from the date of approval. The Japanese Patent Office reviews and approves applications for patent term extension.

Sales and Marketing

We currently do not have a commercial organization for the marketing, sales and distribution of pharmaceutical products. We intend to build the commercial infrastructure necessary to effectively support the commercialization of A4250 in the United States and Europe, if A4250 is approved for PFIC or any other pediatric cholestatic liver disease or disorder. We believe that our commercial organization can be modest in size and targeted to the relatively small number of specialists in the United States and Europe who treat children with orphan cholestatic liver disease.

The commercial infrastructure for orphan products typically consists of a targeted, specialty sales force that calls on a limited and focused group of physicians supported by sales management, internal sales support, an internal marketing group and distribution support. Additional capabilities important to the marketplace include the management of key accounts such as managed care organizations, group purchasing organizations, specialty pharmacies, government accounts and reimbursement support. Based on the number of physicians that treat orphan pediatric cholestatic liver diseases and disorders, we believe that we can effectively target the physician audience for A4250 in the United States and Europe by establishing a sales force either internally or by contract. To develop the appropriate commercial infrastructure, we will have to invest significant amounts of financial and management resources, some of which may be committed prior to any confirmation that A4250 will be approved.

Outside of the United States and Europe, we plan to selectively utilize collaborations, distribution or other marketing arrangements with third parties to commercialize A4250 in any approved indication(s). Likewise, we intend to selectively seek alliances and collaborations to assist us in furthering the development or commercialization of product candidates, such as A3384 and, potentially, elobixibat, targeting large primary care markets that must be served by large sales and marketing organizations.

Manufacturing

We do not own or operate, and currently have no plans to establish, manufacturing facilities for the production of clinical or commercial quantities of A4250, elobixibat, A3384 or any of our other product candidates. We currently rely, and expect to continue to rely, on third parties for the manufacture of our product candidates and any products that we may develop.

We currently engage a single third-party manufacturer to provide the active pharmaceutical ingredient, or API, for A4250 and elobixibat. We also currently engage single third-party manufacturers to provide fill and finish services for the final drug product formulation of each of A4250, elobixibat and A3384 for use in our clinical trials.

We obtain the supplies of our API and drug products from these manufacturers pursuant to agreements that include specific supply timelines, quality and volume expectations. We obtain the supplies of our product candidates from these manufacturers under master services contracts and specific work orders. However, we do not have long-term supply arrangements in place. We do not currently have arrangements in place for redundant supply or a second source for API for any of A4250, elobixibat or A3384. If any of our current manufacturers becomes unavailable to us for any reason, we believe that there are a number of potential replacements, although we might incur some delay in identifying and qualifying such replacements.

A4250 and elobixibat are organic compounds of low molecular weight, and are referred to as "small molecules." A3384 is a specialized formulation of cholestyramine, which is a polymer. A polymer is a chemical compound made up of small molecules arranged in a repeating structure to form a larger molecule. We have selected these compounds based on their potential efficacy and safety, although they are also associated with reasonable cost of goods. We expect to continue to develop product candidates that can be produced cost-effectively at contract manufacturing facilities.

Competition

The biotechnology and pharmaceutical industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. We face potential competition from many different sources, including major pharmaceutical, specialty pharmaceutical and biotechnology companies, academic institutions, government agencies and private and public research institutions. Any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future.

Many of our competitors may have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient enrollment for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs. Smaller or early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with larger or more established companies.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Our competitors also may obtain marketing approvals for their products more rapidly than we obtain approval for our products. In addition, our ability to compete may be affected because in some cases insurers or other third-party payors seek to encourage the use of generic products. This may have the effect of making branded products less attractive, from a cost perspective, to buyers.

The key competitive factors affecting the success of our product candidates are likely to be their efficacy, safety, tolerability, convenience, price and the availability of coverage and reimbursement from government and other third-party payors.

We are aware of other companies that are developing product candidates that, like A4250 and elobixibat, act via IBAT inhibition. Shire plc's SHP625, also known as maralixibat, and formerly known as LUM001 from Lumena Pharmaceuticals, was studied in Phase 2 clinical trials in PFIC and ALGS. In June 2016, Shire announced that the FDA granted breakthrough therapy designation for SHP625 for PFIC, type 2. Shire's SHP626, also known as volixibat, was in Phase 2 development as a treatment for NASH. In November 2018, Shire announced that it licensed exclusive global rights to maralixibat and volixibat to Mirum Pharmaceuticals, Inc. a private company. Mirum has announced plans to initiate Phase 3 trials with maralixibat in PFIC and ALGS in 2019.GlaxoSmithKline's GSK2330672, which GlaxoSmithKline has announced an intent to divest, is at the Phase 2 clinical development stage as a treatment for pruritus in patients with PBC.

The competition in our target indications includes the following.

PFIC and other pediatric cholestatic liver diseases and disorders. For many cholestatic liver diseases and disorders, including in particular PFIC, there are no approved therapies. With regard to the pruritus that is characteristic of these diseases, symptomatic off-label treatment with bile acid sequestrants, such as cholestyramine (marketed as Colestyr, Efensol, Ipocol, Kolestran, Lipocol, Olestyr, Prevalite or Quantalan in various countries), typically provides only modest relief. Bristol Myers Squibb has discontinued manufacture of Questran, but generic versions of the drug are marketed by Upsher-Smith Laboratories, Inc., Par Pharmaceutical Companies, Inc. and Sandoz, the generic pharmaceuticals division of Novartis AG.

A number of other drugs, including UDCA, a bile acid, rifampin, an antibiotic derivative, and naltrexone, an opioid antagonist, are used off-label for patients suffering from cholestatic liver disease. Additionally, surgical interventions, such as PEBD surgery, and external liver filtering procedures are also employed in an attempt to lower bile acid levels, manage pruritus and improve measures of liver function.

As noted above, Mirum plans to initiate Phase 3 trials for maralixibat as a treatment for PFIC and ALGS in 2019. In addition, Intercept Pharmaceuticals' obeticholic acid or OCA, is approved in the United States in combination with UDCA, or as a monotherapy for patients unable to tolerate UDCA, to treat PBC. OCA is also in Phase 2 development as a treatment for biliary atresia.

NASH. There are currently no drugs approved for the treatment of NASH. There are several marketed therapeutics that are currently used off-label for the treatment of NASH, such as vitamin E (an antioxidant), insulin sensitizers (e.g., metformin), antihyperlipidemic agents (e.g., gemfibrozil), pentoxifylline and UDCA, but none has been clearly shown in clinical trials to show a significant reversal in liver fibrosis. Product candidates in Phase 3 clinical development in NASH include Intercept's OCA, Genfit SA's PPAR alpha/delta agonist (elafibranor), Gilead Sciences, Inc.'s ASK-1 inhibitor (selonsertib) and Allergan plc's dual CCR2 and CCR5 inhibitor (cenicriviroc). Madrigal Pharmaceuticals, Inc. has announced plans to initiate a Phase 3 clinical program in NASH with its thyroid hormone receptor selective agonist, MGL-3196. There are many other product candidates in or believed to be in Phase 2 clinical development in NASH.

Chronic Constipation. Linaclotide, marketed by Ironwood Pharmaceuticals, Inc. and Allergan as Linzess in the United States and as Constella in Europe, is approved in the United States for the treatment of CIC and IBS-C and in Europe for the treatment of IBS-C. Linaclotide is also approved for the treatment of IBS-C in Japan, where it is marketed by Astellas. Linaclotide targets guanylate cyclase C in the intestines and, by doing so, induces intestinal chloride secretion, which results in the outpouring of water into the intestine. The primary side effect of linaclotide is diarrhea. In addition, lubiprostone, which is marketed in the United States as Amitiza by Takeda Pharmaceutical Company Limited, is approved in the United States for the treatment of CIC, IBS-C and opioid-induced constipation. Amitiza is also approved for the treatment of CIC in the United Kingdom and Switzerland, and for the treatment of chronic constipation in Japan, where it is marketed by Mylan, N.V. Amitiza binds selectively to and activates the type-2 chloride channel in the intestine releasing chloride and water into the intestine. The primary side effect of Amitiza is nausea. Prucalopride, marketed by Shire in the United States as Motegrity and in the European Union as as Resolor, is a motility agent approved the treatment of CIC.. Motegrity and Resolor are associated with a high rate of headaches, and belong to a class of drugs known as 5-HT receptor drugs that has been linked to cardiovascular safety issues.

Numerous OTC products are available for constipation. These include psyllium husk (such as Metamucil), methylcellulose (such as Citrucel), calcium polycarbophil (such as FiberCon), lactulose (such as Cephulac), polyethylene glycol (such as MiraLax), sennosides (such as Exlax), bisacodyl (such as Ducolax), docusate sodium (such as Colace), magnesium hydroxide (such as Milk of Magnesia), saline enemas (such as Fleet) and sorbitol. Given the low barriers to access, many CIC sufferers first try OTC fiber and laxatives, but these options are not sufficiently effective for many people.

In addition, Synergy Pharmaceuticals, Inc. has a product known as plecanatide, marketed as Trulance, that is approved in the United States to treat CIC and IBS-C. In December of 2018, Synergy filed a voluntary petition for reorganization under Chapter 11 of the U.S. Code with the U.S. Bankruptcy Court for the Southern District of New York. On February 26, 2018, Bausch Health Companies Inc. announced that it was selected as the successful bidder to acquire certain of Synergy's assets for a cash purchase price of approximately $195 million and the assumption of certain of Synergy's liabilities. Plecanatide is, like linaclotide, a guanylate cyclase-C agonist. Ardelyx, Inc. has a product candidate, tenapanor, for which it submitted a new drug application for marketing authorization to the FDA in September 2018. Tenapanor inhibits the sodium transporter NHE3 and reduces sodium uptake from the gut to increase the secretion of water in the intestines.

BAM. There are currently no approved drugs in the United States for the treatment of BAM. The most commonly used off-label treatment has been a bile acid sequestrant/resin, such as conventional cholestyramine (which is approved in some countries in Europe to treat diarrhea associated with certain GI conditions) or colestipol, to keep bile acids from stimulating secretion in the colon. However, the benefits of conventional cholestyramine and colestipol are limited because many patients cannot tolerate these medications because of the texture and taste or because they worsen the diarrhea or cause intolerable nausea, heartburn, wind or bloating. Another bile acid sequestrant sometimes used off label to treat to BAM is colesevelam, a cholesterol-lowering medicine marketed by Daiichi Sankyo Inc. as Welchol in the United States and by Genzyme Europe B.V. as Cholestagel in the European Union. Colesevelam is marketed in a tablet form that has fewer tolerability issues than other bile acid sequestrants, but its utility may be limited because it prevents absorption of other medications and important fat soluble vitamins. In addition, obeticholic acid has previously been studied by Intercept in a Phase 2 clinical trial as a treatment for BAM.

Patients with BAM following ileal resection surgery may also have a more generalized fat malabsorption as part of a short-bowel syndrome. In these patients, a low-fat diet supplemented with medium-chain triglycerides or cholylsarcosine, a synthetic cholic acid conjugate, may be used. Patients with BAM secondary to Crohn's ileitis may be treated with glucocorticoid, a steroid hormone. Microscopic colitis patients may be given budesonide, a glucocorticoid steroid. Patients with BAM secondary to small intestinal bacterial overgrowth may require antibiotic therapy.

Government Regulation

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

Review and Approval of Drugs in the United States

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

restitution, disgorgement of profits, or civil or criminal investigations and penalties brought by the FDA and the Department of Justice, or DOJ, or other governmental entities.

An applicant seeking approval to market and distribute a new drug product in the United States must typically undertake the following:

- completion of preclinical laboratory tests, animal studies and formulation studies in compliance with the FDA's good laboratory practice, or GLP, regulations;
- submission to the FDA of an IND, which must take effect before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, representing each clinical site before each clinical trial may be initiated;
- performance of adequate and well-controlled human clinical trials in accordance with good clinical practices, or GCP, to establish the safety and efficacy of the proposed drug product for each proposed indication;
- satisfactory completion of FDA audits of clinical trial sites to assure compliance with GCPs and the integrity of the clinical data;
- preparation and submission to the FDA of an NDA;
- review of the product by an FDA advisory committee, where appropriate or if applicable;
- satisfactory completion of one or more FDA inspections of the manufacturing facility or facilities at which the product, or components thereof, are produced to assess compliance with current Good Manufacturing Practices, or cGMP, requirements and to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality and purity;
- payment of user fees and securing FDA approval of the NDA; and
- compliance with any post-approval requirements, including Risk Evaluation and Mitigation Strategies, or REMS, and post-approval studies required by the FDA, if applicable.

Preclinical Studies

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

Human Clinical Trials in Support of an NDA

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

protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. An IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA raises concerns or questions related to a proposed clinical trial and places the trial on clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can be initiated or restarted (in cases when the trial is placed on clinical hold after it has already begun).

In addition, an IRB representing each institution that is participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct a continuing review and reapprove the trial at least annually. The IRB must review and approve, among other things, the trial protocol and informed consent information to be provided to clinical trial subjects. An IRB must operate in compliance with FDA regulations. Information about certain clinical trials, including details of the protocol and eventually study results, also must be submitted within specific timeframes to the National Institutes of Health for public dissemination on the ClinicalTrials.gov data registry.

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

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

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

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

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if SAEs occur. In addition, IND safety reports must be submitted to the FDA for any of the following: serious and unexpected suspected adverse reactions; findings from other clinical trials or animal or *in vitro* testing that suggest a significant risk in humans exposed to the drug; and any clinically important increase in the case of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution, = if the clinical trial is not being conducted in accordance with the clinical protocol or GCP or if the drug has been associated with unexpected serious harm to patients. The FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the clinical data submitted.

Submission of an NDA to the FDA

Assuming successful completion of required clinical testing and other requirements, the results of the preclinical studies and clinical trials, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA, which requests approval to market the drug product for one or more indications. Under federal law, the fee for the submission of an NDA for which clinical data is required exceeds $2.5 million for FY2019, and the sponsor of an approved NDA is also subject to an annual program fee, currently exceeding $309,000 per program. These fees are typically increased annually, but exemptions and waivers may be available under certain circumstances (such as a waiver for the first human drug application submitted by a qualifying small business and exemptions for orphan products).

The FDA conducts a preliminary review of an NDA within 60 days of its receipt and informs the sponsor by the 74th day after the FDA's receipt of the submission whether the application is sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. After the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA has agreed to specified performance goals in the review process of NDAs. Most such applications are meant to be reviewed within ten months from the date the NDA is accepted for filing, and most applications for "priority review" products are meant to be reviewed within six months from the date the NDA is accepted for filing. The review process may be extended by the FDA for three additional months to consider new information or in the case of a clarification provided by the applicant to address an outstanding deficiency identified by the FDA following the original submission.

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

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

The FDA often refers an application for a new drug to an advisory committee. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making final approval decisions about a particular NDA.

Fast Track, Breakthrough Therapy and Priority Review Designations

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

Specifically, the FDA may grant a product the fast track designation if it is intended, whether alone or in combination with one or more other drugs, for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition. For fast track products, sponsors may have greater interactions with the FDA and the FDA may initiate review of sections of a fast track product's NDA before the application is complete. This rolling review may be available if the FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a fast track product may be effective. The sponsor must also provide, and the FDA must approve, a schedule for the submission of the remaining information and the sponsor must pay applicable user fees. However, the FDA's time period goal for reviewing a fast track product application does not begin until the last section of the NDA is submitted. In addition, the fast track designation may be

withdrawn by the sponsor or rescinded by the FDA if the designation is no longer supported by data emerging in the clinical trial process. In September of 2018, the FDA granted fast track designation to A4250 for the treatment of pruritus associated with PFIC.

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

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

Accelerated Approval Pathway

The FDA may grant accelerated approval to a drug for a serious or life-threatening condition that generally provides a meaningful therapeutic advantage to patients over existing treatments and based upon a demonstration that the drug has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. The FDA may also grant accelerated approval for such a drug when the product has an effect on an intermediate clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality, or IMM, and that is reasonably likely to predict an effect on IMM or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. Drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval. Depending on the outcome of our double blind, Phase 3 clinical trial of A4250 in patients with PFIC, we may elect to pursue accelerated approval of A4250.

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

The accelerated approval pathway is most often used in settings in which the course of a disease is long and an extended period of time is required to measure the intended clinical benefit of a drug, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly. For example, accelerated approval has been used extensively in the development and approval of drugs for treatment of a variety of cancers in which the goal of therapy is generally to improve survival or decrease morbidity and the duration of the typical disease course requires lengthy and sometimes large clinical trials to demonstrate a clinical or survival benefit.

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

Rare Pediatric Disease Priority Review Voucher

The FDA may grant rare pediatric disease designation for indications in the treatment or prevention of a rare disease or condition that affects fewer than 200,000 individuals in the United States and that is a serious or life-threatening disease that primarily affects individuals aged from birth to 18 years, including age groups often called neonates, infants, children and adolescents. In June of 2018, the FDA granted a rare pediatric disease designation to A4250 for the treatment of PFIC. Under the FDCA, a sponsor who receives approval of an NDA for a product that is for the prevention or treatment of a rare pediatric disease and meets certain additional criteria, may qualify for a rare pediatric disease priority review voucher, or PRV. A PRV can be redeemed to receive priority review under an expedited timeframe for a subsequent marketing application for a different product. A PRV may also be sold or transferred from the initial sponsor to another sponsor and may be further transferred any number of times before it is used. Pursuant to the 21st Century Cures Act, FDA's authority to award rare pediatric disease PRVs has been extended until 2020 and until 2022 for products that receive rare pediatric disease designation by 2020.

The FDA's Decision on an NDA

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

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

Post-Approval Requirements

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

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

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

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

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

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, which regulates the distribution of drugs and drug samples at the federal level, and sets minimum standards for the registration and regulation of drug distributors by the states. Both the PDMA and state laws limit the distribution of prescription pharmaceutical product samples and impose requirements to ensure accountability in distribution. Most recently, the Drug Supply Chain Security Act, or DSCSA, was enacted with the aim of building an electronic system to identify and trace certain prescription drugs distributed in the United States. The DSCSA mandates phased-in and resource-intensive obligations for pharmaceutical manufacturers, wholesale distributors, and dispensers over a 10-year period that is expected to culminate in November 2023.

Abbreviated New Drug Applications for Generic Drugs

In 1984, with passage of the Hatch-Waxman Amendments to the FDCA, Congress authorized the FDA to approve generic drugs that are the same as drugs previously approved by the FDA under the NDA provisions of the statute. To obtain approval of a generic drug, an applicant must submit an abbreviated new drug application, or ANDA, to the agency. In support of such applications, a generic manufacturer may rely on the preclinical and clinical testing conducted for a drug product previously approved under an NDA, known as the reference listed drug, or RLD. Specifically, in order for an ANDA to be approved, the FDA must find that the generic version is identical to the RLD with respect to the active ingredients, the route of administration, the dosage form, and the strength of the drug. At the same time, the FDA must also determine that the generic drug is "bioequivalent" to the innovator drug. Under the statute, a generic drug

is bioequivalent to a RLD if "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug . . ."

Upon approval of an ANDA, the FDA indicates whether the generic product is "therapeutically equivalent" to the RLD in its publication "Approved Drug Products with Therapeutic Equivalence Evaluations," also referred to as the "Orange Book." In addition, by operation of certain state laws and numerous health insurance programs, the FDA's designation of therapeutic equivalence often results in substitution of the generic drug without the knowledge or consent of either the prescribing physician or patient.

Under the Hatch-Waxman Amendments, the FDA may not approve an ANDA until any applicable period of nonpatent exclusivity for the RLD has expired. The FDCA provides a period of five years of nonpatent data exclusivity for a new drug containing a new chemical entity. In cases where such exclusivity has been granted, an ANDA may not be submitted to the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification, in which case the applicant may submit its application four years after the original product approval. The FDCA also provides for a period of three years of exclusivity if the NDA includes reports of one or more new clinical investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the applicant and are essential to the approval of the application. This three-year exclusivity period often protects changes to a previously approved drug product, such as a new dosage form, route of administration, combination or indication.

Hatch-Waxman Patent Certification and the 30-Month Stay

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

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

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

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

Pediatric Clinical Trials and Exclusivity

Under the Pediatric Research Equity Act of 2003 an NDA or supplement thereto must contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. With enactment of the FDASIA in 2012, sponsors must also submit pediatric trial plans prior to the assessment data. Those plans must contain an outline of the proposed pediatric trial or trials the applicant plans to conduct, including trial objectives and design, any deferral or waiver requests and other information required by regulation. The applicant, the FDA, and the FDA's internal review committee must then review the information submitted, consult with each other, and agree upon a final plan. The FDA or the applicant may request an amendment to the plan at any time.

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

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

Orphan Drug Designation and Exclusivity

The FDA has granted orphan drug designation to A4250 for the treatment of PFIC, ALGS, biliary atresia and PBC. 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 designation request is granted, the FDA will disclose the identity of the therapeutic agent and its potential use. Orphan product designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

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

Patent Term Restoration and Extension

The term of a U.S. patent that covers a drug, biological product or approved medical device may also be eligible for patent term extension when FDA approval is granted, provided that certain statutory and regulatory requirements are met. The length of the patent term extension is related to the length of time the drug is under regulatory review while the patent is in force. For drugs, the Hatch-Waxman Act permits a patent term extension of up to five years beyond the

expiration date set for the patent. Patent extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, only one patent applicable to each regulatory review period may be granted an extension, and only those claims reading on the approved drug may be extended. Similar provisions are available in Europe and certain other foreign jurisdictions to extend the term of a patent that covers an approved drug, provided that statutory and regulatory requirements are met. The U.S. Patent and Trademark Office reviews and approves the application for any patent term extension or restoration in consultation with the FDA.

Regulation Outside the United States

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

Regulation and Marketing Authorization in the European Union

Clinical Trial Approval

Requirements for the conduct of clinical trials in the European Union including Good Clinical Practice, or GCP, are implemented in the Clinical Trials Directive 2001/20/EC and the GCP Directive 2005/28/EC. Pursuant to Directive 2001/20/EC and Directive 2005/28/EC, as amended, a system for the approval of clinical trials in the European Union has been implemented through national legislation of the member states. Under this system, approval must be obtained from the competent national authority of an E.U. member state in which a trial is planned to be conducted, or in multiple member states if the clinical trial is to be conducted in a number of member states. To this end, a CTA is submitted, which must be supported by an investigational medicinal product dossier, or IMPD, and further supporting information prescribed by Directive 2001/20/EC and Directive 2005/28/EC and other applicable guidance documents. Furthermore, a clinical trial may only be started after a competent ethics committee has issued a favorable opinion on the clinical trial application in that country.

In April 2014, the European Commission passed the new Clinical Trials Regulation, (EU) No 536/2014, which will replace the current Clinical Trials Directive 2001/20/EC. To ensure that the rules for clinical trials are identical throughout the European Union, the new E.U. clinical trials legislation was enacted as a regulation that is directly applicable in all E.U. member states. All clinical trials performed in the European Union are required to be conducted in accordance with the Clinical Trials Directive 2001/20/EC until the new Clinical Trials Regulation (EU) No 536/2014 becomes applicable.

The new Regulation (EU) No 536/2014 aims to simplify and streamline the approval of clinical trial in the European Union. The main characteristics of the regulation include:

- a streamlined application procedure via a single entry point, the E.U. portal;
- a single set of documents to be prepared and submitted for the application as well as simplified reporting procedures that will spare sponsors from submitting broadly identical information separately to various bodies and different member states;

- a harmonized procedure for the assessment of applications for clinical trials, which is divided in two parts (Part I is assessed jointly by all member states concerned and Part II is assessed separately by each member state concerned);

- strictly defined deadlines for the assessment of clinical trial application; and

- the involvement of the ethics committees in the assessment procedure in accordance with the national law of the member state concerned but within the overall timelines defined by the Regulation (EU) No 536/2014.

PRIME Designation

The European Medicines Agency, or EMA, grants access to the Priority Medicines, or PRIME, program to investigational medicines for which it determines there to be preliminary data available showing the potential to address an unmet medical need and bring a major therapeutic advantage to patients. As part of the program, EMA provides early and enhanced dialogue and support to optimize the development of eligible medicines and speed up their evaluation, aiming to bring promising treatments to patients sooner. The EMA has granted access to the PRIME program at the "proof of concept" stage for A4250 to treat PFIC.

Marketing Authorization

Authorization to market a product in the member states of the European Union proceeds under one of four procedures: a centralized authorization procedure, a mutual recognition procedure, a decentralized procedure or a national procedure.

Centralized Authorization Procedure

The centralized procedure enables applicants to obtain a marketing authorization that is valid in all E.U. member states based on a single application. Certain medicinal products, including products developed by means of biotechnological processes, must undergo the centralized authorization procedure for marketing authorization, which, if granted by the European Commission, is automatically valid in all 28 E.U. member states. The EMA and the European Commission administer this centralized authorization procedure pursuant to Regulation (EC) No 726/2004.

Pursuant to Regulation (EC) No 726/2004, this procedure is mandatory for various types of products, including, among others, products that are designated as orphan medicinal products pursuant to Regulation (EC) No 141/2000.

The centralized authorization procedure is optional for other medicinal products if they contain a new active substance or if the applicant shows that the medicinal product concerned constitutes a significant therapeutic, scientific or technical innovation or that the granting of authorization is in the interest of patients in the European Union.

Administrative Procedure

Under the centralized authorization procedure, the EMA's Committee for Human Medicinal Products, or CHMP, serves as the scientific committee that renders opinions about the safety, efficacy and quality of medicinal products for human use on behalf of the EMA. The CHMP is composed of experts nominated by each member state's national authority for medicinal products, with an expert appointed to act as Rapporteur for the co-ordination of the evaluation with the possible assistance of a further member of the CHMP acting as a Co-Rapporteur. After approval, the Rapporteur(s) continue to monitor the product throughout its life cycle. The CHMP has 210 days to adopt an opinion as to whether a marketing authorization should be granted. The process usually takes longer in case additional information is requested, which triggers clock-stops in the procedural timelines. The process is complex and involves extensive consultation with the regulatory authorities of member states and a number of experts. When an application is submitted for a marketing authorization in respect of a drug that is of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation, the applicant may pursuant to Article 14(9) Regulation (EC) No 726/2004 request an accelerated assessment procedure. If the CHMP accepts such request, the time-limit of 210 days

will be reduced to 150 days but it is possible that the CHMP can revert to the standard time-limit for the centralized procedure if it considers that it is no longer appropriate to conduct an accelerated assessment. Once the procedure is completed, a European Public Assessment Report, or EPAR, is produced. If the opinion is negative, information is given as to the grounds on which this conclusion was reached. After the adoption of the CHMP opinion, a decision on the MAA must be adopted by the European Commission, after consulting the E.U. member states, which in total can take more than 60 days.

Conditional Approval

In specific circumstances, E.U. legislation (Article 14(7) Regulation (EC) No 726/2004 and Regulation (EC) No 507/2006 on Conditional Marketing Authorizsations for Medicinal Products for Human Use) enables applicants to obtain a conditional marketing authorization prior to obtaining the comprehensive clinical data required for an application for a full marketing authorization. Such conditional approvals may be granted for product candidates (including medicines designated as orphan medicinal products) if (1) the risk-benefit balance of the product candidate is positive, (2) it is likely that the applicant will be in a position to provide the required comprehensive clinical trial data, (3) the product fulfills unmet medical needs and (4) the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required. A conditional marketing authorization may contain specific obligations to be fulfilled by the marketing authorization holder, including obligations with respect to the completion of ongoing or new studies, and with respect to the collection of pharmacovigilance data. Conditional marketing authorizations are valid for one year, and may be renewed annually, if the risk-benefit balance remains positive, and after an assessment of the need for additional or modified conditions or specific obligations. The timelines for the centralized procedure described above also apply with respect to the review by the CHMP of applications for a conditional marketing authorization.

Marketing Authorization under Exceptional Circumstances

Under Article 14(8) Regulation (EC) No 726/2004, products for which the applicant can demonstrate that comprehensive data (in line with the requirements laid down in Annex I of Directive 2001/83/EC, as amended) cannot be provided (due to specific reasons foreseen in the legislation) might be eligible for marketing authorization under exceptional circumstances. This type of authorization is reviewed annually to reassess the risk-benefit balance. The fulfillment of any specific procedures/obligations imposed as part of the marketing authorization under exceptional circumstances is aimed at the provision of information on the safe and effective use of the product and will normally not lead to the completion of a full dossier/approval.

Market Authorizations Granted by Authorities of E.U. Member States

In general, if the centralized procedure is not followed, there are three alternative procedures as prescribed in Directive 2001/83/EC:

- The decentralized procedure allows applicants to file identical applications to several E.U. member states and receive simultaneous national approvals based on the recognition by E.U. member states of an assessment by a reference member state.

- The national procedure is only available for products intended to be authorized in a single E.U. member state.

- A mutual recognition procedure similar to the decentralized procedure is available when a marketing authorization has already been obtained in at least one E.U. member state.

A marketing authorization may be granted only to an applicant established in the European Union.

Pediatric Studies

Prior to obtaining a marketing authorization in the European Union, applicants have to demonstrate compliance with all measures included in an EMA-approved Pediatric Investigation Plan, or PIP, covering all subsets of the pediatric population, unless the EMA has granted a product-specific waiver, a class waiver, or a deferral for one or more of the measures included in the PIP. The respective requirements for all marketing authorization procedures are set forth in Regulation (EC) No 1901/2006, which is referred to as the Pediatric Regulation. This requirement also applies when a company wants to add a new indication, pharmaceutical form or route of administration for a medicine that is already authorized. The Pediatric Committee of the EMA, or PDCO, may grant deferrals for some medicines, allowing a company to delay development of the medicine in children until there is enough information to demonstrate its effectiveness and safety in adults. The PDCO may also grant waivers when development of a medicine in children is not needed or is not appropriate, such as for diseases that only affect the elderly population.

Before a marketing authorization application can be filed, or an existing marketing authorization can be amended, the EMA determines that companies actually comply with the agreed studies and measures listed in each relevant PIP.

In 2017, the PDCO agreed to our PIP for A4250 as a treatment for PFIC.

Periods of Authorization and Renewals

A marketing authorization is valid for five years in principle and the marketing authorization may be renewed after five years on the basis of a re-evaluation of the risk-benefit balance by the EMA or by the competent authority of the authorizing member state. To this end, the marketing authorization holder must provide the EMA or the competent authority with a consolidated version of the file in respect of quality, safety and efficacy, including all variations introduced since the marketing authorization was granted, at least six months before the marketing authorization ceases to be valid. Once renewed, the marketing authorization is valid for an unlimited period, unless the European Commission or the competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal. Any authorization which is not followed by the actual placing of the drug on the E.U. market (in case of centralized procedure) or on the market of the authorizing member state within three years after authorization ceases to be valid (the so-called sunset clause).

Orphan Drug Designation and Exclusivity

The European Commission, following an evaluation by the EMA's Committee for Orphan Medicinal Products, has designated A4250 as an orphan medicinal product for the treatment of PFIC, as well as for the treatment of PBC and ALGS. Pursuant to Regulation (EC) No 141/2000 and Regulation (EC) No. 847/2000, the European Commission can grant such orphan medicinal product designation to products for which the sponsor can establish that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10,000 people in the European Union, or a life threatening, seriously debilitating or serious and chronic condition in the European Union and that without incentives it is unlikely that sales of the drug in the European Union would generate a sufficient return to justify the necessary investment. In addition, the sponsor must establish that there is no other satisfactory method approved in the European Union of diagnosing, preventing or treating the condition, or if such a method exists, the proposed orphan drug will be of significant benefit to patients.

Orphan drug designation is not a marketing authorization. It is a designation that provides a number of benefits, including fee reductions, regulatory assistance, and the possibility to apply for a centralized E.U. marketing authorization, as well as ten years of market exclusivity following marketing authorization of the designated orphan drug. During this market exclusivity period, neither the EMA, the European Commission nor the member states can accept an application or grant a marketing authorization for a similar medicinal product. A "similar medicinal product" is defined as a medicinal product containing a similar active substance or substances as those contained in an authorized orphan medicinal product and that is intended for the same therapeutic indication. A "similar active substance" is defined as an active substance that is identical or has the same principal molecular structural features (but not necessarily all of the same molecular features) and acts via the same mechanism as the authorized orphan medicinal product. The

market exclusivity period for the authorized therapeutic indication may be reduced to six years if, at the end of the fifth year, it is established that the orphan designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity. In addition, a competing similar medicinal product may in limited circumstances be authorized prior to the expiration of the market exclusivity period, including if it is shown to be safer, more effective or otherwise clinically superior to the already approved orphan drug. Furthermore, a product can lose orphan designation and the related benefits, prior to us having obtained a marketing authorization, if it is demonstrated that the orphan designation criteria are no longer met.

Regulatory Data Protection

E.U. legislation also provides for a system of regulatory data and market exclusivity. According to Article 14(11) of Regulation (EC) No 726/2004, as amended, and Article 10(1) of Directive 2001/83/EC, as amended, upon receiving marketing authorization, new chemical entities approved on the basis of complete independent data package benefit from eight years of data exclusivity and an additional two years of market exclusivity. Data exclusivity prevents regulatory authorities in the European Union from referencing the innovator's data to assess a generic (abbreviated) application. During the additional two-year period of market exclusivity, a generic marketing authorization can be submitted, and the innovator's data may be referenced, but no generic medicinal product can be marketed until the expiration of the market exclusivity. The overall ten-year period will be extended to a maximum of 11 years if, during the first eight years of those ten years, the marketing authorization holder, or MAH, obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies. Even if a compound is considered to be a new chemical entity and the innovator is able to gain the period of data exclusivity, another company nevertheless could also market another version of the drug if such company obtained marketing authorization based on an MAA with a complete independent data package of pharmaceutical test, preclinical tests and clinical trials. However, products designated as orphan medicinal products enjoy, upon receiving marketing authorization, a period of ten years of orphan market exclusivity—see also "*Orphan Drug Designation and Exclusivity*." Depending upon the timing and duration of the E.U. marketing authorization process, products may be eligible for up to five years' supplementary protection certificates, or SPCs, pursuant to Regulation (EC) No 469/2009. Such SPCs extend the rights under the basic patent for the drug.

Regulatory Requirements After a Marketing Authorization has been Obtained

If we obtain authorization for a medicinal product in the European Union, we will be required to comply with a range of requirements applicable to the manufacturing, marketing, promotion and sale of medicinal products:

Pharmacovigilance and Other Requirements

We will, for example, have to comply with the E.U.'s stringent pharmacovigilance or safety reporting rules, pursuant to which post-authorization studies and additional monitoring obligations can be imposed. Other requirements relate, for example, to the manufacturing of products and APIs in accordance with good manufacturing practice standards. E.U. regulators may conduct inspections to verify our compliance with applicable requirements, and we will have to continue to expend time, money and effort to remain compliant. Noncompliance with E.U. requirements regarding safety monitoring or pharmacovigilance, or requirements related to the development of products for the pediatric population, can also result in significant financial penalties in the European Union. Similarly, failure to comply with the E.U.'s requirements regarding the protection of individual personal data can also lead to significant penalties and sanctions. Individual E.U. member states may also impose various sanctions and penalties in case we do not comply with locally applicable requirements.

Manufacturing

The manufacturing of authorized drugs, for which a separate manufacturer's license is mandatory, must be conducted in strict compliance with the EMA's cGMP requirements and comparable requirements of other regulatory bodies in the European Union, which mandate the methods, facilities and controls used in manufacturing, processing and packing of drugs to assure their safety and identity. The EMA enforces its cGMP requirements through mandatory

registration of facilities and inspections of those facilities. The EMA may have a coordinating role for these inspections although the responsibility for carrying them out rests with the member states' competent authority under whose responsibility the manufacturer falls. Failure to comply with these requirements could interrupt supply and result in delays, unanticipated costs and lost revenues, and could subject the applicant to potential legal or regulatory action, including but not limited to warning letters, suspension of manufacturing, seizure of product, injunctive action or possible civil and criminal penalties.

Marketing and Promotion

The marketing and promotion of authorized drugs, including industry-sponsored continuing medical education and advertising directed toward the prescribers of drugs or the general public, are strictly regulated in the European Union under Directive 2001/83/EC. The applicable regulations aim to ensure that information provided by holders of marketing authorizations regarding their products is truthful, balanced and accurately reflects the safety and efficacy claims authorized by the EMA or by the competent authority of the authorizing member state. Failure to comply with these requirements can result in adverse publicity, warning letters, corrective advertising and potential civil and criminal penalties.

Patent Term Extension

In order to compensate the patentee for delays in obtaining a marketing authorization for a patented product, an SPC may be granted extending the exclusivity period for that specific product by up to five years. Applications for SPCs must be made to the relevant patent office in each E.U. member state and the granted certificates are valid only in the member state of grant. An application has to be made by the patent owner within six months of the first marketing authorization being granted in the European Union (assuming the patent in question has not expired, lapsed or been revoked) or within six months of the grant of the patent (if the marketing authorization is granted first). In the context of SPCs, the term "product" means the active ingredient or combination of active ingredients for a medicinal product and the term "patent" means a patent protecting such a product or a new manufacturing process or application for it. The duration of an SPC is calculated as the difference between the patent's filing date and the date of the first marketing authorization, minus five years, subject to a maximum term of five years.

A six month pediatric extension of an SPC may be obtained where the patentee has carried out an agreed pediatric investigation plan, the authorized product information includes information on the results of the studies and the product is authorized in all member states of the European Union.

Brexit and the Regulatory Framework in the United Kingdom

On June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the European Union (commonly referred to as "Brexit"). Thereafter, on March 29, 2017, the country formally notified the European Union of its intention to withdraw pursuant to Article 50 of the Lisbon Treaty. The withdrawal of the United Kingdom from the European Union will take effect either on the effective date of the withdrawal agreement or, in the absence of agreement, two years after the United Kingdom provides a notice of withdrawal pursuant to the E.U. Treaty. Since the regulatory framework for pharmaceutical products in the United Kingdom covering quality, safety and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales and distribution of pharmaceutical products is derived from European Union directives and regulations, Brexit could materially impact the future regulatory regime which applies to products and the approval of product candidates in the United Kingdom. It remains to be seen how, if at all, Brexit will impact regulatory requirements for product candidates and products in the United Kingdom.

The United Kingdom has a period of a maximum of two years from the date of its formal notification to negotiate the terms of its withdrawal from, and future relationship with, the European Union. If no formal withdrawal agreement is reached between the United Kingdom and the European Union, then it is expected the United Kingdom's membership of the European Union will automatically terminate two years after the submission of the notification of the United Kingdom's intention to withdraw from the European Union. Discussions between the United Kingdom and the European Union focused on finalizing withdrawal issues and transition agreements are ongoing. However, limited progress to date

in these negotiations and ongoing uncertainty within the United Kingdom Government and Parliament sustains the possibility of the United Kingdom leaving the European Union on March 29, 2019 without a withdrawal agreement and associated transition period in place, which is likely to cause significant market and economic disruption.

Pharmaceutical Coverage, Pricing and Reimbursement

Sales of products approved by the FDA will depend, in part, on the extent to which the costs of the products will be covered by third-party payors, including government health programs in the United States such as Medicare and Medicaid, commercial health insurers and managed care organizations. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the product once coverage is approved. Third-party payors may limit coverage to specific products on an approved list, or formulary, which might not include all of the approved products for a particular indication.

In order to secure coverage and reimbursement for any product that might be approved for sale, a company may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA or other comparable regulatory approvals. A payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Third-party reimbursement may not be sufficient to maintain price levels high enough to realize an appropriate return on investment in product development.

In the European Union, pricing and reimbursement schemes vary widely from country to country. Some countries provide that drug products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of our product candidate to currently available therapies (so called health technology assessment, or HTA) in order to obtain reimbursement or pricing approval. For example, the European Union provides options for its member states to restrict the range of drug products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. E.U. member states may approve a specific price for a drug product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the drug product on the market. Other member states allow companies to fix their own prices for drug products but monitor and control prescription volumes and issue guidance to physicians to limit prescriptions. The downward pressure on health care costs in general, particularly prescription drugs, has become intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, there can be considerable pressure by governments and other stakeholders on prices and reimbursement levels, including as part of cost containment measures. Political, economic and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various E.U. member states, and parallel distribution (arbitrage between low-priced and high-priced member states), can further reduce prices. Any country that has price controls or reimbursement limitations for drug products may not allow favorable reimbursement and pricing arrangements.

Healthcare Law and Regulation

If our product candidates are approved in the United States, we will have to comply with various U.S. federal and state laws, rules and regulations pertaining to healthcare fraud and abuse, including anti-kickback laws and physician self-referral laws, rules and regulations. Violations of the fraud and abuse laws are punishable by criminal and civil sanctions, including, in some instances, exclusion from participation in federal and state healthcare programs, including Medicare and Medicaid. These laws include:

- the federal anti-kickback statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or paying remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made, in whole or in part, under a federal healthcare program such as Medicare and Medicaid;

- the federal False Claims Act imposes civil penalties, and provides for civil whistleblower or *qui tam* actions, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government;

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;

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

- the federal transparency requirements under the Physician Payments Sunshine Act require manufacturers of FDA-approved drugs, devices, biologics and medical supplies covered by Medicare or Medicaid to report, on an annual basis, to the Department of Health and Human Services information related to payments and other transfers of value to physicians and teaching hospitals and physician ownership and investment interests; and

- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by nongovernmental third-party payors, including private insurers.

Some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines, or the relevant compliance guidance promulgated by the federal government, in addition to requiring drug manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures to the extent that those laws impose requirements that are more stringent than the Physician Payments Sunshine Act. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Employees

As of March 1, 2019, we employed 39 full-time employees, of whom 13 hold Ph.D. or M.D. degrees, or the foreign equivalent. Of these employees, 23 were engaged in research and development and 16 were engaged in general and administrative functions. Of these employees, 11 were located in Sweden and 28 were located in the United States. Our employees in Sweden are subject to a collective bargaining agreement. We consider our relationship with our employees to be good.

Corporate Information

Our internet address is http://www.albireopharma.com. 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, are available to you free of charge through the Investors section of our website as soon as reasonably practicable after such materials have been electronically filed with, or furnished to, the SEC.

Item 1A. RISK FACTORS

An investment in shares of our common stock involves a high degree of risk. You should carefully consider the following information about these risks, together with the other information appearing elsewhere in this Annual Report on Form 10-K, including our consolidated financial statements and related notes thereto, before deciding to invest in our common stock. The occurrence of any of the following risks could have a material adverse effect on our business,

financial condition, results of operations and future growth prospects. In these circumstances, the market price of our common stock could decline, and you may lose all or part of your investment.

Risks Related to Our Financial Position and Need for Additional Capital

We have incurred significant losses since our inception. We expect to continue to incur losses and may never generate profits from operations or maintain profitability.

Since inception, we have incurred significant operating losses. Our net loss was approximately $46.1 million for the year ended December 31, 2018 and approximately $24.4 million for the year ended December 31, 2017. We had an accumulated deficit of $96.5 million as of December 31, 2018. To date, we have financed our operations primarily through issuances of shares of common stock, preference shares or convertible loan notes, upfront fees paid upon entering into or amending license agreements, payments received upon the achievement of specified milestone events under the license agreements, grants and venture debt borrowings. We have devoted substantially all of our efforts to research and development, including clinical trials. We have not completed the development of any drugs, although our licensee, EA Pharma Co., Ltd. (formerly Ajinomoto Pharmaceuticals Co., Ltd.), or EA Pharma, has received approval in Japan of our product candidate elobixibat to treat chronic constipation. We expect to continue to incur significant expenses and increasing operating losses for at least the next few years as we continue our development of, and seek marketing approvals for, our product candidates, prepare for and begin the commercialization of any approved products, and add infrastructure and personnel to support our product development efforts and operations as a public company in the United States. The net losses we incur may fluctuate significantly from quarter to quarter and year to year.

Our ability to generate profits from operations and thereafter to remain profitable depends heavily on:

- the scope, number, progress, duration, endpoints, cost, results and timing of clinical trials and nonclinical studies of our current or potential future product candidates, including in particular the scope, progress, duration, endpoints, cost, results and timing for initiation and completion of our Phase 3 clinical program for A4250 in patients with progressive familial intrahepatic cholestasis, or PFIC;

- our ability to raise sufficient funds to support the development and potential commercialization of our product candidates;

- the outcomes and timing of regulatory reviews, approvals or other actions;

- our ability to obtain marketing approval for our product candidates;

- whether and to what extent events giving rise to payments to us are achieved under our royalty interest acquisition agreement, or RIAA, with HealthCare Royalty Partners III, L.P., or HCR, or our license agreement with EA Pharma or any potential future licensee or collaborator;

- our ability to establish and maintain additional licensing, collaboration or similar arrangements on favorable terms and whether and to what extent we retain development or commercialization responsibilities under any new licensing, collaboration or similar arrangement;

- the success of any other business, product or technology that we acquire or in which we invest;

- our ability to maintain, expand and defend the scope of our intellectual property portfolio;

- our ability to manufacture any approved products on commercially reasonable terms;

- our ability to establish a sales and marketing organization or suitable third-party alternatives for any approved product; and

- the number and characteristics of product candidates and programs that we pursue.

Based on our current plans, we do not expect to generate significant revenue from product sales unless and until we or a potential future licensee or collaborator obtains marketing approval for, and commercializes, one or more of our current or potential future product candidates (other than elobixibat as a treatment for chronic constipation in Japan), which we do not expect to occur until at least 2021, if at all. Neither we nor a licensee may ever succeed in obtaining marketing approval for, or commercializing, our product candidates besides elobixibat as a treatment for chronic constipation in Japan and, even if we do, may never generate revenues that are significant enough to generate profits from operations. Even if we do generate profits from operations, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to generate profits from operations and remain profitable would decrease our value and could impair our ability to raise capital, expand our business, maintain our research and development efforts, diversify our product offerings or continue our operations. A decline in our value could also cause you to lose all or part of your investment.

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

Our operations to date have been limited to organization and staffing, developing and securing our technology, entering into licensing arrangements for elobixibat, raising capital and undertaking preclinical studies and clinical trials of our product candidates. Although our licensee, EA Pharma, has received approval in Japan of our product candidate elobixibat to treat chronic constipation, we have not yet demonstrated our ability to successfully complete development of any product candidate, obtain marketing approval, manufacture a commercial scale product, or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful product commercialization. Consequently, any predictions you make about our future success or viability may not be as accurate as they could be if we had a longer operating history.

Assuming we obtain marketing approval for any of our product candidates, we will need to transition from a company with a research and development focus to a company capable of supporting commercial activities. We may encounter unforeseen expenses, difficulties, complications and delays and may not be successful in such a transition.

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

We expect our research and development expenses to increase substantially in future periods, particularly as we advance the development of our product candidates in addition to A4250 as a treatment for patients with PFIC. In particular, we expect that our research and development expenses would increase if we conduct clinical trials of any or all of elobixibat for the treatment of nonalcoholic steatohepatitis, or NASH, A3384 for the treatment of bile acid malabsorption, or BAM, A4250 for the treatment of biliary atresia or in additional pediatric cholestatic liver diseases and disorders, or any product candidate advanced in our preclinical program in NASH or we initiate additional preclinical programs for potential future product candidates. In addition, if we obtain marketing approval for any of our product candidates that are not then subject to licensing, collaboration or similar arrangements with third parties, we expect to incur significant commercialization expenses related to product sales, marketing, distribution and manufacturing. Furthermore, we expect to incur additional costs associated with operating as a public company in the United States. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on attractive terms, we could be forced to delay, reduce or eliminate our research and development programs or any future commercialization efforts.

Our future capital requirements will depend on many factors, including:

- the costs, design, duration and any potential delays of the Phase 3 clinical trial of A4250 that may result from, among other things, the factors described below under " – The clinical trial designs, durations, endpoints and outcomes that will ultimately be required to obtain marketing approval of A4250 to treat PFIC patients are uncertain and, in any case, may vary among the FDA, EMA and other regulatory authorities

outside of the United States and European Union. Based on feedback that we have received from the FDA and the EMA, we expect both regulatory authorities to place a greater emphasis on the totality of the data from our Phase 3 clinical trial, including secondary endpoints, than may generally be expected. As a result, there is risk that, even if the primary endpoint of our Phase 3 clinical trial of A4250 for FDA evaluation purposes or for EMA evaluation purposes is met with statistical significance, the applicable regulatory authority may not find the overall results of our Phase 3 trial to be sufficient to support marketing approval of A4250 to treat PFIC, a symptom of PFIC such as pruritus or any other indication, and we may never receive marketing approval. Similar risks also apply for A3384, which is a product candidate for the treatment of BAM." and "If we experience any of a number of possible unforeseen events in connection with our clinical trials, potential marketing approval or commercialization of our product candidates, or entry into licensing, collaboration or similar arrangements, could be delayed or prevented.";

- the same factors that our ability to generate profits from operations and thereafter to remain profitable depend heavily on, as described above under "— We have incurred significant losses since our inception. We expect to continue to incur losses and may never generate profits from operations or maintain profitability.";

- the scope, number, progress, duration, cost, results and timing of clinical trials and nonclinical studies of our current or future product candidates;

- whether and to what extent milestone events are achieved under our license agreement with EA Pharma, our royalty interest acquisition agreement with HCR or any potential future licensee or collaborator;

- the outcomes and timing of regulatory reviews, approvals or other actions;

- our ability to obtain marketing approval for our product candidates;

- our ability to establish and maintain additional licensing, collaboration or similar arrangements on favorable terms and whether and to what extent we retain development or commercialization responsibilities under any new licensing, collaboration or similar arrangement;

- the success of any other business, product or technology that we acquire or in which we invest;

- our ability to maintain, expand and defend the scope of our intellectual property portfolio;

- our ability to manufacture any approved products on commercially reasonable terms;

- our ability to establish a sales and marketing organization or suitable third-party alternatives for any approved product;

- the number and characteristics of product candidates and programs that we pursue;

- the costs of acquiring, licensing or investing in businesses, product candidates and technologies;

- our need and ability to hire additional management and scientific and medical personnel;

- the costs to operate as a public company in the United States, including the need to implement additional financial and reporting systems and other internal systems and infrastructure for our business;

- market acceptance of our product candidates, to the extent any are approved for commercial sale; and

- the effect of competing technological and market developments.

Conducting preclinical testing and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain marketing approval and achieve product sales. In addition, our product candidates, if approved, may not achieve commercial success. Our commercial revenues, if any, will be derived from sales of products that will not be commercially available for sale by us for at least the next few years, if at all. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. In addition, we may seek additional capital due to favorable market conditions or strategic considerations, even if we believe that we have sufficient funds for our current or future operating plans. Additional financing may not be available to us on acceptable terms, or at all. The unavailability of additional financing on acceptable terms, or at all, would have an adverse effect on your investment.

Raising additional capital may cause dilution to our investors, restrict our operations or require us to relinquish rights to our technologies or product candidates.

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity offerings, licensing, collaboration or similar arrangements, grants and debt financings. We do not have any committed external source of funds. We filed a universal shelf registration statement on Form S-3 with the SEC, which was declared effective on December 5, 2017 and pursuant to which we registered for sale up to $125 million of any combination of our common stock, preferred stock, debt securities, warrants, rights, purchase contracts and/or units from time to time and at prices and on terms that we may determine, including up to $50 million of our common stock available for issuance pursuant to an at-the-market offering program sales agreement that we entered into with Cowen and Company, LLC, or Cowen, in October 2017. We refer to this registration statement as the 2017 Form S-3 and we refer to this sales agreement as the 2017 Sales Agreement. Subsequently, in February 2018, we sold 728,862 shares of our common stock for net proceeds of approximately $24.2 million pursuant to the 2017 Sales Agreement. On or about March 6, 2019, we expect to file a new universal shelf registration on Form S-3 with the SEC, pursuant to which we expect to register for sale up to $200 million of any combination of our common stock, preferred stock, debt securities, warrants, rights and/or units from time to time and at prices and on terms that we may determine, which we refer to as the 2019 Form S-3. On or about March 6, 2019, we intend to terminate the 2017 Sales Agreement and enter into a new sales agreement, which we refer to as the 2019 Sales Agreement, with respect to an at-the-market offering program under which we may offer and sell, from time to time at our sole discretion, shares of our common stock having an aggregate offering price of up to $50.0 million. Our issuance and sale, if any, of shares under the 2019 Sales Agreement that we intend to enter into are subject to the effectiveness of the 2019 Form S-3. We make no assurances as to if or when the 2019 Form S-3 will become effective or, if it does become effective, as to the continued effectiveness of the 2019 Form S-3. No additional securities registered under the 2017 Form S-3 will be offered or sold after the date of effectiveness of the 2019 Form S-3. This report shall not constitute an offer to sell or the solicitation of an offer to buy any shares under the 2019 Sales Agreement that we intend to enter into or any securities under the 2019 Form S-3 that we intend to file with the SEC, nor shall there be any sale of such securities in any state in which such offer, solicitation or sale would be unlawful prior to registration or qualification under the securities laws of any such state.

We may seek to raise additional capital at any time. To the extent that we raise additional capital through the sale of equity or convertible debt securities, your ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a holder of our common stock. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends or other distributions.

If we raise additional funds through licensing, collaboration or similar arrangements, we may have to relinquish valuable rights to our technologies, future revenue streams, research and development programs or product candidates or to grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings or other arrangements when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

The comprehensive tax reform bill could adversely affect our business and financial condition.

On December 22, 2017, President Trump signed into law the "Tax Cuts and Jobs Act," or the TCJA, that significantly reforms the Internal Revenue Code of 1986, as amended, or the Code. The TCJA, among other things, includes changes to U.S. federal tax rates, imposes significant additional limitations on the deductibility of interest and net operating loss carryforwards, allows for the expensing of capital expenditures, and puts into effect the migration from a "worldwide" system of taxation to a territorial system. We continue to examine the impact this tax reform legislation may have on our business. The overall impact of the TCJA is uncertain and our business and financial condition could be adversely affected. The impact of this tax reform on holders of our common stock is also uncertain and could be adverse. This report does not discuss any such tax legislation or the manner in which it might affect us or purchasers of our common stock. We urge our stockholders to consult with their legal and tax advisors with respect to such legislation and the potential tax consequences of investing in our common stock.

Inadequate funding for the FDA, the SEC and other government agencies, or a work slowdown or stoppage at those agencies as part of a broader federal government shutdown, could hinder their ability to hire and retain key leadership and other personnel, prevent new products and services from being developed or commercialized in a timely manner, or otherwise prevent those agencies from performing normal business functions on which the operation of our business may rely, which could negatively impact our business.

The ability of the FDA to review and approve new products can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept the payment of user fees, and statutory, regulatory and policy changes. Average review times at the agency have fluctuated in recent years as a result. In addition, government funding of the SEC and other government agencies on which our operations may rely, including those that fund research and development activities, is subject to the political process, which is inherently fluid and unpredictable.

Disruptions at the FDA and other agencies may also slow the time necessary for new drugs to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years, including beginning on December 22, 2018, the U.S. government has shut down several times and certain regulatory agencies, such as the FDA and the SEC, have had to furlough critical FDA, SEC and other government employees and stop critical activities. If a prolonged government shutdown recurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business. Further, future government shutdowns could impact our ability to access the public markets and obtain necessary capital in order to properly capitalize and continue our operations.

Risks Related to the Development and Commercialization of Our Product Candidates

We depend heavily on the success of our lead product candidate, A4250, which we are developing initially for the treatment of patients with PFIC and potentially also for other pediatric cholestatic liver diseases and disorders. If we are unable to commercialize A4250 or experience significant delays in doing so, our business will be materially harmed.

A4250 is in Phase 3 clinical development. Elobixibat has been approved in Japan for the treatment of chronic constipation, but we will not receive additional cash in respect of elobixibat in Japan unless and until HCR has received a specified amount under our RIAA. Our other most advanced product candidates are in Phase 2 or earlier-stage development.

Our ability to generate product revenues, which may not occur for at least the next few years, if at all, will depend heavily on the successful development and commercialization of A4250 as a treatment for patients with PFIC. Our ability to generate product revenues may also depend on the successful development and commercialization of elobixibat

to treat NASH or A3384 to treat BAM. The success of each of these product candidates will depend on a number of factors, including the following:

- our ability to obtain additional capital, whether from our RIAA with HCR or our license agreement with EA Pharma for elobixibat, from potential future licensing, collaboration or similar arrangements or from any future offering of our debt or equity securities;
- our ability to identify and enter into potential future licenses or other collaboration arrangements with third parties and the terms of the arrangements;
- completion of clinical development with successful outcomes;
- receipt of marketing approvals from applicable regulatory authorities;
- establishing commercial manufacturing arrangements with third-party manufacturers;
- obtaining and maintaining patent and trade secret protection and regulatory exclusivity;
- protecting our rights in our intellectual property portfolio;
- establishing sales, marketing and distribution capabilities;
- generating commercial sales of A4250, elobixibat or A3384, as applicable, if and when approved, whether alone or in collaboration with others;
- acceptance of A4250, elobixibat or A3384, as applicable, if and when approved, by patients, the medical community and third-party payors;
- effectively competing with other therapies; and
- maintaining an acceptable safety profile of A4250, elobixibat or A3384, as applicable, following approval.

If we do not achieve one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize A4250, elobixibat or A3384, which would materially harm our business.

If clinical trials of A4250 or any of our other product candidates fail to demonstrate safety and efficacy to the satisfaction of the U.S. Food and Drug Administration, or the FDA, or the European Medicines Agency, or the EMA, or do not otherwise produce favorable results, we may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of the applicable product candidate.

In connection with obtaining marketing approval from regulatory authorities for the sale of any product candidate, we must complete preclinical development and then conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans. Clinical trials are expensive, difficult to design and implement, can take many years to complete and are uncertain as to outcome. A failure of one or more clinical trials can occur at any stage of testing. The outcome of preclinical testing and early clinical trials may not be predictive of the success of later clinical trials. In particular, the small number of subjects and patients in our early clinical trials may make the results of these clinical trials less predictive of the outcome of later clinical trials. The design of a clinical trial can determine whether its results will support approval of a product, and flaws in the design of a clinical trial may not become apparent until the clinical trial is well advanced or completed. There is no assurance that we will be able to design and execute a clinical trial to support marketing approval. Moreover, preclinical and clinical data are often susceptible to varying

interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval of their products.

If we are required to conduct additional or longer clinical trials or other testing of A4250 or any of our other product candidates beyond those that we currently contemplate, if we are unable to successfully complete our clinical trials or other testing, or if the results of these clinical trials or tests are not positive or are only modestly positive or if there are safety concerns, we may:

- be delayed in obtaining marketing approval for our product candidates;
- not obtain marketing approval at all;
- obtain approval for indications or patient populations that are not as broad as we intended or desired;
- obtain approval with labeling that includes significant use or distribution restrictions or safety warnings, including boxed warnings;
- be subject to additional post-marketing testing requirements or restrictions; or
- have the product removed from the market after obtaining marketing approval.

Following consultation with the FDA and EMA, we are using change in pruritus as the primary endpoint for purposes of FDA evaluation and as a key secondary endpoint for EMA evaluation in our planned Phase 3 trial in PFIC patients. Because the assessment of pruritus relies on subjective feedback, it is challenging to evaluate and measure consistently. Moreover, there is no clinical experience with the two outcome instruments that we will use in the trial and either may not be considered adequately reliable or valid for use in PFIC patients.

The primary endpoint in our Phase 3 trial of A4250 in patients with PFIC, for FDA evaluation, and a key secondary endpoint for EMA evaluation, will be an assessment of change in pruritus. Because the assessment of pruritus relies on subjective caregiver feedback, it is challenging to evaluate and measure consistently and, for any patient, a caregiver-reported outcome may vary from the patient's self-reported outcome. The measure of pruritus can be influenced by factors outside of our control and can vary widely from measurement point to measurement point for a particular patient, from patient to patient and from site to site within a clinical trial. Moreover, patients given an inactive agent, or placebo, for comparison to A4250 in a clinical trial may perceive a change in pruritus that is greater than we anticipated when designing the trial or that is comparable to the change experienced by patients given A4250, which could obscure the effect of A4250 in the trial and reduce the likelihood that the trial will be successful.

We have developed caregiver-reported and patient-reported outcome instruments to assess pruritus in the Phase 3 PFIC trial. These outcome instruments, and the manner in which they will be analyzed, represent novel endpoints and measurement methodologies with which the FDA, EMA and other regulatory authorities have no experience. The degree of novelty or other limitations of these endpoints and methodologies may impact the likelihood that our Phase 3 PFIC trial, or any other future clinical trial of A4250, will be successful or otherwise delay or prevent marketing approval of A4250. In addition, we plan to establish the reliability and validity of the outcome instruments that we develop to meet applicable regulatory standards as part of the Phase 3 trial. The FDA or EMA may ultimately determine that either of these outcome instruments is not adequately reliable or valid for use with PFIC patients, whether because it was not applied by clinical investigators sufficiently consistently, was not sufficiently sensitive to detect varying degrees of pruritus, or for any other reason. If this were to occur, our ability to obtain marketing approval for A4250 would be delayed and we may never obtain marketing approval for A4250.

The clinical trial designs, durations, endpoints and outcomes that will ultimately be required to obtain marketing approval of A4250 to treat PFIC patients are uncertain and, in any case, may vary among the FDA, EMA and other regulatory authorities outside of the United States and European Union. Based on feedback that we have received from the FDA and the EMA, we expect both regulatory authorities to place a greater emphasis on the totality of the data from our Phase 3 clinical trial, including secondary endpoints, than may generally be expected. As a result, there is risk that, even if the primary endpoint of our Phase 3 clinical trial of A4250 for FDA evaluation purposes or for EMA evaluation purposes is met with statistical significance, the applicable regulatory authority may not find the overall results of our Phase 3 trial to be sufficient to support marketing approval of A4250 to treat PFIC, a symptom of PFIC such as pruritus or any other indication, and we may never receive marketing approval. Similar risks also apply for A3384, which is a product candidate for the treatment of BAM.

No product is currently approved for the treatment of PFIC in the United States, the European Union or, to our knowledge, any other jurisdiction or for the treatment of BAM in the United States, and there is limited clinical experience in PFIC and in BAM. Accordingly, there is not a well-established development path that, with positive outcomes in clinical trials, would be reasonably assured of receiving marketing approval for these indications.

Our Phase 3 PFIC program includes a single randomized, double blind, placebo controlled, multicenter clinical trial and an open label long-term extension study. The double blind trial is designed to enroll approximately 60 patients with PFIC (type 1 or 2), ages six months to 18 years, at sites in the United States, Canada, Europe, the Middle East and Australia. Patients will be assigned to receive either 40 μg/kg/day or 120 μg/kg/day of A4250, or placebo, for 24 weeks. Patients taking a stable dose of medication to manage pruritus when entering the trial will be permitted to continue such background medication during the trial, subject to specified exceptions. The trial has a primary endpoint for U.S. purposes, a different primary endpoint for E.U. purposes, and several secondary endpoints, including progression to surgery, change in growth markers and liver biochemistry variables, and others. The primary endpoint for FDA evaluation, and a key secondary endpoint for EMA evaluation, will be an assessment of change in pruritus using a proprietary tool that we have developed. The trial's primary endpoint for EMA evaluation, and a key secondary endpoint for FDA evaluation, will be serum bile acid responder rate, where a responder is a patient who achieves either a reduction in serum bile acid levels of 70% or more from baseline or a reduction in serum bile acid levels at least to an absolute level that is specified in between 50 and 100 μmol/l. Patients in the trial will have the opportunity to participate in the open label extension study to assess long-term safety and durability of response.

Based on feedback that we have received from the FDA and the EMA, we expect both regulatory authorities to place a greater emphasis on the totality of the data from our Phase 3 clinical trial, including secondary endpoints, than may generally be expected. As a result, there is risk that, even if the primary endpoint of our Phase 3 clinical trial of A4250 for FDA evaluation purposes or for EMA evaluation purposes is met with statistical significance, the applicable regulatory authority may not find the overall results of our Phase 3 trial to be sufficient to support marketing approval of A4250 to treat PFIC, a symptom of PFIC such as pruritus or any other indication, and we may never receive marketing approval.

Furthermore, the FDA has informed us that showing a clinically meaningful effect only on pruritus could support approval for the treatment of pruritus associated with PFIC and has indicated to us that meaningful improvements on one or more additional clinical benefit endpoints and/or corroborative real-world clinical evidence would be required to support approval for the treatment of PFIC itself. Certain secondary endpoints that we expect to use in our Phase 3 trial may be considered clinical benefit endpoints, including progression to surgery and change in growth markers. The likelihood that a treatment duration of 24 weeks will be long enough for a placebo controlled trial to demonstrate an effect of A4250 on any particular clinical benefit endpoint is uncertain, and, if not, FDA approval of A4250 could be limited to the treatment of pruritus in PFIC patients, if A4250 is approved at all.

To support marketing approval of a drug, the FDA requires a demonstration of efficacy based on an endpoint reflecting clinical benefit. However, under Subpart H regulations, the FDA can grant accelerated approval based on a surrogate endpoint that is reasonably likely to predict clinical benefit. If we elect to seek accelerated approval under Subpart H, the FDA (or EMA under its regulations) may determine that the surrogate endpoint, or that the outcome shown in the planned trial on the surrogate endpoint, does not establish a reasonable likelihood of predicting clinical benefit or otherwise is not sufficient to support approval, even if the surrogate endpoint is met with statistical

significance. For example, if we pursue an accelerated approval of A4250 under Subpart H and the results of the change in pruritus endpoint are not of a magnitude that will be clearly meaningful, it is possible that the FDA will not consider the result to be sufficient to support approval under the Subpart H pathway. If this occurs, our business would be materially harmed.

In addition, if we pursue an accelerated approval under Subpart H for A4250, we will be required to conduct a post-approval clinical outcomes trial to confirm its clinical benefit in PFIC. Whether our planned open label extension study will meet this requirement is uncertain. If not, and if we pursue accelerated approval under Subpart H, we would need to conduct an additional study, which is not currently planned. There can be no assurance that our open label extension study or any other post-approval trial that we conduct will confirm that the surrogate endpoint used for accelerated approval will eventually show an adequate correlation with clinical outcomes. If a clinical outcomes confirmatory trial that we conduct fails to show such adequate correlation, we may not be able to maintain any previously granted marketing approval for A4250 in PFIC that we may obtain.

We have selected serum bile acid responder rate as the primary endpoint for purposes of EMA evaluation and as a key secondary endpoint for FDA evaluation. To support the clinical utility of reduction in serum bile acids in the treatment of patients with PFIC, we are supporting an independent study pooling and analyzing long-term PFIC patient data from a number of leading PFIC academic centers, which we refer to as the PFIC Study Group. Should the data that are being accumulated by the PFIC Study Group come to a different conclusion than we anticipate about the relationship of serum bile acids to beneficial clinical outcomes, the EMA or the FDA may determine the results of the Phase 3 PFIC study not to be adequate to support approval.

Also, it is possible that any marketing authorization we may receive in the future from the EMA for A4250 for the treatment of PFIC could be conditional on post-authorization studies and not be considered a full authorization. Our ability to obtain and maintain conditional marketing authorization in the European Union will be limited to specific circumstances and subject to several conditions and obligations, if obtained at all, including the completion of a clinical outcomes trial to confirm the clinical benefit of A4250 in PFIC. Conditional marketing authorizations based on incomplete clinical data may be granted for a limited number of listed medicinal products for human use, including products designated as orphan medicinal products under European Union law, if (1) the risk-benefit balance of the product is positive, (2) it is likely that the applicant will be in a position to provide the required comprehensive clinical trial data, (3) unmet medical needs will be fulfilled and (4) the benefit to public health of the immediate availability on the market of the medicinal product outweighs the risk inherent in the fact that additional data are still required. Specific obligations, including with respect to the completion of ongoing or new studies, and with respect to the collection of pharmacovigilance data, may be specified in the conditional marketing authorization. Conditional marketing authorizations are valid for one year, and may be renewed annually, if the risk-benefit balance remains positive, and after an assessment of the need for additional or modified conditions.

The FDA and EMA generally require two pivotal clinical trials to support marketing approval of a drug. It is our objective to conduct a single Phase 3 clinical trial in patients with PFIC that, together with data from a long-term, open label extension study, forms the primary support for applications for marketing approval of A4250 in both the United States and European Union for treatment of patients with PFIC. If the FDA or EMA requires us to conduct additional clinical trials beyond the ones that we currently contemplate in order to support marketing approval of A4250 to treat patients with PFIC in the United States or European Union, it would result in a more expensive and potentially longer development program for A4250 than we currently contemplate, which could delay our ability to generate product revenues with A4250, interfere with our ability to enter into any potential licensing or collaboration arrangements with respect to this program, cause our value to decline, and limit our ability to obtain additional financing that may be necessary to complete the planned pivotal program. Even though it is our objective to conduct a single Phase 3 trial of A4250 as the basis, together with safety data from an extension study to evaluate long-term outcomes, for an application for marketing approval for A4250 in PFIC, either the FDA or the EMA may require that we meet the primary endpoint or endpoints in the trial at a higher level of statistical significance than would otherwise be required for a trial to be successful, which would reduce the likelihood of a positive trial.

Likewise, if we conduct any future clinical trial designed to support marketing approval of A3384 as a treatment for BAM, the FDA, EMA or any regulatory authority outside of the United States or the European Union may determine

that the designs or endpoints of the trial, or that the outcomes shown on any particular endpoints in the trial, are not sufficient to establish a clinically meaningful benefit for A3384 in the treatment of BAM or otherwise to support marketing approval, even if the primary endpoint or endpoints of the trial is met with statistical significance.

The design of our Phase 3 clinical trial of A4250 in patients with PFIC does not conform precisely in all respects to the recommendations or preferences expressed by either the FDA or EMA.

Although the feedback on our proposed Phase 3 clinical trial in patients with PFIC that we have received from the FDA and EMA is generally consistent, it is not identical and the design of our Phase 3 clinical trial of A4250 in patients with PFIC does not conform precisely in all respects to the recommendations or preferences expressed by either regulatory authority. As a result, there is increased risk that, even if we view the results of our planned trial as favorable, the FDA or EMA may not find the overall results to be sufficient to support marketing approval of A4250 to treat PFIC, a symptom of PFIC such as pruritus or any other indication.

Favorable results seen to date in clinical trials of A4250, including our open label Phase 2 trial of A4250 in patients with cholestatic liver disease, may not be predictive of favorable results in our Phase 3 clinical trial of A4250 in patients with PFIC, which will be placebo controlled and involve different doses, treatment duration, number of patients and outcome measures and may have other differences in design or execution.

A number of companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in later-stage clinical trials, even after promising results in earlier trials or in preclinical studies. Similarly, companies have experienced disappointing outcomes in later phases of a multiphase clinical trial, even after promising results in an early phase of the trial. A4250 has been evaluated in an open label Phase 2 trial in children with chronic cholestasis and pruritus and in an investigator-initiated Phase 2 clinical trial for the treatment of PBC. Data from our Phase 2 trial in children with chronic cholestasis and pruritus showed a reduction in serum bile acids in a substantial majority of patients and improvement in pruritus that was significantly correlated with the reduction in serum bile acids. In addition, based on data from the PBC trial that we received from the investigator, nine patients with pruritus received A4250 and all of them reported a reduction in pruritus. If the favorable findings on pruritus and serum bile acids seen in these two Phase 2 trials are not replicated in our Phase 3 trial of A4250 in patients with PFIC or in any other future trial of A4250 in patients with PFIC or other pediatric cholestatic liver disease or disorder, we may not obtain marketing approval for A4250 to treat any indication, in which case our business would be materially and adversely affected.

Our Phase 3 trial of A4250 in patients with PFIC will involve a greater number of patients, different outcome measures, doses and treatment duration and may have other differences in trial design, in addition to the difference in patient population, compared with either the prior pediatric chronic cholestasis trial or PBC trial. For example, our Phase 3 trial of A4250 is a randomized, double blind, placebo controlled, multicenter, clinical trial designed to enroll approximately 60 patients with PFIC (type 1 or 2), with a treatment duration of 24 weeks. The primary endpoint for FDA evaluation, and a key secondary endpoint for EMA evaluation, will be an assessment of change in pruritus. The primary endpoint for EMA evaluation, and a key secondary endpoint for FDA evaluation, will be serum bile acid responder rate, where a responder is a patient who achieves either a reduction in serum bile acid levels of 70% or more from baseline or a reduction of serum bile acid levels at least to an absolute level that is specified in between 50 and 100 μmol/l. Although we have assessed the effects of A4250 on serum bile acids in prior clinical trials of A4250, we have not previously utilized this serum bile acid responder rate endpoint. Moreover, we do not have any prior data regarding the effect of a placebo in patients with PFIC on serum bile acid levels, pruritus or any other outcome variable to guide the planning for our Phase 3 PFIC trial, which increases the risk that the trial will not be powered adequately to show a statistically significant separation between A4250 and placebo.

Furthermore, the specific caregiver-reported or patient-reported measures used to assess change in pruritus can vary from trial to trial. For example, the pruritus scales that were used in the PBC trial are not the same as the scales used in our trial in children with chronic cholestasis and pruritus, except that the visual analogue scale of itching, known as VAS-itch, is common to both trials. To assess change in pruritus in our Phase 3 trial of A4250 in patients with PFIC, we plan to use caregiver-reported and patient-reported outcome instruments that we have developed taking into account input from PFIC patients and their caregivers, which employ or rely on different questions or assessments, require a

different outcome to establish a positive response or are otherwise different from the outcome instruments used in our Phase 2 trial in children with chronic cholestasis. The differences in these instruments may reduce the likelihood that data from the Phase 2 trials of A4250 in children with chronic cholestasis or in PBC patients will be predictive of favorable results in the Phase 3 PFIC trial.

In addition, although we expect that patients in the planned trial of approximately the same weight will receive the same total dose of A4250, any difference in relative weights between particular patients receiving the same total dose of A4250 will result in a difference in weight-factored doses between those patients. This may reduce the likelihood that data from the Phase 2 trial will be predictive of favorable results in our planned PFIC trial.

If we experience delays or difficulties in the enrollment of patients in our Phase 3 clinical trial of A4250 in patients with PFIC, our receipt of marketing approval for A4250 could be delayed or prevented.

Recruiting patients for orphan pediatric liver diseases is challenging. We have previously experienced enrollment delays in our clinical trials of A4250 and are aware of at least one third-party clinical trial in PFIC patients that may be ongoing at the time of our Phase 3 trial of A4250 in patients with PFIC. If we are unable to locate and enroll a sufficient number of eligible patients to participate in clinical trials of our product candidates, we may not be able to initiate or continue the clinical trials. In particular, if we experience enrollment delays in our Phase 3 trial of A4250 in patients with PFIC, our cash resources may not be sufficient to enable us to fund the trial to completion, which could cause our value to decline and limit our ability to obtain additional financing.

Potential clinical trial participants may not be adequately diagnosed or identified with the diseases that we are targeting and may not meet the inclusion criteria for our trials. PFIC and other pediatric cholestatic liver diseases or disorders for which we may develop A4250 is a rare disease or disorder with a limited patient population, which could result in slow enrollment of clinical trial participants. Further, there are only a limited number of specialist physicians that treat these diseases and disorders, and major clinical centers that treat these diseases and disorders are concentrated in a few geographic regions.

Patient enrollment is affected by many factors, including:

- size of the target patient population;
- severity of the disease or disorder under investigation;
- eligibility criteria for the clinical trial in question;
- other clinical trials being conducted at the same time involving patients who have the disease or disorder under investigation;
- perceived risks and benefits of the product candidate under study;
- approval and availability of other therapies to treat the disease or disorder that is being investigated in the clinical trial;
- willingness or unwillingness to participate in a placebo controlled clinical trial;
- efforts to facilitate timely enrollment in clinical trials;
- patient referral practices of physicians;
- the ability to monitor patients adequately during and after treatment; and

- proximity and availability of clinical trial sites for prospective patients.

Our inability to enroll a sufficient number of patients in our planned clinical trials of A4250, or any of our other product candidates, would result in significant delays or may require us to abandon one or more clinical trials altogether.

If the commercial opportunity in PFIC is smaller than we anticipate, or if A4250 receives approval to treat only a specific subpopulation of patients with PFIC or only a specific symptom of PFIC such as pruritus, our future revenue from A4250 may be adversely affected and our business may suffer.

If the size of the commercial opportunities in any of our target indications is smaller than we anticipate, we may not be able to achieve profitability and growth. We are developing A4250 initially as a treatment for patients with PFIC and potentially also as a treatment for patients with other pediatric cholestatic liver diseases and disorders. PFIC and these other diseases and disorders are each rare, with a limited patient population. Moreover, we expect that the addressable PFIC patient population for A4250 is only a subset of the overall patient population, specifically patients who have not yet received partial external biliary diversion, or PEBD, surgery or liver transplant surgery or patients who have had PEBD reversal surgery. We are not aware of any available patient registries for PFIC, and we rely on various estimates and assumptions to estimate the addressable PFIC population. In addition, there are different subtypes of PFIC and the beneficial effects of A4250 may vary among patients with different subtypes or among children of different ages. Our Phase 3 clinical trial is enrolling patients with PFIC, type 1 or 2, but not PFIC, type 3. Based on FDA feedback, A4250 may ultimately receive regulatory approval, if at all, as a treatment for only the PFIC subtypes studied. It is also possible that A4250 may ultimately receive regulatory approval, if at all, as a treatment for children with PFIC of some ages but not others. Moreover, we are using change in pruritus as the primary endpoint of our Phase 3 trial for purposes of FDA evaluation. The FDA has informed us that showing a clinically meaningful effect only on pruritus could support approval for the treatment of pruritus associated with PFIC and has indicated to us that meaningful improvements on one or more additional clinical benefit endpoints and/or corroborative real-world clinical evidence would be required to support approval for the treatment of PFIC itself. If the commercial opportunity in PFIC is smaller than we anticipate, whether because our estimates of the addressable patient population prove to be incorrect, because A4250 receives marketing approval, if at all, as a treatment for some but not all PFIC subtypes, for children of some ages but not others, for pruritus associated with PFIC but not PFIC itself or for any other reason, our future revenue from A4250 may be adversely affected and our business may suffer.

It is critical to our ability to grow and become profitable that we successfully identify patients with PFIC and any other rare cholestatic liver diseases and disorders that we may target in the future. Our projections of the number of people who have PFIC or our other potential target cholestatic liver diseases and disorders, as well as the subset who have the potential to benefit from treatment with A4250, are based on a variety of sources, including third-party estimates and analyses in the scientific literature, and may prove to be incorrect. Further, new information may emerge that changes our estimate of the prevalence of these diseases or the number of patient candidates for A4250. The effort to identify patients with PFIC or our other potential target indications is at an early stage, and we cannot accurately predict the number of patients for whom treatment might be possible. Additionally, the addressable patient population for A4250 may be limited or may not be amenable to treatment with A4250, and new patients may become increasingly difficult to identify or gain access to, which would adversely affect our results of operations and our business. Further, even if we obtain significant market share for A4250, we may never achieve profitability because the potential target patient population for A4250 is small.

If we experience any of a number of possible unforeseen events in connection with our clinical trials, potential marketing approval or commercialization of our product candidates, or entry into licensing, collaboration or similar arrangements, could be delayed or prevented.

We may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent our ability to receive marketing approval or commercialize our product candidates, including:

- clinical trials of our product candidates may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional clinical trials or abandon product development programs;

- the number of patients required for clinical trials of our product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate or participants may drop out of these clinical trials at a higher rate than we anticipate;

- we may be unable to recruit and enroll a sufficient number of patients in our clinical trials to ensure adequate statistical power to detect any statistically significant treatment effects;

- our third-party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;

- regulators, institutional review boards or independent ethics committees may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;

- we may experience delays in reaching, or we may fail to reach, agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites;

- we may have to suspend or terminate clinical trials of our product candidates for various reasons, including a finding that the participants are being exposed to unacceptable health risks or undesirable side effects;

- regulators, institutional review boards or independent ethics committees may require that we or our investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks;

- the cost of clinical trials of our product candidates may be greater than we anticipate;

- the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate; and

- our product candidates may have undesirable side effects or other unexpected characteristics, causing us or our investigators, regulators, institutional review boards or independent ethics committees to suspend or terminate the clinical trials.

For example, in March 2015, Ferring International Center S.A., or Ferring, stopped early two Phase 3 clinical trials of elobixibat that Ferring had been conducting pursuant to a now-terminated license agreement with us due to an issue related to the distribution of study drug to study sites that was unrelated to the performance of elobixibat. We were unable as a result of the stopping of the trials to obtain data for the total number of patients for which the trials were designed, and the abbreviated trials are not sufficient to support an application for marketing approval.

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

The benefit of IBAT inhibition in the treatment of patients with PFIC or any of our other target indications is unproven, and we do not know whether we will be able to develop any products of commercial value for these indications.

A4250 is an ileal bile acid transporter, or IBAT, inhibitor. There is no marketed drug in the United States or Europe that relies on IBAT inhibition for the treatment of PFIC or any other indication for which we plan to develop A4250. Shire plc, or Shire, reported that, SHP625, now known as maralixibat, which it licensed to and is now being developed by Mirum Pharmaceuticals, and has been reported to be an IBAT inhibitor, failed to meet the respective

primary endpoints of Phase 2 clinical trials in multiple adult and pediatric indications. We cannot assure you that we will be able to replicate or improve upon our findings from preclinical studies and early clinical trials in later-stage clinical trials of A4250 for the treatment of patients with PFIC or any of our other target indications or that our focus on IBAT inhibition as a medically useful mechanism of action will result in the development of a commercially viable drug that safely and effectively treats PFIC or any of our other target indications.

If the FDA concludes that more clinical or nonclinical data than we currently anticipate is required to support the approval of A3384 for the treatment of BAM under Section 505(b)(2) of the Federal Food Drug and Cosmetics Act, the approval pathway for A3384 will likely take significantly longer, cost significantly more and entail significantly greater complications and risks than anticipated, and in either case may not be successful.

We expect that, if our pending formulation-related patents for A3384 issue in the United States, we may seek FDA approval for A3384 for the treatment of BAM through Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. Section 505(b)(2) permits the filing of a new drug application, or NDA, where at least some of the information required for approval comes from studies that were not conducted by or for the applicant, and for which the applicant has not received a right of reference, which could expedite the development program for A3384 by potentially decreasing the amount of clinical and preclinical data that we would need to generate in order to obtain FDA approval. However, the 505(b)(2) regulatory pathway does not preclude the possibility that additional clinical trials or nonclinical studies may be required; for example, for new indications where the applicant cannot rely on published literature or the FDA's finding of safety and effectiveness. If the FDA requires more data to support the approval of A3384 to treat BAM than we currently anticipate, the time and financial resources required to obtain FDA approval for A3384, and complications and risks associated with A3384, would likely substantially increase. Moreover, if we are unable to pursue the Section 505(b)(2) regulatory pathway for any reason, new competitive products could reach the market more quickly than A3384, which would likely harm our competitive position and prospects. Even if we are allowed to pursue the Section 505(b)(2) regulatory pathway, we cannot assure you that A3384 will receive the requisite approvals for commercialization.

In addition, notwithstanding the approval of a number of products by the FDA under Section 505(b)(2) over the last few years, certain competitors and others have objected to the FDA's interpretation of Section 505(b)(2). If the FDA's interpretation of Section 505(b)(2) is successfully challenged, the FDA may be required to change its 505(b)(2) policies and practices, which could delay or even prevent the FDA from approving any NDA that we submit under Section 505(b)(2). In addition, the pharmaceutical industry is highly competitive, and Section 505(b)(2) NDAs are subject to special requirements designed to protect the patent rights of sponsors of previously approved drugs that are referenced in a Section 505(b)(2) NDA. These requirements may give rise to patent litigation and mandatory delays in approval of our 505(b)(2) NDA for up to 30 months depending on the outcome of any litigation. It is not uncommon for a manufacturer of an approved product to file a citizen petition with the FDA seeking to delay approval of, or impose additional approval requirements for, pending competing products. If successful, such petitions can significantly delay, or even prevent, the approval of the new product. However, even if the FDA ultimately denies such a petition, the FDA may substantially delay approval while it considers and responds to the petition. In addition, even if we are able to utilize the Section 505(b)(2) regulatory pathway, there is no guarantee this would ultimately lead to faster product development or earlier approval. Moreover, even if A3384 is approved under Section 505(b)(2), the approval may be subject to limitations on the indicated uses for which A3384 may be marketed or to other conditions of approval, or may contain requirements for costly post marketing testing and surveillance to monitor the safety or efficacy of the products.

BAM is diagnosed by exclusion and the number of patients suffering from BAM has not been established with precision. If the actual number of patients is smaller than we estimate, we may not be able to recruit patients into our clinical trial in this indication in a timely manner or at all, and we may not be able to obtain regulatory approval for A3384 to treat this condition.

BAM is typically diagnosed by excluding other potential causes of extreme diarrhea, and we are not aware of any patient registry or other method of establishing with precision the actual number of patients with BAM in any geography. The diagnostic method that is believed to be the best currently, the 75Se-Homocholic Acid Taurine test, is not available in many countries and evaluation of bile acid synthesis markers, such as FGF19, and the bile acid intermediate C4 is not a routine diagnostic test. Instead, it is common currently to assess the effect of cholestyramine to

confirm the diagnosis of BAM. We estimate the prevalence of BAM in the United States and the European Union to be approximately 4 million people. We derive our estimated prevalence from a reported estimate of the prevalence of irritable bowel syndrome with diarrhea, or IBS-D, and published third-party studies that suggest approximately one-third of IBS-D patients have BAM. If the estimates on which we have relied are not accurate or if the results of studies on which we have relied are outdated, our estimate of the number of patients with BAM may be inaccurate, we may not be able to recruit patients into any future clinical trial of A3384 in BAM in a timely manner, or at all, and the commercial opportunity for A3384 may be smaller than we anticipate.

If serious or unacceptable side effects are identified during the development of A4250, elobixibat or A3384 or any other product candidate, we may need to abandon or limit our development of that product candidate.

All of our product candidates are in clinical or preclinical development (other than elobixibat for chronic constipation, which has been approved in Japan) and their risk of failure is high. It is impossible to predict when or if any of our product candidates will prove effective or safe in humans or will receive marketing approval. If our product candidates are associated with undesirable side effects or have other unexpected, unacceptable characteristics, we may need to abandon their development or limit development to certain uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective. Many investigational products that initially showed promise in clinical or earlier stage testing have later been found to cause side effects or other safety issues that prevented further development.

For example, the investigator for the investigator-initiated Phase 2 clinical trial of A4250 in PBC determined to conclude the trial prior to its intended completion, citing gastrointestinal side effects. If the GI side effects cited by the investigator in the PBC trial are predictive of an inadequate tolerability profile of A4250, the overall commercial opportunity for A4250 may be lower than we expect. Even if we receive regulatory approval for A4250, if the approved dose of A4250 is not well tolerated, A4250 may not achieve market acceptance by physicians, patients, third-party payors or others in the medical community, which would materially and adversely affect our business.

Even if A4250, elobixibat or A3384 or any potential future product candidate of ours receives marketing approval, it may fail to achieve the degree of market acceptance by physicians, patients, third-party payors and others in the medical community necessary for commercial success.

If A4250, elobixibat, A3384 or any potential future product candidate of ours receives marketing approval, the approved product may nonetheless fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community. If an approved product does not achieve an adequate level of acceptance, we may not generate significant product revenues or any profits from operations. The degree of market acceptance of our product candidates, if approved for commercial sale, will depend on a number of factors, including:

- the efficacy and potential advantages compared to alternative treatments or competitive products;
- the prevalence and severity of any side effects;
- whether physicians will be willing to prescribe A4250 to patients with PFIC notwithstanding that the primary endpoint in our Phase 3 clinical trial of A4250 in patients with PFIC is change in pruritus (FDA) or serum bile acid responder rate (EMA), as opposed to a direct measure of reducing or eliminating progressive liver disease;
- the ability to offer our product candidates for sale at competitive prices;
- convenience and ease of administration compared to alternative treatments;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;

- the strength of marketing and distribution support;
- the adequacy of supply of our product candidates;
- the availability of third-party coverage and adequate reimbursement;
- the timing of any such marketing approval in relation to other product approvals;
- support from patient advocacy groups; and
- any restrictions on concomitant use of other medications.

Our ability to negotiate, secure and maintain third-party coverage and reimbursement for our product candidates may be affected by political, economic and regulatory developments in the United States, the European Union and other jurisdictions. Governments continue to impose cost containment measures, and third-party payors are increasingly challenging prices charged for medicines and examining their cost effectiveness, in addition to their safety and efficacy. These and other similar developments could significantly limit the degree of market acceptance of A4250, elobixibat or A3384 or any potential future product candidate of ours that receives marketing approval.

If we are unable to establish sales and marketing capabilities or enter into agreements with third parties to market and sell A4250 or any of our other current or potential future product candidates, we may not be successful in commercializing the applicable product candidate if it receives marketing approval.

We do not have a sales or marketing infrastructure and have limited experience as a company in the sale or marketing of pharmaceutical products. To achieve commercial success for any approved product, we must either develop a sales and marketing organization or outsource these functions to third parties. If we receive marketing approval in the United States or Europe for A4250 to treat PFIC or any other pediatric cholestatic liver disease or disorder, we plan to build the capabilities to commercialize A4250 in the approved indication(s) in the applicable region with our own focused, specialized sales force. Outside of the United States and Europe, we plan to selectively utilize collaboration, distribution or other marketing arrangements with third parties to commercialize A4250. Also, we intend to selectively seek licensing, collaboration or similar arrangements to assist us in furthering the development or commercialization of product candidates, such as A3384, targeting large primary care markets that must be served by large sales and marketing organizations. There are risks involved with establishing our own sales and marketing capabilities and entering into arrangements with third parties to perform these services. For example, recruiting and training a sales force is expensive and time consuming and could delay any product launch. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

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

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

If we enter into arrangements with third parties to perform sales and marketing services, our product revenues or the profitability of these product revenues are likely to be lower than if we were to market and sell any products that we

develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to sell and market our product candidates or may be unable to do so on terms that are acceptable to us. We likely will have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our products effectively. If we do not establish sales and marketing capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our product candidates.

We face substantial competition, which may result in others discovering, developing or commercializing products to treat our target indications or markets before or more successfully than we do.

The development and commercialization of new drug products is highly competitive. We face competition with respect to our current product candidates and any products we may seek to develop or commercialize in the future from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide.

Competitors may also include academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for research, development, manufacturing and commercialization. Many of our competitors have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining approvals from regulatory authorities and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller and other early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies that may be complementary to or necessary for our programs.

Our commercial opportunities could be reduced or eliminated if our competitors develop and commercialize products that are more effective, safer, have fewer or less severe side effects, are approved for broader indications or patient populations, or are more convenient or less expensive than any products that we develop and commercialize. Our competitors may also obtain marketing approval for their products more rapidly than we may obtain approval for our products, which could result in our competitors establishing a strong market position before we are able to enter the market.

In particular, we are aware of other companies that are developing product candidates that, like our product candidates A4250 and elobixibat, act via IBAT inhibition. Shire plc's SHP625, also known as maralixibat, and formerly known as LUM001 from Lumena Pharmaceuticals, was studied in Phase 2 clinical trials in PFIC and ALGS . In June 2016, Shire announced that the FDA granted breakthrough therapy designation for SHP625 for PFIC, type 2. Shire's SHP626, also known as volixibat, was in Phase 2 development as a treatment for NASH. In November 2018, Shire announced that it licensed exclusive global rights to maralixibat and volixibat to Mirum Pharmaceuticals, a private company. Mirum has announced plans to initiate Phase 3 trials with maralixibat in PFIC and ALGS in 2019.GlaxoSmithKline's GSK2330672, which GlaxoSmithKline has announced an intent to divest, is at the Phase 2 clinical development stage as a treatment for pruritus in patients with PBC.

If approved, our product candidates will compete for a share of the existing market with numerous other products. We believe that the primary competitive products for use in indications that we are currently targeting with our most advanced product candidates include the following.

- For PFIC and many other cholestatic liver diseases, there are currently no approved drug treatments. First-line treatment for PFIC is typically off-label ursodeoxycholic acid, or UDCA, which is approved in the United States and elsewhere for the treatment of PBC. PFIC patients often require surgical intervention such as PEBD surgery or liver transplant. As noted above, Mirum plans to conduct Phase 3 clinical development of maralixibat in PFIC and ALGS. In addition, Intercept Pharmaceuticals' obeticholic acid, which is approved in the United States in combination with UDCA, or as a monotherapy for patients unable to tolerate UDCA, to treat PBC, is in Phase 2 development as a treatment for biliary atresia.

- For the pruritus that is characteristic of many cholestatic liver diseases, symptomatic off-label treatment with: UDCA; bile acid sequestrants, such as generic cholestyramine (marketed as, Efensol, Ipocol, Kolestran, Lipocol, Olestyr, Prevalite or Quantalan in various countries), marketed by Upsher-Smith Laboratories, Inc., Par Pharmaceutical Companies, Inc. and Sandoz, the generic pharmaceuticals division of Novartis AG; rifampin, an antibiotic derivative; or naltrexone, an opioid antagonist.

- For NASH, there are currently no approved drug treatments. There are several marketed therapeutics that are currently used off-label for the treatment of NASH, such as vitamin E (an antioxidant), insulin sensitizers (e.g., metformin), antihyperlipidemic agents (e.g., gemfibrozil), pentoxifylline and UDCA, but none has been clearly shown in clinical trials to demonstrate a significant reversal in liver fibrosis. Product candidates in Phase 3 clinical development in NASH include Intercept's obeticholic acid, Genfit SA's PPAR alpha/delta agonist (elafibranor), Gilead Sciences, Inc.'s ASK-1 inhibitor (selonsertib) and Allergan plc's dual CCR2 and CCR5 inhibitor (cenicriviroc). Madrigal Pharmaceuticals has announced plans to initiate a Phase 3 clinical program in NASH with its thyroid hormone receptor selective agonist, MGL-3196. There are many other product candidates believed to be in Phase 2 clinical development in NASH.

- For chronic constipation: linaclotide, a guanylate cyclase-C agonist, is marketed by Ironwood Pharmaceuticals, Inc. and Allergan as Linzess in the United States and as Constella (for the treatment of a related condition, irritable bowel syndrome with constipation, or IBS-C) in Europe. Linaclotide is also marketed by Astellas Pharma Inc. as Linzess in Japan for the treatment of IBS-C; lubiprostone, a type-2 chloride channel marketed as Amitiza by Takeda Pharmaceutical Company Limited in the United States and select countries in Europe and by Mylan N.V. in Japan; prucalopride, a motility agent marketed by Shire in the United States as Motegrity and in the European Union as Resolor; and numerous over the counter products, including psyllium husk (such as Metamucil), methylcellulose (such as Citrucel), calcium polycarbophil (such as FiberCon), lactulose (such as Cephulac), polyethylene glycol (such as MiraLax), sennosides (such as Exlax), bisacodyl (such as Ducolax), docusate sodium (such as Colace), magnesium hydroxide (such as Milk of Magnesia), saline enemas (such as Fleet) and sorbitol.

- In addition, Synergy Pharmaceuticals, Inc. has a product known as plecanatide, a guanylate cyclase-C agonist marketed as Trulance, which is approved in the United States to treat CIC and IBS-C. In December of 2018, Synergy filed a voluntary petition for reorganization under Chapter 11 of the U.S. Code with the U.S. Bankruptcy Court for the Southern District of New York. On February 26, 2018, Bausch Health Companies Inc. announced that it was selected as the successful bidder to acquire certain of Synergy's assets for a cash purchase price of approximately $195 million and the assumption of certain of Synergy's liabilities. Ardelyx, Inc. has a product candidate, tenapanor, for which it submitted a new drug application to the FDA in September 2018 for marketing approval in the treatment of in IBS-C.

- For BAM, there is currently no approved drug treatment in the United States. Off-label treatments include: bile acid sequestrants, such as conventional cholestyramine (which is approved in some countries in Europe to treat diarrhea associated with certain GI conditions), colestipol and colesevelam, a cholesterol-lowering medicine marketed by Daiichi Sankyo Inc. as Welchol in the United States and by Genzyme Europe B.V. as Cholestagel in the European Union. In addition, obeticholic acid has previously been studied by Intercept in a Phase 2 clinical trial as a treatment for BAM.

Patients with BAM following ileal resection surgery may be treated with a low-fat diet supplemented with medium-chain triglycerides or cholylsarcosine, a synthetic cholic acid conjugate. Patients with BAM secondary to Crohn's ileitis may be treated with glucocorticoid, a steroid hormone. Microscopic colitis patients may be given budesonide, a glucocorticoid steroid. Patients with BAM secondary to small intestinal bacterial overgrowth may require antibiotic therapy.

Even if we are able to commercialize A4250, elobixibat, A3384 or any other product candidate that we develop, the product may become subject to unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, which would harm our business.

The regulations that govern marketing approvals, pricing, coverage and reimbursement for new drug products vary widely from country to country. Current and future legislation may significantly change the approval requirements in ways that could involve additional costs and cause delays in obtaining approvals. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted and, in some markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay our commercial launch of the product, possibly for lengthy time periods, and negatively impact the revenues we are able to generate from the sale of the product in that country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more product candidates, even if our product candidates obtain marketing approval.

Our ability to commercialize A4250, elobixibat, A3384 or any other product candidate successfully also will depend in part on the extent to which coverage and adequate reimbursement for these products and related treatments will be available from government health administration authorities, private health insurers and other organizations. Government authorities and other third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels. A primary trend in the U.S. and E.U. healthcare industries and elsewhere is cost containment. Government authorities and other third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. Increasingly, third-party payors are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. We cannot be sure that coverage and reimbursement will be available for A4250, elobixibat, A3384 or any other product that we commercialize and, if coverage and reimbursement is available, the level of reimbursement. Reimbursement may impact the demand for, or the price of, any product candidate for which we obtain marketing approval. Obtaining and maintaining adequate reimbursement for A4250 may be particularly difficult because of the higher prices typically associated with drugs directed at smaller populations of patients. In addition, third-party payors are likely to impose strict requirements for reimbursement of a higher priced drug, and any launch of a competitive product is likely to create downward pressure on the price initially charged. If reimbursement is not available or is available only to a limited degree, we may not be able to successfully commercialize any product candidate for which we obtain marketing approval.

There may be significant delays in obtaining coverage and reimbursement for newly approved drugs, and coverage may be more limited than the purposes for which the drug is approved by the applicable regulatory authority. Moreover, eligibility for coverage and reimbursement does not imply that any drug will be paid for in all cases or at a rate that covers our costs, including research, development, intellectual property, manufacturing, sale and distribution expenses. Interim reimbursement levels for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement rates may vary according to the use of the drug and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost drugs, and may be incorporated into existing payments for other services. Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. In the United States, third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement policies. In the European Union, reference pricing systems and other measures may lead to cost containment and reduced prices. Our inability to promptly obtain coverage and adequate reimbursement rates from both government-funded and private payors for any approved products that we develop could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize products and our overall financial condition.

Governments outside the United States tend to impose strict price controls, which may adversely affect our revenues, if any.

In some countries, particularly the member states of the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental

authorities can take considerable time after the receipt of marketing approval for a product. In addition, there can be considerable pressure by governments and other stakeholders on prices and reimbursement levels, including as part of cost containment measures. Political, economic and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various E.U. member states and parallel distribution, or arbitrage between low-priced and high-priced member states, can further reduce prices. In some countries, we may be required to conduct a clinical trial or other studies that compare the cost-effectiveness of our product candidate to other available therapies in order to obtain or maintain reimbursement or pricing approval. Publication of discounts by third-party payors or authorities may lead to further pressure on prices or reimbursement levels within the country of publication and other countries. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be adversely affected.

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

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

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

We have separate liability insurance policies that cover each of our clinical trials, as well as a global product/clinical trial policy. These policies provide coverage in varying amounts, with the global policy having a per occurrence and aggregate limit of $10 million. The amount of insurance that we currently hold may not be adequate to cover all liabilities that we may incur. We will need to increase our insurance coverage when and if we begin conducting more expansive clinical development of, or commercializing, A4250, elobixibat, A3384 or any potential future product candidate of ours. Insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise.

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

Because we have limited financial and managerial resources, we focus on specific product candidates. Currently, we are focusing our resources predominantly on A4250. As a result, we may forego or delay pursuit of opportunities with elobixibat, A3384 or potential future product candidates that later could prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market

opportunities. Our spending on current and future research and development programs and product candidates may not yield any commercially viable products.

We have historically based our research and development efforts on IBAT inhibitors, including A4250 and elobixibat, to treat cholestatic liver diseases and CIC and on our proprietary formulations of an established bile acid sequestrant, A3384, to treat BAM. Notwithstanding our investment to date and anticipated future investment, we have not yet developed, and may never successfully develop, any marketed drugs using these approaches. As a result of pursuing the development of product candidates using our proprietary technologies, we may fail to develop product candidates or address indications based on other scientific approaches that may offer greater commercial potential or for which there is a greater likelihood of success. Research programs to identify new product candidates require substantial technical, financial and human resources. These programs may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development.

If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through licensing, collaboration or other royalty or similar arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate.

Risks Related to Our Dependence on Third Parties

We rely on EA Pharma for the successful commercialization of elobixibat to treat chronic constipation in Japan and for the successful development and commercialization of elobixibat to treat chronic constipation in other select markets in Asia. If EA Pharma does not successfully commercialize elobixibat in Japan, we may not receive any future payments under our RIAA with HCR or our license agreement with EA Pharma.

We entered into a license agreement with EA Pharma (formerly known as Ajinomoto Pharmaceuticals) for elobixibat in April 2012. In January 2018, the Japanese Ministry of Health, Labour and Welfare, or MHLW, approved a new drug application filed by EA Pharma for elobixibat for the treatment of chronic constipation. EA Pharma plans to co-market elobixibat in Japan with another company, Mochida Pharmaceutical Co., Ltd, or Mochida, and to co-promote elobixibat in Japan with Eisai Co., Ltd.

In December 2017, we entered into the RIAA pursuant to which we sold to HCR our right to receive all royalties and sales milestones for elobixibat in Japan that may become payable by EA Pharma pursuant to our license agreement, up to a specified maximum amount, or cap amount, equal to 175% of the amount paid by HCR to us under the RIAA plus certain patent-related expenses (if such patent-related expenses become payable by HCR). Under the RIAA, we have received $45 million from HCR and we are eligible to receive an additional $15 million if a specified sales milestone is achieved for elobixibat in Japan. The RIAA also provides that, if the cap amount is reached, we will again become eligible to receive royalties and sales milestones for elobixibat from EA Pharma under the terms of our license agreement. If EA Pharma does not successfully commercialize elobixibat in Japan, we may not receive any future payments under our RIAA with HCR or our license agreement with EA Pharma.

EA Pharma is responsible for all commercialization of elobixibat in its licensed field (namely, all prophylactic or therapeutic uses of a pharmaceutical product for gastrointestinal diseases and disorders, symptoms of constipation of all causes or postoperative ileus, in colonoscopy cleansing procedures and, in specified circumstances, select liver diseases) in Japan and for all future development and commercialization of elobixibat in its licensed field in Indonesia, Korea, Myanmar, Taiwan, Thailand and Vietnam, and has substantial control over the conduct and timing of development efforts with respect to elobixibat in these countries. We have little control over the amount and timing of resources that EA Pharma devotes, or Mochida devotes, to the commercialization of elobixibat in Japan or to the development of elobixibat in these other countries. If EA Pharma or, where applicable, Mochida fails to devote sufficient financial and other resources, the commercialization of elobixibat in Japan and the development and potential commercialization of elobixibat otherwise in EA Pharma's licensed territory would be adversely affected. If this occurs but the cap amount under the RIAA were nevertheless reached, royalties that we could receive on any future elobixibat product sales could be delayed or reduced.

EA Pharma has the right to terminate the elobixibat agreement on a country-by-country basis or in its entirety for an uncured material breach by us or in specified bankruptcy or similar events. EA Pharma also has the right, with 180 days' notice, to terminate the agreement in its entirety or on a country-by-country basis (except for Japan) for any reason.

If EA Pharma terminates the elobixibat agreement at any time, for any reason, it would negatively impact both the likelihood that we would receive any future payments under our RIAA with HCR or our license agreement with EA Pharma and the development of elobixibat in EA Pharma's licensed territory outside of Japan, would materially harm our business and could accelerate our need for additional capital. In particular, we would be required to seek a replacement licensee for Japan under the RIAA.

If we do not pursue the development and potential commercialization of elobixibat for the treatment of CIC in the United States or Europe, whether through a licensing, collaboration or similar arrangement or otherwise, the revenue that we will generate based on elobixibat may be lower.

We have commercial rights to elobixibat in the United States, Europe and otherwise outside of the territories licensed to EA Pharma. We do not have any current plan to seek a license or other partnering transaction with a third party for elobixibat for CIC in the United States or Europe. The cost and duration of the additional clinical trial or trials that would be required by the FDA and EMA to support marketing approval of elobixibat to treat CIC is currently uncertain. Even if we were to seek to establish licensing, collaboration or similar arrangement with a third party for the United States or Europe, the uncertain regulatory requirements may interfere with our ability to do so on acceptable terms, or at all. We do not anticipate that we will conduct future clinical trials of elobixibat in CIC for the United States or Europe independently, whether or not we elect to seek a suitable third-party arrangement. If we do not enter into suitable third-party arrangements and do not ourselves conduct clinical trials of elobixibat in CIC for the United States or Europe, the revenue that we will generate based on elobixibat in CIC will be limited to future payments that we receive, if any, under our agreements with HCR and EA Pharma, which will reduce the overall commercial potential of elobixibat and may harm our business.

We rely on third parties to conduct our clinical trials and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such clinical trials.

We do not independently conduct clinical trials for our product candidates. We rely on third parties, such as contract research organizations, clinical data management organizations, medical institutions, clinical investigators and government agencies, to perform this function. Any of these third parties may terminate their engagements with us at any time. If we need to enter into alternative arrangements, it would delay our product development activities.

Our reliance on these third parties for clinical development activities reduces our control over these activities but does not relieve us of our responsibilities. For example, we remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the clinical trial. Moreover, the FDA and foreign regulatory authorities require us to comply with standards, commonly referred to as Good Clinical Practice, or GCP, for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity of data and confidentiality of clinical trial participants are protected. We are also required to register clinical trials subject to FDA regulation and, with some exceptions, post the results of completed clinical trials on a government-sponsored database, www.ClinicalTrials.gov, within certain timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions. The National Institutes of Health also has announced plans to require sponsors to post results of clinical trials for unapproved products, including unfavorable results in clinical trials for unapproved uses of approved products.

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

and will not be able to, or may be delayed in our efforts to, successfully commercialize our product candidates. Our product development costs will increase if we experience delays in testing or obtaining marketing approvals.

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

Use of third parties to manufacture our product candidates may increase the risk that we will not have sufficient quantities of our product candidates or products or such quantities at an acceptable cost, which could delay, prevent or impair our development or commercialization efforts.

We do not own or operate manufacturing facilities for the production of clinical or commercial supplies of our product candidates. We have limited personnel with experience in drug manufacturing and lack the resources and the capabilities to manufacture any of our product candidates on a clinical or commercial scale. We currently rely on third parties for supply of the active pharmaceutical ingredients, or API, in our product candidates. Our strategy is to outsource all manufacturing of our product candidates and products to third parties.

We do not currently have any agreements with third-party manufacturers for the long-term clinical or commercial supply of any of our product candidates. We currently engage a single third-party manufacturer to provide API for A4250 and elobixibat. We also currently engage single third-party manufacturers to provide fill and finish services for the final drug product formulation of each of our product candidates in development. We may in the future be unable to conclude agreements for commercial supply with third-party manufacturers on acceptable terms, or at all.

Even if we are able to establish and maintain arrangements with third-party manufacturers, reliance on third-party manufacturers entails additional risks, including:

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

Third-party manufacturers may encounter difficulties in achieving volume production, laboratory testing, quality control or quality assurance or suffer shortages of qualified personnel, any of which could result in our inability to manufacture sufficient quantities to meet clinical timelines for a particular product candidate, to obtain marketing approval for the product candidate or to commercialize the product candidate. In addition, third-party manufacturers may not be able to comply with current good manufacturing practice, or GMP, regulations or similar regulatory requirements outside the United States. Our failure, or the failure of our third-party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us, including fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or products, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our product candidates.

Our product candidates and any products that we may develop may compete with other product candidates and products for access to manufacturing facilities. There are a limited number of manufacturers that operate under cGMP regulations and that might be capable of manufacturing for us.

If the third parties that we engage to manufacture product for our preclinical tests and clinical trials cease to continue to do so for any reason, we likely would experience delays in advancing these clinical trials while we identify and qualify replacement suppliers and we may be unable to obtain replacement supplies on terms that are favorable to

us. In addition, if we are not able to obtain adequate supplies of our product candidates or the drug substances used to manufacture them, it will be more difficult for us to develop our product candidates and compete effectively.

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

We may depend on additional collaborations, licenses or similar arrangements with third parties for the development and commercialization of some of our product candidates. If those collaborations are not successful, we may not be able to capitalize on the market potential of these product candidates.

We have licensed rights to develop and commercialize elobixibat for CIC and other gastrointestinal diseases and disorders to EA Pharma in Japan and other select markets in Asia. We may in the future enter into other licensing, collaboration or similar arrangements for the development and commercialization of A4250, elobixibat, A3384 or any potential future product candidate of ours for any or all indications and for any or all territories, except for the rights currently subject to EA Pharma's license with respect to elobixibat.

Our likely counterparties for any licensing, collaboration or similar arrangement include large and mid-size pharmaceutical companies, regional and national pharmaceutical companies and biotechnology companies. Except for our agreement with EA Pharma, we are not currently party to any such arrangement for A4250, elobixibat or A3384. However, if we do enter into any such arrangements with any third parties in the future, we will likely have limited control over the amount and timing of resources that our collaborators dedicate to the development or commercialization of the applicable product candidate. Our ability to generate revenues from these arrangements will depend on our collaborators' abilities and efforts to successfully perform the functions assigned to them in these arrangements.

Any licensing, collaboration or similar arrangement involving our product candidates would pose numerous risks to us, including the following:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations and may not perform their obligations as expected;
- collaborators may deemphasize or not pursue development and commercialization of our product candidates or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborators' strategic focus, including as a result of a sale or disposition of a business unit or development function, or available funding, or external factors such as an acquisition that diverts resources or creates competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- collaborators may independently develop, or develop with third parties, products that compete directly or indirectly with our products or product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- a collaborator with marketing and distribution rights to multiple products may not commit sufficient resources to the marketing and distribution of our product relative to other products;
- collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;

- collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability;

- disputes may arise between us and a collaborator as to the ownership of intellectual property arising during the collaboration;

- we may grant exclusive rights to our collaborators, which would prevent us from collaborating with others or make us a less attractive collaboration partner by narrowing the scope of potential collaborations into which we may enter;

- disputes may arise between us and a collaborator that result in the delay or termination of the research, development or commercialization of our products or product candidates or that result in costly litigation or arbitration that diverts management attention and resources; and

- collaborations may be terminated and, if terminated, may result in a need to identify and enter into a new licensing, collaboration or similar arrangement or obtain additional capital to pursue further development or commercialization of the applicable product candidates.

For example, in March 2015, Ferring terminated a 2012 license agreement with us for the development and commercialization of elobixibat worldwide, excluding the territory licensed to EA Pharma. Ferring's termination of the license agreement followed its stopping early two Phase 3 clinical trials of elobixibat that Ferring had been conducting due to an issue related to the distribution of study drug to study sites that was unrelated to the performance of elobixibat. As a result, to exploit the potential of elobixibat in CIC in the United States, Europe and otherwise outside of EA Pharma's licensed territory, we would need to either identify and enter into additional licensing, collaboration or similar arrangements or expend our own resources to conduct further development of elobixibat. We do not have any current plan to seek a license or other partnering transaction with a third party for elobixibat in CIC in the United States or Europe. Whether or not we elect to seek such a transaction, we do not anticipate that we will conduct future clinical trials of elobixibat in CIC independently.

Collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner or at all. If a collaborator of ours were to be involved in a business combination, the continued pursuit and emphasis on our product development or commercialization program could be delayed, diminished or terminated.

If we are not able to establish additional collaborations, we may have to alter our development and commercialization plans.

Our product development programs and the potential commercialization of our product candidates will require substantial additional cash to fund expenses. For some of our product candidates, we may decide to collaborate with pharmaceutical and biotechnology companies for the development and potential commercialization of those product candidates.

We face significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. Those factors may include the design or results of clinical trials, the likelihood of approval by regulatory authorities, the potential market for the subject product candidate, the costs and complexities of manufacturing and delivering such product candidate to patients, the potential of competing products, the existence of uncertainty with respect to our ownership of technology, which can exist if there is a challenge to such ownership without regard to the merits of the challenge, and industry and market conditions generally. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available to collaborate on and whether such a collaboration could be more attractive than the one with us for our product candidate. We may also be restricted under future license agreements from entering into agreements on certain terms with potential collaborators. Collaborations are complex and time-consuming to negotiate and document. In addition, there have been a significant number of business

combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators.

We may not be able to negotiate collaborations on a timely basis, on acceptable terms, or at all. If we are unable to do so, we may have to curtail the development of a product candidate, reduce or delay our development program or one or more of our other development programs, delay our potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we do not have sufficient funds, we may not be able to further develop our product candidates or bring them to market and generate product revenue.

Risks Related to Our Intellectual Property

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

Our success depends in large part on our ability to obtain and maintain patent protection in the United States and other countries with respect to our proprietary technology and products. We seek to protect our proprietary position by filing patent applications in the United States, in Europe and in certain additional jurisdictions related to our novel technologies and product candidates that are important to our business. This process is expensive and time-consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. Moreover, if we license technology or product candidates from third parties in the future, these license agreements may not permit us to control the preparation, filing and prosecution of patent applications, or to maintain or enforce the patents, covering the licensed technology or product candidates. These agreements could also give our licensors the right to enforce the licensed patents without our involvement, or to decide not to enforce the patents at all. Therefore, in these circumstances, these patents and applications may not be prosecuted or enforced in a manner consistent with the best interests of our business.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our pending and future patent applications may not result in patents being issued which protect our technology or products, in whole or in part, or which effectively prevent others from commercializing competitive technologies and products. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents, narrow the scope of our patent protection or make enforcement more difficult or uncertain.

The laws of other countries may not protect our patent rights to the same extent as the laws of the United States. For example, European patent law restricts the patentability of methods of treatment of the human body more than U.S. law does. For this or other reasons, we may not pursue or obtain patent protection in all major markets or may not obtain protection that enables us to prevent the entry of third parties onto the market.

Assuming the other requirements for patentability are met, currently, the first to file a patent application is generally entitled to the patent. However, prior to March 16, 2013, in the United States, the first to invent was entitled to the patent. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot know with certainty whether we were the first to make the inventions claimed in our U.S. patents or pending U.S. patent applications filed prior to March 16, 2013.

Moreover, we may be subject to a third party preissuance submission of prior art to the U.S. Patent and Trademark Office, or the USPTO, or become involved in opposition, derivation, reexamination, reissue, inter partes review, post grant review, interference proceedings or other patent office proceedings, court litigation or International Trade

Commission proceedings, in the United States or elsewhere, challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation concerning our patent rights could reduce the scope of or prevent the enforceability of, or invalidate, our patent rights, allowing third parties to commercialize our technology or products, or equivalent or similar technology or products, and so to compete directly with us, without payment to us, or, where such proceedings involve third-party patents, result in our inability to manufacture or commercialize products without infringing third-party patent rights. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened or narrowed by operation of any of the foregoing, such an event could dissuade companies from collaborating with us to license, develop or commercialize current or potential future product candidates of ours.

Even if our patent applications issue as patents, they may not issue in a form that will provide us with adequate protection to prevent competitors from competing with us or otherwise to provide us with any competitive advantage. Our competitors may be able to circumvent our owned or licensed patents by developing similar, improved or alternative technologies or products in a noninfringing manner. For example, although A3384 is the subject matter of pending patent applications that claim pharmaceutical formulations, patent protection is not available for composition-of-matter claims that only recite the API for A3384 without limitation to its formulation. Because A3384 lacks composition-of-matter protection for its API, competitors will, subject to obtaining marketing approval, be able to offer and sell products with the same API so long as these competitors do not infringe any of our issued patents. Moreover, method-of-treatment patent claims are more difficult to enforce than composition-of-matter claims for reasons including off-label sale, potential divided infringement issues and use of the subject compound in noninfringing manners. Physicians are permitted to prescribe an approved product for uses that are not described in the product's labeling. Although off-label prescriptions may infringe our method-of-treatment patents, the practice is common across medical specialties and such infringement is difficult to prevent or prosecute. Off-label sales would limit our ability to generate revenue from the sale of our product candidates, if approved for commercial sale. In addition, if a third party were able to design around our dosage-form and formulation patents and create a different formulation and dosage form that is not covered by our patents or patent applications, we would likely be unable to prevent that third party from manufacturing and marketing our product.

In addition, other companies may attempt to circumvent any regulatory data protection or market exclusivity that we obtain under applicable legislation, such as orphan drug exclusivity in the United States, which may require us to allocate significant resources to preventing such circumvention. Legal and regulatory developments in the European Union and elsewhere may also result in clinical trial data submitted as part of a marketing authorization application becoming publicly available. Such developments could enable other companies to use our clinical trial data to assist in their own product development and to obtain marketing authorizations in the European Union and in other jurisdictions. Such developments may also require us to allocate significant resources to prevent other companies from circumventing or violating our intellectual property rights. Our attempts to prevent third parties from circumventing our intellectual property and other rights may ultimately be unsuccessful. We may also fail to take the required actions or pay the necessary fees to maintain our patents.

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our owned and licensed patents may be challenged in the courts or patent offices in the United States, Europe and elsewhere. Such challenges may result in loss of exclusivity or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and products. Future changes in U.S. statutory or case law beyond our control could affect some or all of the foregoing possibilities. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. This could be the case even after giving effect to patent term extensions and data exclusivity provisions preventing third parties from relying on clinical trial data filed by us for marketing approval in support of their own applications for such approval. As a result, our patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

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

Competitors may infringe our patents, trademarks, copyrights or other intellectual property. To counter infringement or unauthorized use, we may be required to file claims, which can be expensive and time consuming. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their intellectual property or that our patent and other intellectual property rights are invalid or unenforceable, including for antitrust reasons. As a result, in a patent infringement proceeding, a court or administrative body may decide that a patent of ours is invalid or unenforceable, in whole or in part, or may construe the patent's claims narrowly and so refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the competitor technology in question. Even if we are successful in a patent infringement action, the unsuccessful party may subsequently raise antitrust issues and bring a follow-on action. Antitrust issues may also provide a bar to settlement or constrain the permissible settlement terms. Further, settlement agreements in the pharmaceutical sector are the subject of ongoing review by the antitrust authorities in the European Union.

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

Our commercial success depends upon our ability and the ability of our current or potential future licensees or collaborators to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing the intellectual property and other proprietary rights of third parties. There is considerable intellectual property litigation in the biotechnology and pharmaceutical industries, and we may become party to, or threatened with, future adversarial proceedings or litigation regarding intellectual property rights with respect to our products and technology, including interference, derivation, inter partes review, reexamination, reissue or post-grant review proceedings before the USPTO. The risks of being involved in such litigation and office proceedings may also increase as our product candidates approach commercialization, and as our business gains greater visibility operating as a publicly traded company in the United States. Third parties may assert infringement claims against us based on existing or future intellectual property rights and so restrict our freedom to operate. Third parties may also seek injunctive relief against us, whereby they would attempt to prevent us from practicing our technologies altogether pending outcome of any litigation against us. We may not be aware of all such intellectual property rights potentially relating to our product candidates prior to their assertion against us. For example, we have not conducted an in depth freedom-to-operate search or analysis for A4250, for elobixibat as a treatment for NASH or for A3384. Any freedom-to-operate search or analysis previously conducted may not have uncovered all relevant patents and pending patent applications, and there may be pending or future patent applications that, if issued, would block us from commercializing A4250, elobixibat or A3384. Thus, we do not know with certainty whether A4250, elobixibat, A3384 or any other product candidate, or our commercialization of any such product candidate, does not and will not infringe any third party's intellectual property.

If we are found to infringe a third party's intellectual property rights, or in order to avoid or settle litigation, we could be required to obtain a license to enable us to continue developing and marketing our products and technology. However, we may not be able to obtain any required license on commercially reasonable terms, or at all. Even if we were able to obtain a license, it could be nonexclusive, thereby giving our competitors access to the same technologies that we have then licensed, and could require us to make substantial payments. Absent a license, we could be forced, including by court order, to cease commercializing the infringing technology or product. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees if we are found to have willfully infringed a patent or other intellectual property right. A finding of infringement could prevent us from commercializing our product candidates or force us to cease some of our business operations, which could materially harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties, or claims that we derived inventions from another, could have a similar negative impact on our business.

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

Many of our employees were previously employed at universities or other biotechnology or pharmaceutical companies. Although we try to ensure that our employees do not use the proprietary or otherwise confidential information or know-how of others in their work for us, we may be subject to claims that we or these employees have without authorization used or disclosed intellectual property, including trade secrets or other proprietary or confidential information, of any such employee's former employer. Litigation may be necessary to defend against these claims.

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

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

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

Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses, and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development, sales, marketing or distribution activities. We may not have sufficient financial or other resources to adequately conduct such litigation or proceedings. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources. Accordingly, costs and lost management time, as well as uncertainties resulting from the initiation and continuation of patent litigation or other proceedings, could have a material adverse effect on our ability to compete in the marketplace.

If we do not obtain protection under the Hatch-Waxman Act and similar legislation outside of the United States by extending the patent terms and obtaining data exclusivity for our product candidates, our business may be materially harmed.

Depending upon the timing, duration and specifics of FDA marketing approval of A4250, elobixibat, A3384 or potential future product candidates of ours, if any, one or more of our U.S. patents may be eligible for limited patent term restoration under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Act. The Hatch-Waxman Act permits a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, we may not be granted an extension if, for example, we fail to apply within applicable deadlines, we fail to apply prior to expiration of relevant patents or if we otherwise fail to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we are unable to obtain patent term extension or restoration or the term of any such extension is less than we request, the period during which we will have the right to exclusively market our products will be shortened and our competitors may obtain approval of competing products following our patent expiration, and our revenue could be reduced, possibly materially. In the event that we are unable to obtain any patent term extension, the issued U.S. composition of matter patent for A4250 is expected to expire in 2022 assuming it withstands any challenge. In the event that we are unable to obtain any patent term extension, the issued U.S. composition of matter patent for elobixibat is expected to expire in 2022, assuming it withstands any challenge. We

expect that the other U.S. patents and patent applications for A4250 and elobixibat, if issued, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, would expire from 2031 to 2039. We also expect that our patent applications for A3384, which to date have been filed as PCT applications being initially nationalized in the United States or as priority applications in Sweden, if ultimately issued in the United States and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, would expire in 2037 or 2038.

A3384 could be subject to competition arising from off-label use from conventional cholestyramine.

We have pending patent applications covering pharmaceutical formulations of A3384. Even if these patents ultimately issue in the United States or elsewhere, we do not have patent rights covering the composition of matter of cholestyramine. As a result, we may be limited in our ability to prevent others from exploiting cholestyramine, which could have a negative impact on the commercial potential of A3384. In addition, cholestyramine is currently approved in the United States and some countries in Europe for various indications, including in some countries in Europe for diarrhea associated with certain GI conditions. Physicians currently prescribe cholestyramine for other indications that are not approved by the FDA or regulatory authorities outside of the United States, such as BAM. If we are unable to establish that A3384 is a superior drug to conventional cholestyramine in the treatment of BAM, physicians may be likely to continue to prescribe conventional cholestyramine and our potential future revenue from sales of A3384 would likely be materially and adversely affected.

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

In addition to seeking patents for some of our technology and products, we also rely on trade secrets, including unpatented know-how, technology and other proprietary and confidential information, to maintain our competitive position. We seek to protect these trade secrets, in part, by entering into nondisclosure and confidentiality agreements with parties who have access to them, such as our employees, corporate collaborators, outside scientific collaborators, contract manufacturers, consultants, advisors and other third parties. However, we cannot guarantee that we have executed these agreements with each party that may have or have had access to our trade secrets or that the agreements we have executed will provide adequate protection. Any party with whom we have executed such an agreement may breach that agreement and disclose our proprietary or confidential information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. In addition, some courts inside and outside the United States are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent them, or those to whom they communicate the trade secret, from using that technology or information to compete with us. If any of our trade secrets, particularly unpatented know-how, were to be obtained or independently developed by a competitor, our competitive position would be harmed.

Risks Related to Regulatory Approval and Marketing of Our Product Candidates

A rare pediatric disease designation may not lead to the receipt of a rare pediatric disease priority review voucher, even if A4250 is approved.

The FDA has awarded rare pediatric disease priority review vouchers, or PRVs, to sponsors of drug products intended to treat rare pediatric disease products if the treatment and product application meet certain criteria. Under this program, upon the approval of a qualifying NDA or biologics license application, BLA, for the treatment or prevention of a rare pediatric disease, the sponsor of the application may be eligible for a PRV that can be used to obtain priority review for a subsequent NDA or BLA. The PRV may be sold or transferred an unlimited number of times. The FDA has granted rare pediatric disease designation for A4250 for PFIC. The PRV program is now set to expire at the end of September 2020, although a drug that has been designated under the program as of September 30, 2020 may still receive a PRV if it is approved for marketing before October 1, 2022. Therefore, there is no guarantee that we will receive a PRV for A4250 even if it is approved by the FDA to treat a rare pediatric disease.

If prior to any marketing approval in the European Union of A4250 to treat PFIC, Mirum's maralixibat is approved in the European Union to treat PFIC and at the time of approval maintains its designation as an orphan medicinal product, and if A4250 is deemed to be a similar medicinal product, within the meaning of E.U. law, to maralixibat, we may not be able to obtain marketing approval of A4250 in the European Union for a significant period of time. In addition, A4250 may not be entitled to orphan drug exclusivity for A4250 in the United States or European Union notwithstanding its current orphan designation.

Regulatory authorities in some jurisdictions, including the United States and European Union, may designate drugs for relatively small patient populations as orphan drugs. The FDA has granted orphan drug designation to A4250, which is an IBAT inhibitor, for the treatment of PFIC, biliary atresia, PBC and ALGS, and the European Commission has designated A4250 as an orphan medicinal product for the treatment of PFIC, biliary atresia, PBC and ALGS. Mirum's maralixibat, which has also been reported to be an IBAT inhibitor, has also been granted orphan drug designation by the FDA and as an orphan medicinal product by the European Commission.

Generally, if a designated orphan medicinal product receives the first marketing approval in the European Union for the orphan indication for which it has been designated and maintains under applicable criteria its designation as an orphan medicinal product at the time of approval, the product is entitled to a period of market exclusivity in the European Union. Subject to certain exceptions, this market exclusivity precludes the EMA from accepting another marketing application for a "similar medicinal product" for the same indication for 10 years, which can be reduced to six years if a drug no longer meets the criteria for orphan drug designation (including if the drug is sufficiently profitable so that market exclusivity is no longer justified). Under E.U. law, a "similar medicinal product" is a medicinal product that contains a similar active substance or substances as contained in the authorized orphan medicinal product and that is intended for the same therapeutic indication and a "similar active substance" is an active substance that is identical or has the same principal molecular structural features (but not necessarily all of the same molecular features) and acts via the same mechanism as the authorized orphan medicinal product.

Maralixibat has been evaluated to date in a greater number of PFIC patients than has A4250. If (1) prior to marketing approval, if any, of A4250 to treat PFIC in the European Union, maralixibat is approved in the European Union to treat PFIC and at the time of approval maintains its designation as an orphan medicinal product, (2) A4250 is deemed to be a similar medicinal product to maralixibat and (3) we are not able to establish that A4250 provides a significant benefit to patients compared with maralixibat, we may not be able to obtain marketing approval of A4250 in the European Union for at least several years.

Moreover, we may not be able to obtain orphan drug exclusivity in the United States or the European Union for A4250 for PFIC or any other indication, notwithstanding the fact that A4250 has been designated as an orphan drug in the United States or an orphan medicinal product in the European Union. For example, if a competitive product that is the same drug as A4250 is shown to be clinically superior, any orphan drug exclusivity that we have obtained in the United States will not block the approval of such competitive product. In addition, orphan drug exclusivity will not prevent the approval in the United States of a product that is the same drug as our product candidate if the FDA finds that we cannot assure the availability of sufficient quantities of the drug to meet the needs of the persons with the disease or condition for which the drug was designated. Moreover, if prior to marketing approval, if any, of A4250 to treat PFIC in the European Union, maralixibat or any other product is approved in the European Union to treat PFIC, A4250 may not be entitled to orphan drug exclusivity if we are not able to establish that it provides a significant benefit to patients compared with maralixibat. Finally, even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different drug products can be approved for the same condition.

Even if we complete the necessary clinical trials, the marketing approval process is expensive, time consuming and uncertain and may prevent us from obtaining approvals for the commercialization of some or all of our product candidates. If we are not able to obtain, or if there are delays in obtaining, required marketing approvals, we will not be able to commercialize our product candidates, and our ability to generate revenue will be materially impaired.

Our product candidates, including A4250, elobixibat and A3384, and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping,

labeling, storage, approval, advertising, promotion, sale and distribution, are subject to comprehensive regulation by the FDA and by comparable authorities in other countries. Failure to obtain marketing approval for a product candidate will prevent us from commercializing the product candidate. Other than the approval of elobixibat received by EA Pharma for the treatment of chronic constipation in Japan, we have not received approval to market A4250, elobixibat, A3384 or any other product candidate from regulatory authorities in any jurisdiction.

We have only limited experience in filing and supporting the applications necessary to obtain marketing approvals for product candidates and expect to rely on third-party contract research organizations to assist us in this process. Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information to regulatory authorities for each therapeutic indication to establish the product candidate's safety and effectiveness. Securing marketing approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the regulatory authorities. Regulatory authorities may determine that A4250, elobixibat, A3384 or any potential future product candidate of ours is not effective, is only moderately effective or has undesirable or unintended side effects, toxicities, safety profiles or other characteristics that preclude us from obtaining marketing approval or that prevent or limit commercial use.

The process of obtaining marketing approvals is expensive, may take many years, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional preclinical studies, clinical trials or other trials. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent marketing approval of a product candidate. Any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable. If we experience delays in obtaining approval or if we fail to obtain approval of our product candidates, the commercial prospects for our product candidates may be harmed and our ability to generate revenues will be materially impaired.

Additionally, on June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the European Union, commonly referred to as "Brexit." On March 29, 2017, the country formally notified the European Union of its intention to withdraw pursuant to Article 50 of the Lisbon Treaty. Since a significant proportion of the regulatory framework in the United Kingdom is derived from European Union directives and regulations, Brexit could materially impact the regulatory regime with respect to the approval of any product candidates in the United Kingdom or the European Union. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would prevent us from commercializing any product candidates in the United Kingdom and/or the European Union and restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek regulatory approval in the United Kingdom and/or European Union for our product candidates, which could significantly and materially harm our business.

The United Kingdom has a period of a maximum of two years from the date of its formal notification to negotiate the terms of its withdrawal from, and future relationship with, the European Union. If no formal withdrawal agreement is reached between the United Kingdom and the European Union, then it is expected the United Kingdom's membership of the European Union will automatically terminate two years after the submission of the notification of the United Kingdom's intention to withdraw from the European Union. Discussions between the United Kingdom and the European Union focused on finalizing withdrawal issues and transition agreements are ongoing. However, limited progress to date in these negotiations and ongoing uncertainty within the United Kingdom government and Parliament sustains the possibility of the United Kingdom leaving the European Union on March 29, 2019 without a withdrawal agreement and associated transition period in place, which is likely to cause significant market and economic disruption.

Our failure to obtain marketing approval in jurisdictions other than the United States and Europe would prevent our product candidates from being marketed in these other jurisdictions. Any approval that we are granted for our product candidates in the United States or Europe would not assure approval of product candidates in the other or in any other jurisdiction.

In order to market and sell A4250, elobixibat, A3384 or any potential future product candidate of ours in jurisdictions other than the United States or Europe, we or a current or potential future licensee or collaborator must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ from that required to obtain FDA or EMA approval. The regulatory approval process outside the United States and Europe generally includes all of the risks associated with obtaining FDA and EMA approval. In addition, some countries outside the United States and Europe require approval of the sales price of a drug before it can be marketed. In many countries, separate procedures must be followed to obtain reimbursement. We or a current or potential future licensee or collaborator may not obtain marketing, pricing or reimbursement approvals outside the United States and Europe on a timely basis, if at all.

Approval by the FDA does not ensure approval by the EMA, approval by the EMA does not assure approval by the FDA, and approval of either or both of the FDA and EMA does not assure approval by regulatory authorities in other countries or jurisdictions. Likewise, approval by any regulatory authority in any country or jurisdiction outside the United States or Europe, such as Japan, does not assure approval by regulatory authorities in other countries or jurisdictions or by the FDA or EMA. We and any current or potential future licensee or collaborator may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our product candidates in any market. Marketing approvals in countries outside the United States and Europe do not ensure pricing approvals in those countries or in any other countries, and marketing approvals and pricing approvals do not ensure that reimbursement will be obtained.

Our ability to obtain and maintain conditional marketing authorizations in the European Union is limited to specific circumstances and subject to several conditions and obligations. A failure to renew any conditional approval that we obtain prior to full approval for the applicable indication would prevent us from continuing to market our products.

Conditional marketing authorizations in the European Union based on incomplete clinical data may be granted for a limited number of listed medicinal products for human use, including products designated as orphan medicinal products under E.U. law, if (1) the risk-benefit balance of the product is positive, (2) it is likely that the applicant will be in a position to provide the required comprehensive clinical trial data, (3) unmet medical needs will be fulfilled and (4) the benefit to public health of the immediate availability on the market of the medicinal product outweighs the risk inherent in the fact that additional data are still required. Specific obligations, including with respect to the completion of ongoing or new studies or trials, and with respect to the collection of pharmacovigilance data, may be specified in the conditional marketing authorization. Conditional marketing authorizations are valid for one year and may be renewed annually, if the risk-benefit balance remains positive, and after an assessment of the need for additional or modified conditions. Even if we obtain conditional approval for A4250 for the treatment of PFIC or any other pediatric cholestatic liver disease or disorder, we may not be able to renew such conditional approval.

Even if we obtain marketing approval for our product candidates, the terms of approvals and ongoing regulation of our products may limit how we manufacture or market our products and compliance with such requirements may involve substantial resources, which could materially impair our ability to generate profit.

Even if marketing approval of a product candidate is granted, an approved product and its manufacturer and marketer are subject to ongoing review and extensive regulation, including the possible requirement to implement a risk evaluation and mitigation strategy or to conduct costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of the product. We must also comply with requirements concerning advertising and promotion for any of our product candidates for which we obtain marketing approval. Promotional communications with respect to prescription drugs are subject to a variety of legal and regulatory restrictions and must be consistent with the

information in the product's approved labeling. Thus, we will not be able to promote any products we develop for indications or uses for which they are not approved. In addition, manufacturers of approved products and those manufacturers' facilities are required to ensure that quality control and manufacturing procedures conform to cGMP, which include requirements relating to quality control and quality assurance as well as the corresponding maintenance of records and documentation and reporting requirements. We and our contract manufacturers could be subject to periodic unannounced inspections by the FDA to monitor and ensure compliance with cGMP.

Accordingly, to the extent we receive marketing approval for one or more of our product candidates, we and our contract manufacturers will continue to expend time, money and effort in all areas of regulatory compliance, including manufacturing, production, product surveillance and quality control. If we are not able to comply with post-approval regulatory requirements, we could have marketing approval for any of our products withdrawn by regulatory authorities and our ability to market any future products could be limited, which could adversely affect our ability to achieve or sustain profitability. Thus, the cost of compliance with post-approval regulations may have a negative effect on our operating results and financial condition.

Any product candidate for which we obtain marketing approval will be subject to strict enforcement of post-marketing requirements and we could be subject to substantial penalties, including withdrawal of our products from the market, if we fail to comply with all regulatory requirements or if we experience unanticipated problems with our products, when and if any of them are approved.

Any product candidate for which we obtain marketing approval, along with the manufacturing processes, post-approval clinical data, labeling, advertising and promotional activities for such product, will be subject to continual requirements of and review by the FDA and other regulatory authorities. These requirements include, but are not limited to, restrictions governing promotion of an approved product, submissions of safety and other post-marketing information and reports, registration and listing requirements, cGMP requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, and requirements regarding the distribution of samples to physicians and recordkeeping.

The FDA closely regulates compliance with all requirements governing prescription drug products, including requirements pertaining to marketing and promotion of drugs in accordance with the provisions of the approved labeling and manufacturing of products in accordance with cGMP requirements. Violations of such requirements may lead to investigations alleging violations of the Food, Drug and Cosmetic Act and other statutes, including the False Claims Act and other federal and state health care fraud and abuse laws as well as state consumer protection laws. Our failure to comply with all regulatory requirements, and later discovery of previously unknown adverse events or other problems with our products, manufacturers or manufacturing processes, may yield various results, including:

- litigation involving patients taking our products;
- restrictions on such products, manufacturers or manufacturing processes;
- restrictions on the labeling or marketing of a product;
- restrictions on product distribution or use;
- requirements to conduct post-marketing studies or clinical trials;
- warning or untitled letters;
- withdrawal of the products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of products;

- fines, restitution or disgorgement of profits or revenues;
- suspension or withdrawal of marketing approvals;
- damage to relationships with any potential collaborators;
- unfavorable press coverage and damage to our reputation;
- refusal to permit the import or export of our products;
- product seizure; or
- injunctions or the imposition of civil or criminal penalties.

Our noncompliance, or noncompliance by any future licensee or collaborator, with regulatory requirements relating to safety monitoring or pharmacovigilance, to the development of products for the pediatric population or to the protection of personal information can lead to significant penalties and sanctions.

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

If a drug is intended for the treatment of a serious or life threatening condition and the drug demonstrates the potential to address unmet medical needs for the condition, the drug sponsor may apply for FDA fast track designation. The designation offers the sponsor opportunities for interactions with the FDA review team and the possibility of a rolling review for certain portions of the marketing application. The FDA has granted fast track designation for A4250 for pruritis associated with PFIC, but there is no assurance that A4250 will receive marketing approval from the FDA or that approval will be granted within any particular timeframe. We may also seek fast track designation for other current or potential future product candidates of ours. Even if the FDA grants fast track designation to one or more of these product candidates, we may not experience a faster development process, review or approval compared to conventional FDA procedures. In addition, the FDA may withdraw fast track designation that may in the future be granted to any of our product candidates if it believes that the designation is no longer supported by data from our clinical development program for that product candidate. Fast track designation alone does not guarantee qualification for the FDA's priority review procedures.

Priority review designation by the FDA may not lead to a faster regulatory review or approval process and, in any event, does not assure FDA approval.

If the FDA determines that a product candidate intended to treat a serious disease, if approved, would provide a significant improvement in safety or effectiveness of the treatment of the disease, the FDA may designate the drug application for that product candidate for priority review. A priority review designation means that the goal for the FDA to review the marketing application is six months from the date of NDA acceptance for filing, rather than the standard review period of ten months from the date of NDA acceptance for filing. We may request priority review for A4250 or other current or potential future product candidates of ours at the time that the marketing application is submitted. The FDA has broad discretion with respect to whether or not to grant priority review status to an individual marketing application. As a result, even if we believe a particular product candidate is eligible for such designation or status, the FDA may decide not to grant it. Moreover, a priority review designation does not necessarily mean a faster regulatory review process or necessarily confer any advantage with respect to approval compared to conventional FDA procedures. Receiving a priority review designation from the FDA does not guarantee approval of the drug application within the six-month review cycle or any time thereafter.

Our relationships with customers, healthcare providers and professionals and third-party payors will be subject to applicable anti-kickback, fraud and abuse and other healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings.

Healthcare providers, physicians and third-party payors play a primary role in the recommendation and prescription of any product candidate, including A4250, elobixibat or A3384, for which we obtain marketing approval. Our future arrangements with customers, healthcare providers and professionals, and third-party payors may expose us to broadly applicable federal and state fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell or distribute any product candidate for which we obtain marketing approval.

The federal anti-kickback statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or paying remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made, in whole or in part, under a federal healthcare program such as Medicare and Medicaid. This statute has been broadly interpreted to apply to manufacturer arrangements with prescribers, purchasers and pharmacy benefit managers, among others. Several other countries, including the United Kingdom, have enacted similar anti-kickback laws and regulations.

The federal False Claims Act imposes civil penalties, and provides for civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government. Both the government and qui tam relators have brought False Claims Act actions against pharmaceutical companies on the theory that their practices have caused false claims to be submitted to the government.

The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program or for knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH Act, and its implementing regulations, also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information.

The federal Physician Payments Sunshine Act requirements under the Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010, referred to together as the Affordable Care Act, require manufacturers of FDA-approved drugs, devices, biologics and medical supplies covered by Medicare or Medicaid to report to the Department of Health and Human Services information related to payments and other transfers of value made to or at the request of covered recipients, such as physicians and teaching hospitals, and physician ownership and investment interests in such manufacturers. Among other payments, the law requires payments made to physicians and teaching hospitals for clinical trials be disclosed.

Analogous state laws and regulations, such as state anti-kickback and false claims laws, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by nongovernmental third-party payors, including private insurers. Some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines, or the relevant compliance guidance promulgated by the federal government, in addition to requiring drug manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures to the extent that those laws impose requirements that are more stringent than the Physician Payments Sunshine Act. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply, we may be subject to significant civil, criminal and administrative penalties, damages, fines, exclusion from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. Violation of certain of these laws could also result in exclusion, suspension and debarment from government funded healthcare programs. Exclusion, suspension or debarment would significantly impact our ability to commercialize, sell or distribute any product candidate for which we obtain regulatory approval. If any of the physicians or other providers or entities with whom we expect to do business are found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

Legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates and affect the prices we may obtain for any product that receives marketing approval.

In the United States and in some other jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of A4250, elobixibat, A3384 or any potential future product candidates of ours, restrict or regulate post-approval activities, or affect our ability to profitably sell any product candidates, including A4250, elobixibat or A3384, for which we obtain marketing approval. In addition, increased scrutiny by the U.S. Congress of the FDA's approval process may significantly delay or prevent marketing approval, as well as subject us to more stringent product labeling and post-marketing testing and other requirements.

In the United States, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the Medicare Modernization Act, changed the way Medicare covers and pays for pharmaceutical products. The legislation expanded Medicare coverage for drug purchases by the elderly and introduced a new reimbursement methodology based on average sales prices for physician administered drugs. In addition, this legislation provided authority for limiting the number of drugs that will be covered in any therapeutic class. Cost reduction initiatives and other provisions of this legislation could decrease the coverage and price that we receive for any approved products. While the Medicare Modernization Act applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own reimbursement rates. Therefore, any reduction in reimbursement that results from the Medicare Modernization Act may result in a similar reduction in payments from private payors.

In March 2010, the Affordable Care Act, or ACA, became law in the United States. The ACA is a sweeping law intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add new transparency requirements for health care and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms. Both Congress and President Trump have expressed an intention to repeal or repeal and replace the ACA, and as a result certain sections of the ACA have not been fully implemented or effectively repealed. The uncertainty around the future of the ACA, and in particular the impact to reimbursement levels, may lead to uncertainty or delay in the purchasing decisions of our customers, which may in turn negatively impact our product sales. If there are not adequate reimbursement levels, our business and results of operations could be adversely affected. Similarly, there are a number of state and local legislative and regulatory efforts related to drug pricing, including a drug price transparency law in Vermont that applies to pharmaceutical manufacturers, that may have an impact on our business.

In addition, the Drug Supply Chain Security Act imposes new obligations on manufacturers of pharmaceutical products related to product tracking and tracing. Legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. We are unsure whether additional legislative changes will be enacted, or whether the current regulations, guidance or interpretations will be changed, or whether such changes will have any impact on our business.

In the European Union, similar political, economic and regulatory developments may affect our ability to profitably commercialize our products. In addition to continuing pressure on prices and cost containment measures, legislative developments at the European Union or E.U. member state level may result in significant additional requirements or obstacles that may increase our operating costs.

We expect that the ACA, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and lower reimbursement, and additional downward pressure on the price that we receive for any approved product. Any reduction in reimbursement from Medicare or other government-funded programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms could result in reduced demand for our product candidates or additional pricing pressures, and may prevent us from being able to generate revenue, attain profitability or commercialize our drugs.

We are subject to anti-corruption laws, as well as export control laws, data protection laws, customs laws, sanctions laws and other laws governing our operations. If we fail to comply with these laws, we could be subject to civil or criminal penalties, other remedial measures and legal expenses, which could adversely affect our business, results of operations and financial condition.

Our operations are subject to anti-corruption laws, including the U.S. Foreign Corrupt Practices Act, or the FCPA, and other anti-corruption laws that apply in countries where we do business and may do business in the future. The FCPA and these other laws generally prohibit us, our officers, and our employees and intermediaries from bribing, being bribed or making other prohibited payments to government officials or other persons to obtain or retain business or gain some other business advantage. We may in the future operate in jurisdictions that pose a high risk of potential FCPA violations and we may participate in collaborations and relationships with third parties whose actions could potentially subject us to liability under the FCPA or local anti-corruption laws. In addition, we cannot predict the nature, scope or effect of future regulatory requirements to which our international operations might be subject or the manner in which existing laws might be administered or interpreted.

We are also subject to other laws and regulations governing our international operations, including regulations administered by the government of the United States and authorities in the European Union, including applicable export control regulations, economic sanctions on countries and persons, customs requirements and currency exchange regulations, collectively referred to as the Trade Control laws In addition, various statutes and rules in Europe and elsewhere around the world regulate privacy and data protection, which affect our collection, use, storage, and transfer of information both abroad and in the United States. New laws and regulations are periodically being enacted in this area, which remains in a state of flux. Monitoring and complying with these laws requires substantial financial resources. In particular, the European Union's General Data Protection Regulation, or GDPR, took effect in May 2018, and will require us to meet new and more stringent requirements regarding the handling of personal data about European Union residents. The GDPR is a complex law and the regulatory guidance is still evolving. Furthermore, many of the countries within the European Union are still in the process of drafting supplementary data protection legislation in key fields where the GDPR allows for national variation, including the fields of clinical study and other health-related information. Failure to meet GDPR requirements could result in penalties of up to 4% of our worldwide revenue. While we have taken steps to comply with the GDPR, including reviewing our security procedures, updating our website, revising our clinical study informed consent forms, and entering into data processing agreements with relevant contractors, we cannot assure you that our efforts to remain in compliance will be fully successful.

There is no assurance that we will be completely effective in ensuring our compliance with all applicable anti-corruption laws, including the FCPA or other legal requirements, including Trade Control laws. If we are not in compliance with the FCPA and other anti-corruption laws or Trade Control laws, we may be subject to criminal and civil penalties, disgorgement and other sanctions and remedial measures, and legal expenses, which could have an adverse impact on our business, financial condition, results of operations and liquidity. Likewise, any investigation of any potential violations of the FCPA, other anti-corruption laws or Trade Control laws by U.S. or other authorities could also have an adverse impact on our reputation, our business, results of operations and financial condition.

We rely significantly on information technology and any failure, inadequacy, interruption or security lapse of that technology or loss of data, including any cyber security incidents, could compromise sensitive information related to our business, prevent us from accessing critical information or expose us to liability which could harm our ability to operate our business effectively and adversely affect our business and reputation.

In the ordinary course of our business, we, our contract research organizations and other third parties on which we rely collect and store sensitive data, including legally protected patient health information, personally identifiable information about our employees, intellectual property, and proprietary business information. We manage and maintain our applications and data utilizing on-site systems. These applications and data encompass a wide variety of business-critical information including research and development information and business and financial information.

The secure processing, storage, maintenance and transmission of this critical information is vital to our operations and business strategy. Despite the implementation of security measures, our internal computer systems and those of third parties with which we contract are vulnerable to damage from cyber-attacks, computer viruses, breaches unauthorized access, interruptions due to employee error or malfeasance or other disruptions, or damage from natural disasters, terrorism, war and telecommunication and electrical failures. Any such event could compromise our networks and the information stored there could be accessed by unauthorized parties, publicly disclosed, lost or stolen. We have measures in place that are designed to detect and respond to such security incidents and breaches of privacy and security mandates. Any such access, disclosure or other loss of information could result in legal claims or proceedings, liability under laws that protect the privacy of personal information, government enforcement actions and regulatory penalties. Unauthorized access, loss or dissemination could also disrupt our operations, including our ability to conduct research, development and commercialization activities, process and prepare company financial information, manage various general and administrative aspects of our business and damage our reputation, in addition to possibly requiring substantial expenditures of resources to remedy, any of which could adversely affect our business. The loss of clinical trial data could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. In addition, there can be no assurance that we will promptly detect any such disruption or security breach, if at all. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and our product research, development and commercialization efforts could be delayed.

Risks Related to Our Business Operations, Employee Matters and Managing Growth

We have identified material weaknesses in our internal control over financial reporting. If we are not able to remediate the material weaknesses and otherwise to maintain an effective system of internal control over financial reporting, the reliability of our financial reporting, investor confidence in us and the value of our common stock could be materially and adversely affected.

Under standards established by the United States Public Company Accounting Oversight Board, a material weakness is a deficiency, or combination of deficiencies, in internal control over financial reporting such that there is a reasonable possibility that a material misstatement of annual or interim financial statements will not be prevented or detected and corrected on a timely basis.

We became a public company in November 2016 and have reported pervasive material weaknesses in our internal controls over financial reporting. See Part II, Item 9A. “Controls and Procedures” of this Annual Report on Form 10-K.

Our management remains committed to the implementation of remediation efforts to address the material weaknesses and even though progress has been made to strengthen our controls, further remediation is needed. Management is in the process of executing a remediation plan with a new chief financial officer hired in October 2018 and a senior director of finance hired in September 2018 to provide enhanced oversight and governance of all financial reporting activities. A new financial reporting system was implemented in the second quarter of 2018 and we are continuing to strengthen our control processes and procedures with enhanced control documentation and additional management reviews to address these weaknesses and to ensure that we become compliant with the requirements of

Section 404 of the Sarbanes-Oxley Act 2002. As we continue to evaluate and work to improve our internal control over financial reporting, our management may take additional measures.

We estimate that we will remediate the material weaknesses during 2019, but we may not ever be able to remediate the material weaknesses. If we are unable to successfully remediate the material weaknesses and otherwise to establish and maintain an effective system of internal control over financial reporting, the reliability of our financial reporting, investor confidence in us and the value of our common stock could be materially and adversely affected.

If we fail to establish and maintain an effective system of internal control over financial reporting, we may not be able to accurately report our financial results or prevent fraud. As a result, stockholders could lose confidence in our financial and other public reporting, which would harm our business and the trading price of our common stock.

Effective internal control over financial reporting is necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, is designed to prevent fraud. Any failure to implement required new or improved controls, or difficulties encountered in their implementation, could cause us to fail to meet our reporting obligations. In addition, any testing by us conducted in connection with Section 404 of the Sarbanes-Oxley Act, or Section 404, or any subsequent testing by our independent registered public accounting firm may reveal deficiencies in our internal control over financial reporting that are deemed to be material weaknesses or that may require prospective or retroactive changes to our consolidated financial statements or identify other areas for further attention or improvement. Inferior internal controls could also cause investors to lose confidence in our reported financial information, which could have a negative effect on the trading price of our common stock.

Pursuant to Section 404, we are required to furnish a report by our management on the effectiveness of our internal control over financial reporting and an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404, we are engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we have hired additional internal resources, engaged outside consultants and adopted a detailed work plan to remediate the material weakness in internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. We and our independent registered public accounting firm were not able to conclude that our internal control over financial reporting was effective at December 31, 2018 as required by Section 404. This could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our consolidated financial statements.

Our future success depends on our ability to retain our chief executive officer and other key executives and to attract, retain and motivate qualified personnel.

We are highly dependent on Ron Cooper, our President and Chief Executive Officer, and other principal members of our management and scientific teams. Although we have formal employment agreements with each of our executive officers, these agreements do not prevent our executives from terminating their employment with us at any time. We do not maintain “key person” insurance on any of our executive officers. The unplanned loss of the services of any of these persons could materially impact the achievement of our research, development and commercialization objectives.

Recruiting and retaining qualified scientific, clinical, manufacturing and sales and marketing personnel, including in the United States and Sweden, will also be critical to our success. We may not be able to attract and retain these personnel on acceptable terms given the competition among numerous biotechnology and pharmaceutical companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us.

We have initiated litigation that may be costly, divert time and efforts away from business operations, require us to pay costs and expenses and/or otherwise have an adverse material impact on our business, and we could become subject to additional litigation in the future.

On February 19, 2019, we filed a complaint for breach of contract and breach of implied covenant of good faith and fair dealing against Ferring International Center S.A. (the "Respondent") in the United States District Court for the Southern District of New York. We previously entered into the License Agreement, dated July 2, 2012, as amended as of October 2013 (the "License Agreement"), by and between Respondent and us, pursuant to which Respondent, among other things, conducted two Phase 3 clinical trials to evaluate the efficacy and safety of elobixibat as a treatment for chronic idiopathic constipation, known as Echo 1 and Echo 2, which ended in 2014. As previously disclosed, the Respondent stopped Echo 1 and Echo 2 early citing an issue related to the distribution of study drug to study sites that was unrelated to the performance of elobixibat and terminated the License Agreement. The complaint alleges that Respondent breached its obligations under the License Agreement to (i) make earned milestone payments, (2) use good clinical practices, good laboratory practices and good manufacturing practices, and (3) use commercially reasonable efforts. The complaint also alleges that Respondent violated the covenant of good faith and fair dealing implied in the License Agreement. In the complaint, we are seeking, among other things, compensatory damages of at least € 37 million.

We have retained outside counsel under a contingency fee arrangement, and as a result, we will not incur attorneys' fees for litigating the matter, but counsel will receive a contingent fee of 33 1/3% of the net recovery (after deduction of expenses) in the event a recovery is received.

Due to their nature, it is difficult to predict the outcome or the costs involved in any litigation. Furthermore, the Respondent may have significant resources and interest to litigate and therefore, although we have a contingency fee arrangement, this litigation could be protracted and may ultimately involve significant legal expenses.

We expect to expand our capabilities and, as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.

We expect to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of drug development, regulatory affairs, finance and administration and sales and marketing. To manage our anticipated future growth, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Due to our limited financial resources and the limited experience of our management team in managing a company with such anticipated growth, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. The physical expansion of our operations may lead to significant costs and may divert our management and business development resources. Any inability to manage growth could delay the execution of our business plans or disrupt our operations.

We incur significant costs and demands as a result of operating as a public company.

We incur significant legal, accounting and other expenses to meet our obligations as a publicly traded company. In addition, the Sarbanes-Oxley Act, the Dodd-Frank Act, the listing requirements of the Nasdaq Stock Market and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Stockholder activism, the current political environment and the current high level of government intervention and regulatory reform may lead to substantial new regulations and disclosure obligations, which may lead to additional compliance costs and impact the manner in which we operate our business in ways that are not currently anticipated. Our management and other personnel will need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will increase our legal and financial compliance costs and will make some activities more time-consuming and costly. For example, these rules and regulations may make it difficult and expensive for us to maintain director and officer liability insurance coverage. As a result, it may be more difficult for us to attract and retain qualified individuals

to serve on our board of directors or as our executive officers, which may adversely affect investor confidence in us and could cause our business or stock price to suffer.

We are exposed to risks related to currency exchange rates.

We conduct a significant portion of our operations outside of the United States. Because our consolidated financial statements are presented in U.S. dollars, changes in currency exchange rates have had and could have in the future a significant effect on our operating results when our operating results are translated into U.S. dollars. Exchange rate fluctuations between local currencies, the euro and the dollar create risk in several ways, including the following: weakening of the dollar may increase the cost of overseas research and development expenses and the cost of sourced product components outside the United States; strengthening of the dollar may decrease the value of our revenues denominated in other currencies; the exchange rates on nondollar transactions and cash deposits can distort our financial results; and commercial pricing and profit margins may be affected.

Our employees, principal investigators, consultants and commercial partners may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements and insider trading, which could cause significant liability for us and harm our reputation.

We are exposed to the risk of fraud or other misconduct by our employees, principal investigators, consultants and collaborators, including intentional failures to comply with FDA or Office of Inspector General regulations or similar regulations of comparable non-U.S. regulatory authorities, provide accurate information to the FDA or comparable non-U.S. regulatory authorities, comply with manufacturing standards we have established, comply with federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable non-U.S. regulatory authorities, report financial information or data accurately or disclose unauthorized activities to us. Misconduct by these parties could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. It is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws, standards or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and results of operations, including the imposition of significant fines or other sanctions.

The United Kingdom's "Brexit" vote in favor of withdrawing from the European Union could adversely impact operations, make it more difficult for us to do business in Europe and impose additional regulatory costs and challenges in securing approval of our candidate products.

On June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the European Union, commonly referred to as "Brexit." Thereafter, on March 29, 2017, the country formally notified the European Union of its intention to withdraw pursuant to Article 50 of the Lisbon Treaty. The withdrawal of the United Kingdom from the European Union will take effect either on the effective date of the withdrawal agreement or, in the absence of agreement, two years after the United Kingdom provided its notice of withdrawal.

It appears likely that this withdrawal will involve a process of lengthy negotiations between the United Kingdom and European Union member states to determine the future terms of the United Kingdom's relationship with the European Union. This could lead to a period of considerable uncertainty and volatility, particularly in relation to United Kingdom financial and banking markets. Weakening of economic conditions or economic uncertainties tend to harm our business, and if such conditions emerge in the U.K. or in the rest of Europe, it may have a material adverse effect on operations and sales.

Currency exchange rates in the pound sterling and the euro with respect to each other and the U.S. dollar have already been adversely affected by Brexit and that may continue to be the case. In addition, depending on the terms of Brexit, the United Kingdom could lose the benefits of global trade agreements negotiated by the European Union on

behalf of its members, which may result in increased trade barriers which could make doing business in Europe more difficult.

We may also face new and additional regulatory costs and challenges from Brexit that could have a material adverse effect on operations. Since a significant proportion of the regulatory framework in the United Kingdom is derived from European Union directives and regulations, the referendum could materially impact the regulatory regime with respect to the approval of our product candidates in the United Kingdom or the European Union. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would prevent us from commercializing product candidates in the United Kingdom and/or the European Union and restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek regulatory approval in the United Kingdom and/or European Union for our product candidates, which could significantly and materially harm our business.

Risks Related to Our Common Stock

Our stock price is expected to continue to be volatile, and the market price of our common stock may drop.

The market price of our common stock could continue to be subject to significant fluctuations. Market prices for securities of clinical-stage pharmaceutical, biotechnology and other life sciences companies have historically been particularly volatile. Some of the factors that may cause the market price of our common stock to fluctuate include:

- the progress, scope, cost, duration or results of our current and any future clinical trials of our product candidates;
- the timing and success of submission, acceptance and approval of regulatory filings;
- our ability to obtain regulatory approvals for our product candidates, delays or failures to obtain such approvals and any restrictions, limitations or warnings in the label of any approved product candidates;
- failure of any of our product candidates, if approved, to achieve commercial success;
- issues in manufacturing our approved products, if any, or product candidates;
- the entry into, or termination of, licensing, collaboration or similar agreements, or other key agreements, and the agreement terms;
- the initiation of, material developments in, or conclusion of litigation to enforce or defend any of our intellectual property rights or defend against the intellectual property rights of others;
- announcements by commercial partners or competitors of new commercial products, clinical progress or the lack thereof, significant contracts, commercial relationships or capital commitments;
- adverse publicity relating to the markets in which we compete, including with respect to other products and potential products in such markets;
- the introduction of technological innovations or new therapies that compete with our product candidates or products, if any;
- the loss of key employees;
- changes in estimates or recommendations by securities analysts, if any, who cover our common stock;

- low trading volume;
- general and industry-specific economic conditions that may affect our research and development expenditures;
- changes in the structure of health care payment systems;
- failure to maintain compliance with listing requirements of The Nasdaq Capital Market; and
- period-to-period fluctuations in our financial results.

Moreover, the stock markets in general have experienced substantial volatility that has often been unrelated to the operating performance of individual companies. These broad market fluctuations may also adversely affect the trading price of our common stock.

In the past, following periods of volatility in the market price of a company's securities, stockholders have often instituted class action securities litigation against those companies. Such litigation, if instituted, could result in substantial costs and diversion of management attention and resources, which could significantly harm our profitability and reputation.

Our stock price may be especially volatile because of, and investor interest in our common stock may be negatively affected by, unauthorized trading of our common stock on stock exchanges in Germany.

We are aware that our common stock may be trading on multiple stock exchanges in Germany, which we have not authorized. These German exchanges have been rumored to allow short selling of stock without assurance that shares sufficient to cover the trade are available, also known as "naked" short selling, or otherwise not comply with exchange requirements that are customary in the United States. The trading of our common stock on these German stock exchanges may make the market price of our common stock more volatile than it would otherwise be. This increased volatility, or the potential for this increased volatility, could have a negative impact on investor interest in our common stock, which could depress the market price of our common stock.

Our executive officers and directors and their affiliates have the ability to control or significantly influence all matters submitted to our stockholders for approval.

As of March 1, 2019, our executive officers and directors, and their affiliates, beneficially own or control approximately 9.4% of our outstanding shares of common stock (after giving effect to the exercise of all outstanding vested and unvested options to purchase shares of our common stock held by our executive officers and directors). Accordingly, these executive officers, directors and their affiliates, acting as a group, will have substantial influence over the outcome of corporate actions requiring stockholder approval, including the election of directors, any merger, consolidation or sale of all or substantially all of our assets or any other significant corporate transactions. These stockholders may also delay or prevent a change of control of us, even if such a change of control would benefit our other stockholders. The significant concentration of stock ownership may cause the price of our common stock to decline if investors perceive that conflicts of interest may exist or arise.

We do not anticipate that we will pay any cash dividends in the foreseeable future.

We currently expect to retain our future earnings to fund the development and growth of our business. As a result, capital appreciation, if any, of our common stock will be your sole source of gain, if any, for the foreseeable future.

Future sales of shares by existing stockholders could cause our stock price to decline.

If any of our executive officers or directors, or their affiliates, sell, or indicate an intention to sell, substantial amounts of our common stock in the public market, the trading price of our common stock could decline. As of March 1,

2019, we had outstanding a total of approximately 12.0 million shares of common stock. Of these shares, approximately 11.9 million shares of common stock are freely tradable, without restriction, in the public market as of March 1, 2019.

Because the share exchange completed pursuant to the Exchange Agreement resulted in an ownership change under Section 382 of the Code, the pre-exchange net operating loss carryforwards and certain other tax attributes of Biodel will be subject to limitations. Our net operating loss carryforwards and other tax attributes may also be subject to additional limitations as a result of ownership changes.

If a corporation undergoes an "ownership change" within the meaning of Section 382 of the Code, or Section 382, the corporation's net operating loss carryforwards and certain other tax attributes arising from before the ownership change are subject to limitations on use after the ownership change. In general, an ownership change occurs if there is a cumulative change in the corporation's equity ownership by certain stockholders that exceeds fifty percentage points over a rolling three-year period. Similar rules may apply under state tax laws. The share exchange resulted in an ownership change for Biodel and, accordingly, the ability to use the net operating loss carryforwards and certain other tax attributes of Biodel will be limited. Our net operating loss carryforwards may also be subject to limitation as a result of shifts in equity ownership or the completed share exchange. Additional ownership changes, such as our public offerings of common stock in May 2017 and January 2018 and sales of common stock under our at-the-market program sales agreement with Cowen, or other transactions in the future could result in additional limitations on our net operating loss carryforwards. Consequently, even if we achieve profitability, we may not be able to utilize a material portion of these net operating loss carryforwards and other tax attributes, which could have a material adverse effect on our cash flow and results of operations.

We may become involved in securities class action litigation that could divert management's attention and harm our business and insurance coverage may not be sufficient to cover all costs and damages.

In the past, securities class action or shareholder derivative litigation often follows certain significant business transactions, such as the sale of a business division or announcement of a merger. We may become involved in this type of litigation in the future. Litigation often is expensive and diverts management's attention and resources, which could adversely affect our business.

Provisions in our corporate charter documents and under Delaware law could make an acquisition of us, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management.

Provisions in our certificate of incorporation and bylaws may discourage, delay or prevent a merger, acquisition or other change in control of us that stockholders may consider favorable, including transactions in which you might otherwise receive a premium for your shares. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Because our board of directors is responsible for appointing the members of our management team, these provisions could in turn affect any attempt by our stockholders to replace current members of our management team.

Among others, these provisions:

- establish a classified board of directors such that not all members of the board are elected at one time;
- allow the authorized number of our directors to be changed only by resolution of our board of directors;
- limit the manner in which stockholders can remove directors from the board of directors;
- establish advance notice requirements for stockholder proposals that can be acted on at stockholder meetings and nominations to our board of directors;

- require that stockholder actions must be effected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent;

- limit who may call stockholder meetings;

- authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a stockholder rights plan or "poison pill" that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board of directors; and

- require the approval of the holders of at least 75% of the votes that all of our stockholders would be entitled to cast to amend or repeal certain provisions of our charter or bylaws.

In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which generally prohibits a person who owns 15% or more of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired 15% or more of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner.

Item 1B. UNRESOLVED STAFF COMMENTS

None.

Item 2. PROPERTIES

We lease approximately 5,116 square feet of office space in the building located at 10 Post Office Square, Boston, Massachusetts, which serves as our corporate headquarters. The lease expires on April 30, 2022, and we have the option to extend the term one time for an additional 5-year period. The base monthly payment on the lease is $21,423 as of March 1, 2019, subject to specified annual increases of approximately 2% during the term of the lease and not including operating expenses, utilities, taxes and insurance for which we are responsible. In addition, we lease approximately 5,100 square feet of office space in Gothenburg, Sweden under a lease that expires in February 2022. The current quarterly payment under the lease is 329,358 Swedish Kronor (approximately $36,780, based on the Swedish Krona to U.S. Dollar exchange rate at December 31, 2018), subject to change based on applicable taxes and otherwise to increase based on changes in the Swedish Consumer Price Index. The lease renews automatically for consecutive three-year terms, unless notice of nonrenewal is given by either party at least nine months prior to the end of the current term and subject to our right to terminate the lease at any time upon six months' notice. We believe that our existing facilities are adequate to meet our current needs and that suitable alternative spaces will be available in the future on commercially reasonable terms.

Item 3. LEGAL PROCEEDINGS

On February 19, 2019, we filed a complaint for breach of contract and breach of implied covenant of good faith and fair dealing against Ferring International Center S.A. (the "Respondent") in the United States District Court for the Southern District of New York. We previously entered into the License Agreement, dated July 2, 2012, as amended as of October 2013 (the "License Agreement"), by and between Respondent and us, pursuant to which Respondent, among other things, conducted two Phase 3 clinical trials to evaluate the efficacy and safety of elobixibat as a treatment for chronic idiopathic constipation, known as Echo 1 and Echo 2, which ended in 2014. As previously disclosed, the Respondent stopped Echo 1 and Echo 2 early citing an issue related to the distribution of study drug to study sites that was unrelated to the performance of elobixibat, and terminated the License Agreement. The complaint alleges that Respondent breached its obligations under the License Agreement to (i) make earned milestone payments, (2) use good clinical practices, good laboratory practices and good manufacturing practices, and (3) use commercially reasonable efforts. The complaint also alleges that Respondent violated the covenant of good faith and fair dealing implied in the License Agreement. In the complaint, we are seeking, among other things, compensatory damages of at least € 37 million.

We have retained outside counsel under a contingency fee arrangement, and as a result, we will not incur attorneys' fees for litigating the matter, but counsel will receive a contingent fee of 33 1/3% of the net recovery (after deduction of expenses) in the event a recovery is received.

Due to their nature, it is difficult to predict the outcome, or the costs involved in any litigation. Furthermore, the Respondent may have significant resources and interest to litigate and therefore, although we have a contingency fee arrangement, this litigation could be protracted and may ultimately involve significant legal expenses.

Item 4. MINE SAFETY DISCLOSURES

Not applicable.

PART II

Item 5. MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES

Market Information

Our common stock is traded on The NASDAQ Capital Market under the symbol "ALBO".

Stockholders

As of March 1, 2019, we had 12,026,25 outstanding shares of common stock and no outstanding shares of preferred stock. As of March 1, 2019, there were approximately 27 holders of record of our common stock.

Unregistered Sales of Securities

Not applicable.

Issuer Purchases of Equity Securities

We did not purchase any of our registered equity securities during the quarter ended December 31, 2018.

Item 6. SELECTED FINANCIAL DATA

Not required for smaller reporting companies.

Item 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

You should read the following discussion and analysis of our financial condition and results of operations together with our consolidated financial statements and the related notes included elsewhere in this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Form 10-K, including information with respect to our plans and strategy for our business and related financing, includes forward-looking statements that involve risks and uncertainties. You should read the "Risk Factors" section of this Annual Report on Form 10-K (see Part I, Item 1A) for a discussion of important factors that could cause actual results to differ materially from the results described in or implied by any forward-looking statement contained in the following discussion and analysis.

Overview

On November 3, 2016, we completed a reverse merger with Biodel, Inc. We are a biopharmaceutical company focused on the development and commercialization of novel bile acid modulators to treat orphan pediatric liver diseases and other liver or gastrointestinal diseases and disorders. The initial target indication for our lead product candidate, A4250, is progressive familial intrahepatic cholestasis, or PFIC, a rare, life-threatening genetic disorder affecting young children for which there is currently no approved drug treatment. We completed a Phase 2 clinical trial of A4250 in children with chronic cholestasis and pruritus, and in May of 2018 we enrolled the first patient in our Phase 3 clinical trial for A4250 in patients with PFIC, which we refer to as PEDFIC 1. In June of 2018, the FDA granted a rare pediatric disease designation to A4250 for the treatment of PFIC, which affirms our eligibility to apply for a rare pediatric disease priority review voucher upon submission of a new drug application for A4250. In September of 2018, the FDA granted fast track designation for A4250 for the treatment of pruritus associated with PFIC. In October of 2018 the FDA granted orphan drug designation to A4250 for the treatment of Alagille syndrome, or ALGS, a rare, life threatening disease that affects the liver and for which there is no approved pharmacologic treatment option. In December of 2018, the European Commission granted orphan designation to A4250 for the treatment of biliary atresia another rare, life threatening disease that affects the liver and for which there is no approved pharmacologic treatment option. In January of 2019, the FDA granted orphan drug designation to A4250 for the treatment of biliary atresia. In addition to PFIC, we plan to initiate a pivotal clinical trial for A4250 in biliary atresia, which we believe to be one of the most common rare pediatric liver diseases, in the second half of 2019, and we plan to conduct clinical development of A4250 in 2020 as a treatment for one or more other pediatric cholestatic liver diseases and disorders. Our most advanced product candidates in addition to A4250 include elobixibat, which is approved in Japan for the treatment of chronic constipation and with which we anticipate initiating a Phase 2 clinical trial as a treatment for NAFLD and NASH, in the second quarter of 2019, and A3384, which is a product candidate to treat bile acid malabsorption, or BAM. In June 2018, we were granted a patent for a method of using Elobixibat to treat NASH in both the U.S. and Europe. We also have a preclinical program in NASH.

Since inception, we have incurred significant operating losses. As of December 31, 2018, we had an accumulated deficit of $96.5 million. We expect to continue to incur significant expenses and increasing operating losses for at least the next few years as we continue our development of, and seek marketing approvals for, our product candidates, prepare for and begin the commercialization of any approved products, and add infrastructure and personnel to support our product development efforts and operations as a public company in the United States.

As a clinical-stage company, our revenues, expenses and results of operations are likely to fluctuate significantly from quarter to quarter and year to year. We believe that period-to-period comparisons of our results of operations should not be relied upon as indicative of our future performance.

As of December 31, 2018, we had approximately $163.9 million in cash and cash equivalents.

Financial Operations Overview

The following discussion sets forth certain components of our consolidated statements of operations as well as factors that impact those items.

Revenue

We generate revenue primarily from the receipt of royalty revenue, upfront or license fees, milestone payments and payment for pharmaceutical ingredient or related procurement services that are made pursuant to license agreements or related supply agreements. License agreements with commercial partners generally include nonrefundable upfront fees and milestone payments, the receipt of which is dependent upon the achievement of specified development, regulatory or commercial milestone events, as well as royalties on product sales of licensed products, if and when such product sales occur, and payments for pharmaceutical ingredient or related procurement services. For these agreements, management applies judgment in the allocation of total agreement consideration to the performance obligations on a reliable basis that reasonably reflects the selling prices that might be expected to be achieved in stand-alone transactions. For additional information about our revenue recognition, refer to Note 1 to our condensed consolidated financial statements included in this Annual Report on Form 10-K.

For the years ended December 31, 2018 and 2017, we recognized into revenue of $12.7 million and $1,000, respectively, related to our agreement from EA Pharma. We expect that any future revenue recognized under our license agreement with EA Pharma will fluctuate from quarter to quarter and year to year as a result of royalties for the period from EA Pharma, as well as, the uncertain timing of future milestone payments, if any.

Operating Expenses

Research and Development Expenses

Research and development expenses consist primarily of personnel costs (including salaries, benefits and other staff-related costs) for employees in research and development functions, costs associated with preclinical and clinical development services, including clinical trials and related manufacturing costs, third-party contract research organizations, or CROs, and related services and other outside costs, including fees for third-party professional services such as consultants. Our preclinical studies and clinical studies are performed by CROs. We expect to continue to focus our research and development efforts on preclinical studies and clinical trials of our product candidates. As a result, we expect our research and development expenses to continue to increase for the foreseeable future.

Our direct research and development expenses are tracked on a program-by-program basis and consist primarily of external costs such as fees paid to CROs and others in connection with our preclinical and clinical development activities and related manufacturing. We do not allocate employee costs or facility expenses, including depreciation or other indirect costs, to specific product development programs because these costs are deployed across multiple product development programs and, as such, are not separately classified.

Successful development of our current and potential future product candidates is highly uncertain. Completion dates and costs for our programs can vary significantly by product candidate and are difficult to predict. As a result, we cannot estimate with any degree of certainty the costs we will incur in connection with development of any of our product candidates. We anticipate we will make determinations as to which programs and product candidates to pursue and how much funding to direct to each program and product candidate on an ongoing basis in response to the results of ongoing and future clinical trials, our ability to enter into licensing, collaboration and similar arrangements with respect to current or potential future product candidates, success of research and development programs and assessments of commercial potential.

General and Administrative Expenses

General and administrative expenses consist primarily of personnel costs (including salaries and benefits) for our executive, finance and other administrative employees. In addition, general and administrative expenses include fees for third-party professional services, including consulting, information technology, legal and accounting services and other corporate expenses.

Critical Accounting Policies and Estimates

Our management's discussion and analysis of financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with United States generally accepted accounting principles. The preparation of these financial statements requires us to make estimates and assumptions that affect the reported amounts of assets, liabilities, revenues and expenses. We base our estimates and assumptions on historical experience and on various assumptions that we believe are reasonable under the circumstances, and we evaluate them on an ongoing basis. These estimates and assumptions form the basis for making judgments about the carrying values of assets and liabilities and the recording of revenues and expenses that are not readily apparent from other sources. Actual results and experiences may differ materially from these estimates and judgments. In addition, our reported financial condition and results of operations could vary if new accounting standards are enacted that are applicable to our business.

Our significant accounting policies are described in Note 1 to our audited consolidated financial statements for the year ended December 31, 2018 in this Annual Report on Form 10-K. We believe that our accounting policies relating to revenue recognition, research and development expenses and accounting for the liability related to sale of future royalties are the most critical to understanding and evaluating our reported financial results. We have identified these policies as critical because they both are important to the presentation of our financial condition and results of operations and require us to make judgments and estimates on matters that are inherently uncertain and may change in future periods. For more information regarding these policies, you should refer to Note 1 of our audited consolidated financial statements included in this Annual Report on Form 10-K.

Revenue Recognition

We generate revenue primarily from the receipt of upfront or license fees, milestone payments, royalties, and payments for pharmaceutical ingredient or related procurement services that are made pursuant to license agreements or related supply agreements. Substantially all of our revenue to date has been derived from our license agreement with EA Pharma and a now-terminated license agreement with Ferring International Center S.A., or Ferring.

We enter into licensing agreements which are within the scope of ASC 606, under which it may exclusively license rights to research, develop, manufacture and commercialize its product candidates to third parties. The terms of these arrangements may include payment to us of one or more of the following: non-refundable, upfront license fees; reimbursement of certain costs; development, regulatory and commercial milestone payments; and royalties on net sales of licensed products.

In determining the appropriate amount of revenue to be recognized we fulfill our obligations under each of our agreements, we perform the following steps: (i) identification of the promised goods or services in the contract; (ii) determination of whether the promised goods or services are performance obligations, including whether they are distinct in the context of the contract; (iii) measurement of the transaction price, including the constraint on variable consideration; (iv) allocation of the transaction price to the performance obligations; and (v) recognition of revenue when (or as) we satisfy each performance obligation. As part of the accounting for these arrangements, the Company must use significant judgment to determine: (a) the number of performance obligations based on the determination under step (ii) above and (b) the transaction price under step (iii) above. We use our judgment to determine whether milestones or other variable consideration, except for royalties, should be included in the transaction price as described further below. The transaction price is allocated to each performance obligation on a relative stand-alone selling price basis, for which we recognize revenue as or when the performance obligations under the contract are satisfied.

Amounts received prior to revenue recognition are recorded as deferred revenue. Amounts expected to be recognized as revenue within the 12 months following the balance sheet date are classified as current portion of deferred revenue in the accompanying consolidated balance sheets. Amounts not expected to be recognized as revenue within the 12 months following the balance sheet date are classified as deferred revenue, net of current portion.

Milestone Payments

At the inception of each arrangement that includes development milestone payments, the Company evaluates whether the milestones are considered probable of being achieved and estimates the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within the control of the Company or the licensee, such as regulatory approvals, are not considered probable of being achieved until those approvals are received. The Company evaluates factors such as the scientific, clinical, regulatory, commercial, and other risks that must be overcome to achieve the particular milestone in making this assessment. There is considerable judgment involved in determining whether it is probable that a significant revenue reversal would not occur. At the end of each subsequent reporting period, the Company reevaluates the probability of achievement of all milestones subject to constraint and, if necessary, adjusts its estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect revenues and earnings in the period of adjustment.

Royalties

For arrangements that include sales-based royalties, including milestone payments based on a level of sales, and the license is deemed to be the predominant item to which the royalties relate, the Company recognizes revenue at the later of (i) when the related sales occur, or (ii) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied).

Research and Development Expenses

Research and development costs are expensed as incurred. We recognize costs for certain development activities based on an evaluation of the progress to completion of specific tasks using information and data provided by CROs and other third-party vendors, including clinical trial sites. We determine accrual estimates through financial models that take into account discussion with applicable personnel and service providers as to the progress or state of completion of particular research and development activities, including clinical trials. Our preclinical study and clinical trial accrued liabilities and prepaid assets are dependent, in part, upon the receipt of timely and accurate reporting from CROs and other third party vendors, including clinical trial sites. Although we do not expect our estimates to differ materially from amounts we actually incur, our understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and may result in reported amounts that are too high or too low for any particular period. When contracts for research and development services require advance payment, they are recorded on our consolidated balance sheet as prepaid items and expensed when the service is provided or reaches a specific milestone outlined in the contract.

Monetization of Future Royalties

In December 2017, we executed the RIAA with HCR pursuant to which it sold to HCR the right to receive all royalties from sales in Japan and sales milestones achieved from any covered territory potentially payable to the Company under the Agreement, up to a specified maximum “cap” amount of $78.8 million, based on the funds the Company received from HCR to date. We received $44.5 million from HCR, net of certain transaction expenses. The Company is obligated to make royalty interest payments to HCR under the RIAA only to the extent it receives future Japanese royalties, sales milestones or other specified payments from EA Pharma. The Company recorded the $44.5 million as a liability related to sale of future royalties (royalty obligation). The royalty obligation will be amortized using

the effective interest rate method, based on the Company's best estimate of the time it will take to reach the capped amount.

In order to determine the amortization of the royalty obligation, the Company is required to estimate the total amount of future royalty payments to be received and submitted to HCR, as noted above, based on the Company's best estimate of the time it will take to reach the cap amount and when milestones will be received. The sum of these amounts less the $44.5 million proceeds the Company received will be recorded as interest expense over the life of the royalty obligation. Since inception, the Company's estimate of its total interest expense resulted in a quarterly effective interest rate of approximately 4.27%. The Company periodically assesses the estimated royalty payments to HCR and to the extent such payments are greater or less than its initial estimates or the timing of such payments is materially different than its original estimates, the Company will prospectively adjust the accretion of interest on the royalty obligation. There are a number of factors that could materially affect the amount and the timing of royalty payments, most of which are not within the Company's control. Such factors include, but are not limited to, the rate of elobixibat prescriptions, the number of doses administered, the introduction of competing products, manufacturing or other delays, patent protection, adverse events that result in governmental health authority imposed restrictions on the use of the drug products, significant changes in foreign exchange rates as the royalties remitted to HCR are in U.S. dollars while sales of elobixibat are in Japanese yen, and sales never achieving forecasted numbers, which would result in reduced royalty payments and reduced non-cash interest expense over the life of the royalty obligation.

Results of Operations

Years Ended December 31, 2018 and December 31, 2017

Revenue

	December 31,		Change
	2018	2017	$
	In thousands		
Revenue	$ 12,740	$ 1	$ 12,739

Revenue was $12.7 million for the year ended December 31, 2018, compared with revenue of $1,000 for the year ended December 31, 2017, an increase of $12.7 million. The higher revenue is due to a $11.2 million milestone payment received from EA Pharma due to the approval by the Japanese MHLW of the new drug application for elobixibat for the treatment of chronic constipation and $1.5 million in royalty revenue received from EA Pharma for elobixibat for the period.

Research and development expenses

	December 31,		Change
	2018	2017	$
	In thousands		
Research and development expenses	$ 31,732	$ 12,991	$ 18,741

Research and development expenses were $31.7 million for the year ended December 31, 2018 compared with $13.0 million for the year ended December 31, 2017, an increase of $18.7 million. The higher research and development expenses for 2018 were principally due to an increase of $9.5 million in costs associated with the development of A4250, including costs incurred for manufacturing and clinical development activities for our Phase 3 clinical trial in patients with PFIC, an increase of $4.9 million in personnel and related expenses as we continue to increase our headcount, and an increase of $2.4 million in preclinical work primarily associated with NASH.

The following table summarizes our principal product development programs and the out-of-pocket third-party expenses incurred with respect to each clinical-stage product candidate and our preclinical programs for the years ended December 31, 2018 and 2017.

	December 31,		Change
	2018	2017	$
		(in thousands)	
Direct third-party project costs:			
A4250	$ 16,533	$ 7,078	$ 9,455
Elobixibat	836	76	760
A3384	770	364	406
Preclinical	2,605	165	2,440
Total	$ 20,744	$ 7,683	$ 13,061
Other project costs[1]:			
Personnel costs	$ 7,106	$ 2,174	$ 4,932
Other costs[2]	3,882	3,134	748
Total	$ 10,988	$ 5,308	$ 5,680
Total research and development costs	$ 31,732	$ 12,991	$ 18,741

(1) Other project costs are leveraged across multiple programs.
(2) Other costs include facility, supply, consultant and overhead costs that support multiple programs.

General and administrative expenses

	December 31,		Change
	2018	2017	$
		(in thousands)	
General and administrative expenses	$ 18,061	$ 15,246	$ 2,815

General and administrative expenses were $18.1 million for the year ended December 31, 2018 compared with $15.2 million for the year ended December 31, 2017, an increase of $2.8 million. The increased general and administrative expenses for 2018 were principally attributable to an increase in personnel and stock-based compensation costs and recruitment costs.

Other operating (income) expense, net

	December 31,		Change
	2018	2017	$
		In thousands	
Other operating (income) expense, net	$ 837	$ (3,659)	$ 4,496

Other operating (income) expense, net totaled $837,000 of expense for the year ended December 31, 2018 compared with $3.7 million of income for the year ended December 31, 2017, a difference of $4.5 million. The difference in other operating (income) expense, net was primarily due to a gain of $3.5 million from our sale of certain legacy intellectual property of Biodel in October 2017, as well as changes in the currency exchange rates between the two periods.

Interest income (expense), net

	December 31,		Change
	2018	2017	$
		In thousands	
Interest income (expense), net	$ (4,838)	$ 40	$ (4,878)

Interest income (expense), net totaled $4.8 million of expense for the year ended December 31, 2018 compared with $40,000 of income for the year ended December 31, 2017, a difference of $4.9 million. The difference was principally attributable to $7.0 million in non-cash interest expense recorded in connection with the sale of future royalties relating to sales of elobixibat in Japan, partially offset by interest income for the 2018 period, compared to lower interest expense offset by interest income in 2017.

Other non-operating income (expense), net

	Year Ended December 31,		Change
	2018	2017	$
	In thousands		
Other non-operating income (expense), net	$ (3,363)	$ 335	$ (3,698)

Other non-operating income (expense), net was $3.4 million of expense for the year ended December 31, 2018 compared with $335,000 of income for the year ended December 31, 2017, a difference of $3.7 million. The difference is primarily related to the foreign currency transaction expenses associated with our royalty monetization offset by the exercise of warrants by our lender in May 2017.

Income tax

	Year Ended December 31,		Change
	2018	2017	$
	In thousands		
Income tax	$ 20	$ 212	$ (192)

Income tax expense was $20,000 for the year ended December 31, 2018 compared to $212,000 for the year ended December 31, 2017.

Liquidity and Capital Resources

Sources of Liquidity

We do not expect to generate significant revenue from product sales unless and until we or a potential future licensee or collaborator obtains marketing approval for, and commercializes, one or more of our current or potential future product candidates (other than elobixibat as a treatment for chronic constipation in Japan), which we do not expect to occur until at least 2021, if at all. We anticipate that we will continue to generate losses for the foreseeable future, and we expect the losses to increase as we continue the development of and seek regulatory approvals for our product candidates. We are subject to all of the risks applicable to the development of new pharmaceutical products and may encounter unforeseen expenses, difficulties, complications, delays and other unknown factors that may harm our business. We expect that we will need substantial additional funding to complete development of and potentially commercialize our product candidates.

Our operations have historically been financed primarily through issuances of equity or convertible debt, upfront fees paid upon entering into license agreements, payments received upon the achievement of specified milestone events under license agreements, grants and venture debt borrowings. Our primary uses of capital are, and we expect will continue to be, personnel-related costs, third party expenses associated with our research and development programs, including the conduct of clinical trials, and manufacturing-related costs for our product candidates.

As of December 31, 2018, our cash and cash equivalents were approximately $163.9 million.

During the first quarter of 2018, following the Japanese MHLW's approval of elobixibat for the treatment of chronic constipation in January 2018, we received a $45 million payment, net of certain transaction expenses, from HCR

under our RIAA. Under the terms of the RIAA, we are eligible to receive an additional $15 million if a specified sales milestone is achieved for elobixibat in Japan. Additionally, this approval triggered a milestone payment to us from EA Pharma of $11.2 million.

As of March 1, 2019, we have received approximately $45.4 million in upfront and milestone payments from EA Pharma under a license agreement for the development and commercialization of elobixibat in specified countries in Asia. We are eligible to receive additional amounts of up to $4.9 million under the amended agreement, if a specified regulatory event is achieved for elobixibat. In addition, subject to the terms of the RIAA with HCR, we may in the future also become eligible under the license agreement to receive up to $31.9 million, if specified sales milestones are achieved for elobixibat and stepped royalties at rates beginning in the high single digits on any future elobixibat product sales.

On or about March 6, 2019, we expect to file a new universal shelf registration on Form S-3 with the SEC, pursuant to which we expect to register for sale up to $200 million of any combination of our common stock, preferred stock, debt securities, warrants, rights and/or units from time to time and at prices and on terms that we may determine, which we refer to as the 2019 Form S-3. On or about March 6, 2019, we intend to terminate the 2017 Sales Agreement and enter into a new sales agreement, which we refer to as the 2019 Sales Agreement, with respect to an at-the-market offering program under which we may offer and sell, from time to time at our sole discretion, shares of our common stock having an aggregate offering price of up to $50.0 million. Our issuance and sale, if any, of shares under the 2019 Sales Agreement is subject to the effectiveness of the 2019 Form S-3. We make no assurances as to if or when the 2019 Form S-3 will become effective or, if it does become effective, as to the continued effectiveness of the 2019 Form S-3. No additional securities registered under the 2017 Form S-3 (defined below) will be offered or sold after date of effectiveness of the 2019 Form S-3. This report shall not constitute an offer to sell or the solicitation of an offer to buy any shares under the 2019 Sales Agreement that we intend to enter into or any securities under the 2019 Form S-3 that we intend to file with the SEC, nor shall there be any sale of such securities in any state in which such offer, solicitation or sale would be unlawful prior to registration or qualification under the securities laws of any such state.

In January 2018, we completed an underwritten public offering of 2,265,500 shares of our common stock for net proceeds of approximately $69.9 million under our universal shelf registration on Form S-3, which was declared effective on December 7, 2017 and pursuant to which we registered for sale up to $125 million of any combination of our common stock, preferred stock, debt securities, warrants, rights, purchase contracts and/or units from time to time and at prices and on terms that we may determine, which we refer to as the 2017 Form S-3. Subsequently, in February 2018, we sold 728,862 shares of our common stock for net proceeds of approximately $24.2 million pursuant to an at-the-market offering program Sales Agreement that we entered into with Cowen in October 2017.

In October 2017, we entered into an asset purchase agreement pursuant to which we sold legacy intellectual property of our predecessor, Biodel, for $4.5 million.

In May 2017, we completed an underwritten public offering of 2,530,000 shares of our common stock for net proceeds of $48.5 million.

Cash Flows

Years ended December 31, 2018 and December 31, 2017

	December 31,	
	2018	2017
	(in thousands)	
Net cash provided by (used in):		
Operating activities	$ (26,802)	(27,566)
Investing activities	(47)	4,310
Financing activities	139,182	45,838
Total	$ 112,333	22,582
Effect of exchange rate changes on cash and cash equivalents	(1,679)	718
Net increase in cash and cash equivalents	$ 110,654	$ 23,300

Operating activities

Net cash used in operating activities for the year ended December 31, 2018 was $26.8 million compared to $27.6 million for 2017. The change is primarily due to the milestone payment from EA Pharma of $11.2 million during the 2018 period offset by increased R&D expenses and $7.0 million in non-cash interest expense on liability related to royalty monetization.

Investing activities

Net cash used in investing activities for the year ended December 31, 2018 was $47,000 compared to $4.3 million provided by investing activities for 2017. The change is due to the sale of intellectual property of $4.5 million in 2017.

Financing activities

Net cash provided by financing activities for the year ended December 31, 2018 was $139.2 million compared to $45.8 million for 2017. The difference was principally due to our receipt of (i) $94.2 million in aggregate net proceeds from our public offering in January 2018 and our sales through our at-the-market offering program sales agreement in February 2018, and (ii) $44.5 million in net proceeds from HCR under our RIAA in February 2018. Net cash provided by financing activities for the year ended December 31, 2017 was $45.8 million primarily driven by our receipt of $48.5 million in net proceeds from a public offering completed in May 2017, partially offset by principal payments on a former loan facility.

Funding Requirements

Cash used to fund operating expenses is affected by the timing of when we pay expenses, as reflected in the change in our outstanding accounts payable and accrued expenses. We believe that our existing cash and cash equivalents will be sufficient to meet our projected operating requirements at least into 2021, including for our Phase 3 clinical program for A4250 in PFIC, but we will need additional financing to develop A4250 for the treatment of one or more pediatric cholestatic liver diseases in 2020. However, our operating plans may change as a result of many factors, including those described below and we may need additional funds sooner than planned to meet operational needs and capital requirements. In addition, if the conditions for raising capital are favorable we may seek to raise additional funds at any time.

Our future funding requirements will depend on many factors, including the following:

- the costs, design, duration and any potential delays of the Phase 3 clinical trial of A4250;

- the scope, number, progress, duration, cost, results and timing of clinical trials and nonclinical studies of our current or future product candidates;
- whether and to what extent milestone events are achieved under our license agreement with EA Pharma, our RIAA with HCR or any potential future licensee or collaborator;
- the outcomes and timing of regulatory reviews, approvals or other actions;
- our ability to obtain marketing approval for our product candidates;
- our ability to establish and maintain additional licensing, collaboration or similar arrangements on favorable terms and whether and to what extent we retain development or commercialization responsibilities under any new licensing, collaboration or similar arrangement;
- the success of any other business, product or technology that we acquire or in which we invest;
- our ability to maintain, expand and defend the scope of our intellectual property portfolio;
- our ability to manufacture any approved products on commercially reasonable terms;
- our ability to establish a sales and marketing organization or suitable third-party alternatives for any approved product;
- the number and characteristics of product candidates and programs that we pursue;
- the costs of acquiring, licensing or investing in businesses, product candidates and technologies;
- our need and ability to hire additional management and scientific and medical personnel;
- the costs to operate as a public company in the United States, including the need to implement additional financial and reporting systems and other internal systems and infrastructure for our business;
- market acceptance of our product candidates, to the extent any are approved for commercial sale; and
- the effect of competing technological and market developments.

We cannot determine precisely the completion dates and related costs of our development programs due to inherent uncertainties in outcomes of clinical trials and the regulatory approval process. We cannot be certain that we will be able to successfully complete our research and development programs or establish licensing, collaboration or similar arrangements for our product candidates. Our failure or the failure of any current or potential future licensee to complete research and development programs for our product candidates could have a material adverse effect on our financial position or results of operations.

We expect to continue to incur losses. Our ability to achieve and maintain profitability is dependent upon the successful development, regulatory approval and commercialization of our product candidates and achieving a level of revenues adequate to support our cost structure. We may never achieve profitability.

If the conditions for raising capital are favorable, we may seek to finance future cash needs through public or private equity or debt offerings or other financings. Additionally, if we need to raise additional capital to fund our operations, complete clinical trials, or potentially commercialize our product candidates, we may likewise seek to finance future cash needs through public or private equity or debt offerings or other financings. The necessary funding may not be available to us on acceptable terms or at all.

We filed a universal shelf registration statement on Form S-3 with the SEC, which was declared effective on December 5, 2017 and pursuant to which we registered for sale up to $125 million of any combination of our common stock, preferred stock, debt securities, warrants, rights, purchase contracts and/or units from time to time and at prices and on terms that we may determine. As of March 1, 2019, approximately $25.2 million of securities remain available for issuance under this shelf registration statement, including up to $25.0 million of our common stock available for issuance pursuant to the at-the-market offering program sales agreement that we entered into with Cowen in October 2017, as described above, but which sales agreement we expect to terminate on or about March 6, 2019. On or about March 6, 2019, we expect to file a new universal shelf registration on Form S-3 with the SEC, pursuant to which we expect to register for sale up to $200 million of any combination of our common stock, preferred stock, debt securities, warrants, rights and/or units from time to time and at prices and on terms that we may determine, which we refer to as the 2019 Form S-3, including up to $50.0 million of our common stock pursuant to the new sales agreement with respect to an at-the-market offering program. We make no assurances as to if or when the 2019 Form S-3 will become effective or, if it does become effective, as to the continued effectiveness of the 2019 Form S-3. No additional securities registered under the 2017 Form S-3 will be offered or sold after the date of effectiveness of the 2019 Form S-3. This report shall not constitute an offer to sell or the solicitation of an offer to buy any shares under the 2019 Sales Agreement that we intend to enter into or any securities under the 2019 Form S-3 that we intend to file with the SEC, nor shall there be any sale of such securities in any state in which such offer, solicitation or sale would be unlawful prior to registration or qualification under the securities laws of any such state.

The sale of additional equity or convertible debt securities may result in significant dilution to our stockholders, and the terms may include liquidation or other preferences that adversely affect the rights of our stockholders. The incurrence of additional debt financing would result in debt service obligations and the instruments governing such debt may provide for operating and financing covenants that would restrict our operations. We may also seek to finance future cash needs through potential future licensing, collaboration or similar arrangements. These arrangements may not be available on acceptable terms or at all, and we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or to grant licenses on terms that may not be favorable to us. If adequate funds are not available, we may be required to delay, reduce the scope of or eliminate our development programs or obtain funds through third-party arrangements that may require us to relinquish rights to certain product candidates that we might otherwise seek to develop or commercialize independently.

Off-Balance Sheet Arrangements

We have no off-balance sheet arrangements as defined under the applicable SEC rules.

Item 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

Not required for smaller reporting companies.

Item 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

ALBIREO PHARMA, INC.

Item 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE

Not applicable.

Item 9A. CONTROLS AND PROCEDURES

Evaluation of Disclosure Controls and Procedures

Our principal executive officer and principal financial officer, after evaluating the effectiveness of our disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) as of the end of the period covered by this Form 10-K, have concluded that, based on such evaluation and the material weaknesses discussed below under "Management's Report on Internal Control over Financial Reporting," our disclosure controls and procedures were not effective to ensure that information required to be disclosed by us in the reports that we file or submit under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the SEC's rules and forms, and is accumulated and communicated to our management, including our principal executive and principal financial officers, or persons performing similar functions, as appropriate to allow timely decisions regarding required disclosure.

Notwithstanding the identified material weaknesses, management, including our principal executive officer and principal financial officer, believes the consolidated financial statements included in this Form 10-K fairly represent in all material respects our financial condition, results of operations and cash flows as of and for the periods presented in accordance with U.S. generally accepted accounting principles (GAAP). As discussed below, we have taken steps to remediate the material weaknesses.

Management's Report on Internal Control over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting. Internal control over financial reporting is defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act, as a process designed by, or under the supervision of, our principal executive and principal financial officers and effected by our board of directors, management and other personnel to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. Our internal control over financial reporting includes those policies and procedures that:

- pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of our assets;
- provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that our receipts and expenditures are being made only in accordance with authorizations of our management and directors; and
- provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of our assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Our management conducted an assessment of the effectiveness of our internal control over financial reporting as of December 31, 2018, and, in making this assessment, used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) in Internal Control-Integrated Framework (2013 framework).

As of December 31, 2018, based on our assessment management concluded that the identified material weaknesses previously disclosed are pervasive in our internal control processes and involve the control environment, risk assessment, control activity and monitoring activities of the COSO framework, remain unremediated. A material weakness is a deficiency, or a combination of deficiencies, in internal control over financial reporting, such that there is a reasonable possibility that a material misstatement of our annual or interim financial statements will not be prevented or detected on a timely basis. Specifically, the material weaknesses relate to: an insufficiently staffed finance organization with the requisite knowledge of U.S. GAAP and SEC reporting or skills in and ability to focus on internal control over financial reporting matters; not fully designing, implementing and monitoring policies or financial reporting controls that identify and sufficiently mitigate risks of material misstatement to the financial statements; and insufficient design, implementation and monitoring of general information technology controls to support the effective operation of financial controls. Because of the material weaknesses described above, our management believes that, as of December 31, 2018, our internal control over financial reporting was not effective.

Our independent registered public accounting firm has issued an audit report on our assessment of our internal control over financial reporting. This report appears further below in this Item 9A.

Remediation of the Material Weaknesses in Internal Control Over Financial Reporting

Our management remains committed to the implementation of remediation efforts to address the material weaknesses and even though progress has been made to strengthen our controls, further remediation is needed. Management is in the process of executing a remediation plan with a new chief financial officer hired in October 2018 and a senior director of finance hired in September 2018 to provide enhanced oversight and governance of all financial reporting activities. Additionally, new accounting staff with the requisite knowledge of internal controls over financial reporting matters were hired in February 2019. A new financial reporting system was implemented in the second quarter of 2018 and we are continuing to implement and augment our control processes and procedures and related documentation, including additional management reviews to address these weaknesses and to ensure that we become compliant with the requirements of Section 404 of the Sarbanes-Oxley Act 2002. However, the material weaknesses will not be considered remediated until the enhanced controls operate for a sufficient period of time and management has concluded, through testing, that the controls are operating effectively. As we continue to evaluate and work to improve our internal control over financial reporting, our management may take additional measures.

Changes in Internal Control over Financial Reporting

Other than the ongoing remediation efforts described above, there was no change in our internal control over financial reporting that occurred during the fourth fiscal quarter of the period covered by this report that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Report of Independent Registered Public Accounting Firm

The Board of Directors and Stockholders of Albireo Pharma, Inc.

Opinion on Internal Control over Financial Reporting

We have audited Albireo Pharma, Inc.'s internal control over financial reporting as of December 31, 2018, based on criteria established in Internal Control — Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) (the COSO criteria). In our opinion, because of the effect of the material weaknesses described below on the achievement of the objectives of the control criteria, Albireo Pharma, Inc. (the Company) has not maintained effective internal control over financial reporting as of December 31, 2018, based on the COSO criteria.

A material weakness is a deficiency, or combination of deficiencies, in internal control over financial reporting, such that there is a reasonable possibility that a material misstatement of the company's annual or interim financial statements will not be prevented or detected on a timely basis. The following material weaknesses have been identified and included in management's assessment: Management concluded that the material weaknesses previously disclosed are pervasive to the internal control processes and involve the control environment, risk assessment, control activity and monitoring activities of the COSO framework, and remain unremediated at December 31, 2018. Specifically, the material weaknesses relate to: an insufficiently staffed finance organization with the requisite knowledge of U.S. GAAP and SEC reporting or skills in and ability to focus on internal control over financial reporting matters; not fully designing, implementing and monitoring policies or financial reporting controls that identify and sufficiently mitigate risks of material misstatement to the financial statements; and insufficient design, implementation and monitoring of general information technology controls to support the effective operation of financial controls.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the consolidated balance sheets of the Company as of December 31, 2018 and 2019, the related consolidated statements of operations, comprehensive loss, stockholders' equity and cash flows for each of the two years in the period ended December 31, 2018, and the related notes. These material weaknesses were considered in determining the nature, timing and extent of audit tests applied in our audit of the 2018 consolidated financial statements, and this report does not affect our report dated March 6, 2019, which expressed an unqualified opinion thereon.

Basis for Opinion

The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Management's Report on Internal Control over Financial Reporting. Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects.

Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

Definition and Limitations of Internal Control Over Financial Reporting

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ Ernst & Young LLP

Boston, Massachusetts
March 6, 2019

Item 9B. OTHER INFORMATION

Employment Arrangements

On March 6, 2019, we entered into amended and restated employments agreements with certain of our executive officers, including our named executive officers Ronald H.W. Cooper, our President and Chief Executive Officer, and Martha J. Carter, our Chief Regulatory Officer.

Amended and Restated Employment Agreement with Ronald H.W. Cooper

The amended and restated employment agreement, effective as of March 6, 2019, by and between the Company and Mr. Cooper (the "Cooper Employment Agreement") provides for a base salary of $551,000 per year, that he is eligible to participate in an annual bonus plan provided by the Company, and that his annual target bonus opportunity is 50% of his base salary, with the actual amount of the bonus, if any, to be determined by our board of directors or compensation committee. Mr. Cooper is also eligible to participate in our employee benefit plans from time to time in effect for similarly-situated employees of the Company, which may include short-term disability, long-term disability and 401(k) retirement savings plans, and to reimbursement of business expenses.

The Cooper Employment Agreement also provides that if we terminate Mr. Cooper's employment without cause or if Mr. Cooper terminates his employment for good reason, he will be entitled to the following, subject to obtaining from him a general release of claims (the "Cooper Severance Benefits"): (i) severance payments for 12 months at his then-current base salary, (ii) an amount equal to his then-current target bonus, payable over 12 months, (iii) a pro-rated annual bonus for the fiscal year in which the termination occurs, and (iv) payment for 12 months of the portion of the healthcare premiums that we paid prior to his termination if he elects and remains eligible for Consolidated Omnibus Budget Reconciliation Act ("COBRA") (or mini-COBRA) health benefits; provided that if such termination occurs within 12 months following a change of control, his severance payments will be for 18 months at his then-current base salary, the amount equal to his then-current target bonus will be payable over 18 months, and the payment of healthcare premiums will be for 18 months. He will also be entitled to receive any base salary earned but not paid through the termination date, any business expenses incurred but unreimbursed on the termination date, and any annual bonus earned but not paid for the fiscal year preceding the fiscal year in which the termination occurs (the "Cooper Final Compensation"). In addition, all outstanding equity awards held by Mr. Cooper will become fully vested if we terminate

Mr. Cooper's employment without cause or if Mr. Cooper terminates his employment for good reason within 12 months following a change of control. If Mr. Cooper's employment is terminated due to his disability, death or for cause, he or his estate will be entitled to receive the Cooper Final Compensation and, except in the case of a termination of his employment for cause, a pro-rated annual bonus for the fiscal year in which the termination occurs. If Mr. Cooper terminates his employment without good reason, he will be entitled to the Cooper Final Compensation (other than reimbursement of expenses).

Mr. Cooper is subject to confidentiality and protection of intellectual property provisions as well as to noncompetition and nonsolicitation provisions during his employment with us and the 12 months thereafter. Unless we waive Mr. Cooper's noncompetition obligations (which are effective following the termination of his employment only to the extent we terminate Mr. Cooper's employment for restricted cause or Mr. Cooper terminates his employment for any reason), we will pay Mr. Cooper a noncompetition payment equal to 50% of his then-current base salary, reduced by any Cooper Severance Benefits that Mr. Cooper is eligible to receive from us, subject to obtaining from him a general release of claims.

Amended and Restated Employment Agreement with Martha J. Carter

The amended and restated employment agreement, effective as of March 6, 2019, by and between the Company and Ms. Carter (the "Carter Employment Agreement") provides for a base salary of $387,660 per year, that she is eligible to participate in an annual bonus plan provided by the Company, and that her annual target bonus opportunity is 35% of her base salary, with the actual amount of the bonus, if any, to be determined by our board of directors or compensation committee. Ms. Carter's annual base salary and target bonus opportunity are subject to adjustment upward, but not downward, from time to time by our board of directors in its sole discretion. Ms. Carter is also eligible to participate in our employee benefit plans from time to time in effect for similarly-situated employees of the Company, which may include short-term disability, long-term disability and 401(k) retirement savings plans, and to reimbursement of business expenses.

The Carter Employment Agreement also provides that if we terminate Ms. Carter's employment without cause or if Ms. Carter terminates her employment for good reason, she will be entitled to the following, subject to obtaining from her a general release of claims (the "Carter Severance Benefits"): (i) severance payments for 12 months at her then-current base salary, (ii) an amount equal to her then-current target bonus, payable over 12 months, and (iii) payment for 12 months of the portion of the healthcare premiums that we paid prior to her termination if she elects and remains eligible for COBRA (or mini-COBRA) health benefits (or, if she is not eligible for COBRA (or mini-COBRA), the portion of the healthcare premiums we paid for similarly situated executives); provided that if such termination occurs within 12 months following a change of control, her severance payments will be for 15 months at her then-current base salary, the amount equal to her then-current target bonus will be payable over 15 months, and the payment of healthcare premiums will be for 15 months. She will also be entitled to receive any base salary earned but not paid through the termination date, any business expenses incurred but unreimbursed on the termination date, and any annual bonus earned but not paid for the fiscal year preceding the fiscal year in which the termination occurs (the "Carter Final Compensation"). In addition, all outstanding equity awards held by Ms. Carter will become fully vested if we terminate Ms. Carter's employment without cause or if Ms. Carter terminates her employment for good reason within 12 months following a change of control; provided that any outstanding equity awards held by Ms. Carter that were granted prior to January 1, 2019 will become fully vested upon a change of control. If Ms. Carter's employment is terminated due to her disability, death or for cause, she or her estate will be entitled to receive the Carter Final Compensation. If Ms. Carter terminates her employment without good reason, she will be entitled to the Carter Final Compensation (other than reimbursement of expenses).

Ms. Carter is subject to confidentiality and protection of intellectual property provisions as well as to noncompetition and nonsolicitation provisions during her employment with the Company and the 12 months thereafter. Unless we waive Ms. Carter's noncompetition obligations (which are effective following the termination of her employment only to the extent we terminate Ms. Carter's employment for restricted cause or Ms. Carter terminates her employment for any reason), we will pay Ms. Carter a noncompetition payment equal to 50% of her then-current base salary, reduced by any Carter Severance Benefits that Ms. Carter is eligible to receive from us, subject to obtaining from her a general release of claims.

The summary of the Cooper Employment Agreement and the Carter Employment Agreement is qualified in its entirety by reference to the full text of such agreements, copies of which are attached to this report as Exhibit 10.1 and 10.4, respectively, and are incorporated herein by reference.

PART III

Item 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

The response to this item is incorporated by reference from the discussion responsive thereto under the captions "Management and Corporate Governance," "Section 16(a) Beneficial Ownership Reporting Compliance," and "Corporate Code of Conduct and Ethics" in our proxy statement for the 2019 annual meeting of stockholders.

Item 11. EXECUTIVE COMPENSATION

The response to this item is incorporated by reference from the discussion responsive thereto under the caption "Executive Officer and Director Compensation" in our proxy statement for the 2019 annual meeting of stockholders.

Item 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS

The response to this item is incorporated by reference from the discussion responsive thereto under the captions "Security Ownership of Certain Beneficial Owners and Management," "Equity Compensation Plan Information" and "Proposal 2: Approval of the Amendment to the Albireo Pharma, Inc. 2018 Equity Incentive Plan" in our proxy statement for the 2019 annual meeting of stockholders.

Item 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS, AND DIRECTOR INDEPENDENCE

The response to this item is incorporated by reference from the discussion responsive thereto under the captions "Certain Relationships and Related Person Transactions" and "Management and Corporate Governance" in our proxy statement for the 2019 annual meeting of stockholders.

Item 14. PRINCIPAL ACCOUNTING FEES AND SERVICES

The response to this item is incorporated by reference from the discussion responsive thereto under the caption "Ratification of Appointment of Independent Registered Public Accounting Firm" in our proxy statement for the 2019 annual meeting of stockholders.

PART IV

Item 15. EXHIBITS, FINANCIAL STATEMENT SCHEDULES

Item 15(a) The following documents are filed as part of this Annual Report on Form 10-K:

Item 15(a)(1) and (2) See "Index to Consolidated Financial Statements and Financial Statement Schedules" at Item 8 to this Annual Report on Form 10-K. Other financial statement schedules have not been included because they are not applicable or the information is included in the financial statements or notes thereto.

Item 15(a)(3) Exhibits

The following is a list of exhibits filed as part of this Annual Report on Form 10-K.

Exhibit Number	Exhibit Description	Filed Herewith	Incorporated by Reference herein from Form or Schedule	Filing Date	SEC File/ Reg. Number
2.1	Amended and Restated Share Exchange Agreement, dated as of July 13, 2016, by and among the Registrant (formerly Biodel Inc.), Albireo Limited and the Sellers listed on Schedule I thereto.		8-K (Exhibit 2.1)	7/13/2016	001-33451
3.1.1	Restated Certificate of Incorporation, as amended, of the Registrant.		S-3 (Exhibit 4.1.1)	10/13/2017	333-220958
3.2	Amended and Restated Bylaws of the Registrant.		S-8 (Exhibit 4.2)	7/6/2007	333-144407
4.1	Form of common stock certificate.		10-K (Exhibit 4.1)	12/22/2016	001-33451
10.1*	Amended and Restated Employment Agreement, dated as of March 6, 2019, by and between the Registrant and Ronald H.W. Cooper	X			
10.2*	Employment Agreement, dated as of October 4, 2018, by and between the Registrant and Simon N. R. Harford.		10-Q (Exhibit 10.3)	11/8/2018	001-33451
10.3*	Amended and Restated Employment Agreement, dated as of March 6, 2019, by and between Albireo, AB and Jan P. Mattsson, Ph.D.	X			
10.4*	Amended and Restated Employment Agreement, dated as of March 6, 2019, by and between the Registrant and Martha J. Carter.	X			
10.5*	Amended and Restated Employment Agreement, dated as of March 6, 2019, by and between the Registrant and Patrick Horn.	X			

Exhibit Number	Exhibit Description	Filed Herewith	Incorporated by Reference herein from Form or Schedule	Filing Date	SEC File/ Reg. Number
10.6*	Amended and Restated Employment Agreement, dated as of March 6, 2019, by and between Albireo, Inc. and Jason G. Duncan.	X			
10.7*	Employment Agreement dated as of August 4, 2016, by and between Albireo, Inc. and Thomas A. Shea.		8-K (Exhibit 10.5)	11/04/2016	001-33451
10.8*	Separation Agreement, dated as of October 4, 2018, by and between the Registrant and Thomas A. Shea.		10-Q (Exhibit 10.4)	11/08/2018	001-33451
10.9*	Employment Agreement dated as of September 6, 2016, by and between Albireo, Inc. and Paresh N. Soni, M.D., Ph.D.		8-K (Exhibit 10.6)	11/04/2016	001-33451
10.10*	Separation Agreement, effective as of July 31, 2018, by and between the Registrant and Paresh N. Soni, M.D., Ph.D.		10-Q (Exhibit 10.2)	11/08/2018	001-33451
10.11*	Albireo Pharma, Inc. 2018 Equity Incentive Plan.		10-Q (Exhibit 10.1)	08/09/20018	001-33451
10.12*	Form of Stock Option Agreement under the Albireo Pharma, Inc. 2018 Equity Incentive Plan.		10-Q (Exhibit 10.2)	08/09/2018	001-33451
10.13*	Form of Restricted Stock Unit Agreement under the Albireo Pharma, Inc. 2018 Equity Incentive Plan.		10-Q (Exhibit 10.5)	08/09/2018	001-33451
10.14*	Albireo Pharma, Inc. 2018 Employee Stock Purchase Plan.		10-Q (Exhibit 10.3)	08/09/2018	001-33451
10.15*	Inducement Stock Option Agreement, dated as of October 10, 2018, by and between the Registrant and Simon N.R. Harford.		10-Q (Exhibit 10.5)	11/8/2018	001-33451
10.16*	Inducement Restricted Stock Unit Agreement, dated as of October 10, 2018, by and between the Registrant and Simon N.R. Harford.		10-Q (Exhibit 10.6)	11/8/2018	001-33451
10.17*	Albireo Pharma, Inc. 2017 Inducement Equity Incentive Plan.		10-Q (Exhibit 10.1)	11/14/2017	001-33451
10.18*	Form of Stock Option Agreement under the Albireo Pharma, Inc. 2017 Inducement Equity Incentive Plan.		10-K (Exhibit 10.11)	03/27/18	001-33451

Exhibit Number	Exhibit Description	Filed Herewith	Incorporated by Reference herein from Form or Schedule	Filing Date	SEC File/ Reg. Number
10.19*	Albireo Pharma, Inc. 2016 Equity Incentive Plan.		8-K (Exhibit 10.9)	11/4/2016	001-33451
10.20*	Form of Stock Option Agreement under the Albireo Pharma, Inc. 2016 Equity Incentive Plan.		10-K (Exhibit 10.13)	12/22/2016	001-33451
10.21*	Replacement Stock Options granted to Ronald H.W. Cooper in connection with the closing of the Biodel Transaction.		10-K (Exhibit 10.14)	12/22/2016	001-33451
10.22*	2010 Stock Incentive Plan, as amended.		Schedule 14A (Exhibit A)	1/26/2012	001-33451
10.23*	2010 Incentive Stock Option Agreement.		10-Q (Exhibit 10.2)	5/7/2010	001-33451
10.24*	2010 Non Statutory Stock Option Agreement.		10-Q (Exhibit 10.3)	5/7/2010	001-33451
10.25*	2010 Restricted Stock Unit Agreement.		10-Q (Exhibit 10.4)	5/7/2010	001-33451
10.26*	Amended and Restated 2004 Stock Incentive Plan.		S-1/A (Exhibit 10.3)	3/27/2007	333-140504
10.27*	Form of Incentive Stock Option Agreement for 2004 Amended and Restated Stock Incentive Plan.		10-K (Exhibit 10.19)	12/21/2007	001-33451
10.28*	2005 Non-Employee Directors' Stock Option Plan.		S-1/A (Exhibit 10.5)	3/27/2007	333-140504
10.29*	Form of Option Agreement for 2005 Non-Employee Directors' Stock Option Plan.		10-K (Exhibit 10.20)	12/21/2007	001-33451
10.30*	Form of Indemnification Agreement, by and between the Registrant and each of its directors and executive officers.		8-K (Exhibit 10.8)	11/4/2016	001-33451
10.31*	Nonemployee Director Compensation Policy.		10-K (Exhibit 10.25)	03/27/18	001-33451
10.32	Asset Purchase and License Agreement, dated as of September 2, 2016, by and among Unilife Corporation, Unilife Medical Solution, Inc. and Biodel Inc.		8-K (Exhibit 10.1)	9/9/2016	001-33451
10.33.1**	License Agreement, dated as of April 2, 2012, by and between Elobix AB, as assignee of Albireo AB, and EA Pharma Co., Ltd. (formerly known as Ajinomoto Pharmaceuticals Co., Ltd.).		10-K (Exhibit 10.28.1)	3/27/2017	001-33451

Exhibit Number	Exhibit Description	Filed Herewith	Incorporated by Reference herein from Form or Schedule	Filing Date	SEC File/ Reg. Number
10.33.2**	First Amendment to the License Agreement, dated as of January 30, 2015, by and between Elobix AB, as assignee of Albireo AB, and EA Pharma Co., Ltd. (formerly known as Ajinomoto Pharmaceuticals Co., Ltd.).		10-K (Exhibit 10.28.2)	3/27/2017	001-33451
10.33.3**	Second Amendment to the License Agreement, dated as of April 6, 2016, by and between Elobix AB and EA Pharma Co., Ltd. (formerly known as Ajinomoto Pharmaceuticals Co., Ltd.).		10-K (Exhibit 10.28.3)	3/27/2017	001-33451
10.33.4**	Third Amendment to the License Agreement, dated as of December 7, 2017, by and between Elobix AB and EA Pharma Co., Ltd. (formerly known as Ajinomoto Pharmaceuticals Co., Ltd.).		10-K (Exhibit 10.27.4)	03/27/18	001-33451
10.34**	Royalty Interest Acquisition Agreement, dated as of December 28, 2017, by and among Elobix AB, HealthCare Royalty Partners III, L.P. and, solely for the purposes specified therein, the Registrant.		10-K (Exhibit 10.28)	03/27/18	001-33451
10.35	Office Lease Agreement dated as of February 7, 2017, by and between the Registrant and SHIGO 10 PO Owner LLC.		8-K (Exhibit 10.1)	02/10/2017	001-33451
21.1	Subsidiaries.		10-K (Exhibit 21.1)	03/27/18	001-33451
23.1	Consent of Ernst & Young LLP.	X			
31.1	Certification of the Chief Executive Officer.	X			
31.2	Certification of the Chief Financial Officer.	X			
32.1	Certification pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.	X			
101	INS XBRL Instance Document.	X			
	SCH XBRL Taxonomy Extension Schema Document.	X			
	CAL XBRL Taxonomy Extension Calculation Linkbase Document.	X			

Exhibit Number	Exhibit Description	Filed Herewith	Incorporated by Reference herein from Form or Schedule	Filing Date	SEC File/ Reg. Number
	DEF XBRL Taxonomy Extension Definition.	X			
	LAB XBRL Taxonomy Extension Label Linkbase Document.	X			
	PRE XBRL Taxonomy Presentation Linkbase Document.	X			

* Management contract or compensatory plan or arrangement.

** Confidential treatment has been granted with respect to certain portions of this Exhibit, which portions have been omitted and filed separately with the Securities and Exchange Commission as part of an application for confidential treatment pursuant to the Securities Exchange Act of 1934, as amended.

Item 16. FORM 10-K SUMMARY.

None.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

ALBIREO PHARMA, INC.

Date: March 6, 2019

By: /s/ Ronald H.W. Cooper
Ronald H.W. Cooper
President and Chief Executive Officer

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Signatures	Title	Date
/s/ Ronald H.W. Cooper Ronald H.W. Cooper	President, Chief Executive Officer and Director (principal executive officer)	March 6, 2019
/s/ Simon N.R. Harford Simon N.R. Harford	Chief Financial Officer and Treasurer (principal financial officer and principal accounting officer)	March 6, 2019
/s/ David Chiswell, Ph.D. David Chiswell, Ph.D.	Chairman of the Board	March 6, 2019
/s/ Anne Klibanski, M.D. Anne Klibanski, M.D.	Director	March 6, 2019
/s/ Michael Gutch, Ph.D. Michael Gutch, Ph.D.	Director	March 6, 2019
/s/ Roger A. Jeffs, Ph.D. Roger A. Jeffs, Ph.D.	Director	March 6, 2019
/s/ Stephanie S. Okey, M.S. Stephanie S. Okey, M.S.	Director	March 6, 2019
/s/ Davey S. Scoon Davey S. Scoon	Director	March 6, 2019

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Report of Independent Registered Public Accounting Firm

To the Board of Directors and Stockholders of Albireo Pharma, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Albireo Pharma, Inc. (the Company) as of December 31, 2018 and 2017, the related consolidated statements of operations, comprehensive loss, stockholders' equity and cash flows for each of the two years in the period ended December 31, 2018, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2018 and 2017, and the results of its operations and its cash flows for each of the two years in the period ended December 31, 2018, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company's internal control over financial reporting as of December 31, 2018, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) and our report dated March 6, 2019 expressed an adverse opinion thereon.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2016.
Boston, Massachusetts
March 6, 2019

Albireo Pharma, Inc.

Consolidated Balance Sheets
(in thousands, except share and per share data)

	December 31, 2018	December 31, 2017
ASSETS		
Current assets:		
Cash and cash equivalents	$ 163,885	$ 53,231
Prepaid expenses and other assets	850	1,054
Other receivables	2,915	726
Total current assets	167,650	55,011
Property and equipment, net	187	178
Goodwill	17,260	17,260
Other noncurrent assets	369	775
Total assets	$ 185,466	$ 73,224
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Trade payables	$ 4,352	$ 1,350
Accrued expenses	8,165	6,105
Other liabilities	308	474
Total current liabilities	12,825	7,929
Liability related to sale of future royalties	49,969	—
Long-term liabilities	35	42
Total liabilities	62,829	7,971
Stockholders' Equity:		
Common stock, $0.01 par value per share — 30,000,000 authorized at December 31, 2018 and December 31, 2017; 11,969,928 and 8,902,784 issued and outstanding at December 31, 2018 December 31, 2017	120	89
Additional paid in capital	214,694	114,522
Accumulated other comprehensive income	4,293	1,001
Accumulated deficit	(96,470)	(50,359)
Total stockholders' equity	122,637	65,253
Total liabilities and stockholders' equity	$ 185,466	$ 73,224

See accompanying Notes to Consolidated Financial Statements.

Albireo Pharma, Inc.

Consolidated Statements of Operations
(in thousands, except share and per share data)

	Year Ended December 31,	
	2018	2017
Revenue	$ 12,740	$ 1
Operating expenses:		
Research and development	31,732	12,991
General and administrative	18,061	15,246
Other operating (income) expense, net	837	(3,659)
Total operating expenses	50,630	24,578
Operating loss	(37,890)	(24,577)
Interest income (expense), net	(4,838)	40
Other non-operating income (expense), net	(3,363)	335
Net loss before income taxes	(46,091)	(24,202)
Income tax	20	212
Net loss	$ (46,111)	$ (24,414)
Net loss per share attributable to holders of common stock:		
Net loss per share - basic and diluted	$ (3.94)	$ (3.12)
Weighted average shares outstanding - basic and diluted	11,702,785	7,819,302

See accompanying Notes to Consolidated Financial Statements.

Albireo Pharma, Inc.

Consolidated Statements of Comprehensive Loss
(in thousands)

	Year Ended December 31,	
	2018	2017
Net loss	$ (46,111)	$ (24,414)
Other comprehensive loss:		
Foreign currency translation adjustment	3,292	(495)
Total other comprehensive income (loss)	3,292	(495)
Total comprehensive loss	$ (42,819)	$ (24,909)

See accompanying Notes to Consolidated Financial Statements.

Albireo Pharma, Inc.

Consolidated Statements of Stockholders' Equity
(in thousands, except share amounts)

	Common Stock		Additional Paid-In Capital	Accumulated Other Comprehensive Income	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount				
Balance--December 31, 2016	6,292,644	$ 63	$ 61,338	$ 1,496	$ (25,945)	$ 36,952
Share based compensation expense	—	—	3,700	—	—	3,700
Exercise of options	50,309	1	384	—	—	385
Exercise of warrants	29,831		617	—	—	617
Issuance of common stock, net of costs	2,530,000	25	48,483	—	—	48,508
Other comprehensive loss	—	—	—	(495)	—	(495)
Net loss	—	—	—	—	(24,414)	(24,414)
Balance— , December 31, 2017	8,902,784	$ 89	$ 114,522	$ 1,001	$ (50,359)	$ 65,253
Share based compensation expense	—	—	5,546	—	—	5,546
Exercise of options	72,782	1	506	—	—	507
Issuance of common stock, net of costs	2,994,362	30	94,120	—	—	94,150
Other comprehensive income	—	—	—	3,292	—	3,292
Net loss	—	—	—	—	(46,111)	(46,111)
Balance— , December 31, 2018	11,969,928	$ 120	$ 214,694	$ 4,293	$ (96,470)	$ 122,637

See accompanying Notes to Consolidated Financial Statements.

Albireo Pharma, Inc.

Consolidated Statements of Cash Flows
(in thousands)

	Year Ended December 31,	
	2018	2017
Cash flows from operating activities:		
Net loss	$ (46,111)	$ (24,414)
Adjustments to reconcile net loss to net cash used in operating activities:		
Non cash interest expense on liability related to royalty monetization	6,975	—
Accretion of debt discount and amortization of issuance costs	—	163
Depreciation and amortization	45	35
Gain from the sale of IPR&D		(3,500)
Change in fair value of financial instruments	—	(251)
Gain on sale of property, plant and equipment	(14)	—
Stock-based compensation expense	5,546	3,700
Unrealized foreign exchange (gain) loss	4,631	(1,107)
Changes in operating assets and liabilities:		
Trade receivables	(597)	28
Prepaid expenses and other current assets	196	(467)
Other receivables	(1,703)	(339)
Other non-current assets	403	(245)
Trade payables	3,171	263
Accrued expenses	854	(1,705)
Other liabilities and long-term liabilities	(198)	273
Net cash used in operating activities	(26,802)	(27,566)
Cash flows from investing activities:		
Purchase of property, plant and equipment	(61)	(190)
Proceeds from sale of property, plant and equipment	14	4,500
Net cash used in investing activities	(47)	4,310
Cash flows from financing activities:		
Proceeds from issuance of common stock, net of issuance costs	94,150	48,508
Proceeds from royalty agreement	44,525	—
Exercise of options	507	385
Payments of principal on borrowings	—	(3,055)
Net cash provided by financing activities	139,182	45,838
Effect of exchange rate changes on cash and cash equivalents	(1,679)	718
Net increase in cash and cash equivalents	110,654	23,300
Cash and cash equivalents—beginning of period	53,231	29,931
Cash and cash equivalents—end of period	$ 163,885	$ 53,231
Supplemental disclosures of cash flow information:		
Cash paid for interest	$ —	$ 178
Shares issued upon cashless exercise of Kreos warrants	—	617

See accompanying Notes to Consolidated Financial Statements.

Albireo Pharma, Inc.

Notes to Consolidated Financial Statements

1. Summary of significant accounting policies and basis of presentation

Organization and Share Exchange

Albireo Pharma, Inc. (Parent), together with its direct and indirect subsidiaries (the Company), is a clinical-stage biopharmaceutical company focused on the development and commercialization of novel bile acid modulators to treat orphan pediatric liver diseases and other liver and gastrointestinal diseases and disorders. The Company's clinical pipeline includes a Phase 3 product, a Phase 2 product candidate, and elobixibat, which is approved in Japan for the treatment of chronic constipation. A4250, the Company's Phase 3 lead product, is in development initially for the treatment of patients with progressive familial intrahepatic cholestasis (PFIC), a rare, life-threatening genetic disorder affecting young children.

Basis of presentation

These Consolidated Financial Statements have been prepared in conformity with generally accepted accounting principles in the United States (U.S. GAAP). Any reference in these notes to applicable guidance is meant to refer to the authoritative U.S. GAAP as found in the Accounting Standards Codification (ASC) and Accounting Standards Update (ASU) of the Financial Accounting Standards Board (FASB). Any reference in these Consolidated Financial Statements to common stock or options or warrants to purchase shares of common stock of the Company means the common stock or options or warrants to purchase shares of common stock of Parent.

Principles of consolidation

The accompanying Consolidated Financial Statements include the accounts of Parent and its direct or indirect wholly owned subsidiaries. All intercompany balances and transactions have been eliminated in consolidation.

Foreign currency translation

Functional and presentation currency

Items included in the financial statements of each entity comprising the Company are measured using the currency of the primary economic environment in which the entity operates (the functional currency).

Transactions and balances

Foreign currency transactions in each entity comprising the Company are remeasured into the functional currency of the entity using the exchange rates prevailing at the respective transaction dates. Foreign exchange gains and losses resulting from the settlement of such transactions and from the remeasurement at year-end exchange rates of monetary assets and liabilities denominated in foreign currencies are recognized within Other operating (income) expense, net except for changes related to the liability related to the sale of future royalties which are recorded in Other non-operating (income) expense, net in the Consolidated Statements of Operations.

The results and financial position of the Company that have a functional currency different from the USD are translated as follows:

a. assets and liabilities presented are translated at the closing exchange rate as of December 31, 2018 and 2017;

b. income and expenses for the statements of operations and comprehensive loss are translated at average exchange rates that are relevant for the respective periods for which the income and expenses occurred; and

c. significant transactions use the exchange rate on the date of the transaction;

All resulting exchange differences arising from such translations are recognized directly in other comprehensive income (loss) and presented as a separate component of equity.

Use of estimates

The preparation of financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the amounts of assets, liabilities, revenues and expenses reported in the financial statements and accompanying notes. Management must apply significant judgment in this process. On an ongoing basis, the Company evaluates its estimates and assumptions, including but not limited to accruals, deferred tax assets and the accretion of interest on the monetization liability. Actual results could materially differ from these estimates.

Segment information

The Company's entire business is managed by a single management team, which reports to the chief executive officer. The chief executive officer is the chief operating decision maker. The Company has determined it has one operating segment as its chief operating decision maker allocates resources and assesses the performance of the business at this level. Accordingly, the Company has one reporting segment, which is the research and development of novel treatments for liver and gastrointestinal diseases and disorders.

Cash and cash equivalents

The Company considers all short-term highly liquid investments with an original maturity at the date of purchase of three months or less to be cash equivalents.

Concentration of risk

Credit risk

Financial instruments that potentially subject the Company to significant concentration of credit risk consist primarily of cash and cash equivalents. For banks and financial institutions, only independent financial institutions with a high credit rating are utilized. The Company's current license agreement is with an established and reputable pharmaceutical company and, historically, the Company has not had any material collection risk related to its accounts receivable.

Concentration of revenue and accounts receivable

The Company generally does not require collateral or other security in support of accounts receivable. Allowances are provided for individual accounts receivable when the Company becomes aware of a customer's inability to meet its financial obligations, such as in the case of bankruptcy, deterioration in the customer's operating results or change in financial position. If circumstances related to a customer change, estimates of the recoverability of receivables would be further adjusted. The Company also considers broad factors in evaluating the sufficiency of its allowances for doubtful accounts, including the length of time receivables are past due, significant one-time events, creditworthiness of customers and historical experience. There is no allowance for doubtful accounts as of December 31, 2018 or 2017.

Equipment, net

Equipment is stated at historical cost less depreciation and consists of computers, furniture and fixtures, and other equipment. Depreciation is computed using a straight-line method over the estimated useful lives. Computers and other equipment purchased for less than $2,000 or the equivalent thereof are expensed immediately.

Gains and losses on disposals of equipment are determined by comparing the proceeds with the carrying amount and are recognized within Other operating (income) expense, net in the Consolidated Statements of Operations.

Impairment of long-lived assets

Long-lived assets are reviewed for impairment whenever events or changes in circumstances indicate that the carrying amount of such assets may not be recoverable. In such instances, the recoverability of assets to be held and used is measured first by a comparison of the carrying amount of an asset group to future undiscounted net cash flows expected to be generated by the assets. If such assets are considered to be impaired, an impairment loss would be recognized if the carrying amount of the asset exceeds the fair value of the asset. There were no impairments recorded for the years ended December 31, 2018 and 2017.

Research and development expenses

Research and development costs are expensed as incurred and include primarily salaries, benefits and other staff-related costs; clinical trial and related clinical manufacturing costs; contract services and other outside costs.

The Company's nonclinical studies and clinical trials are performed by third-party contract research organizations (CROs). Some of these expenses are billed monthly for services performed, while others are billed based upon milestones achieved. For nonclinical studies, the significant factors used in estimating accruals include the percentage of work completed to date and contract milestones achieved. For clinical trial expenses, the significant factors used in estimating accruals include the number of patients enrolled and percentage of work completed to date or contract milestones achieved. The Company's estimates are highly dependent upon the timeliness and accuracy of the data provided by the respective CROs regarding the status of the contracted activity, with adjustments made when deemed necessary.

Revenue recognition

The Company enters into licensing agreements which are within the scope of ASC 606, under which it may exclusively license rights to research, develop, manufacture and commercialize its product candidates to third parties. The terms of these arrangements may include payment to the Company of one or more of the following: non-refundable, upfront license fees; reimbursement of certain costs; development, regulatory and commercial milestone payments; and royalties on net sales of licensed products.

In determining the appropriate amount of revenue to be recognized as the Company fulfills its obligations under each of its agreements, the Company performs the following steps: (i) identification of the promised goods or services in the contract; (ii) determination of whether the promised goods or services are performance obligations, including whether they are distinct in the context of the contract; (iii) measurement of the transaction price, including the constraint on variable consideration; (iv) allocation of the transaction price to the performance obligations; and (v) recognition of revenue when (or as) the Company satisfies each performance obligation. As part of the accounting for these arrangements, the Company must use significant judgment to determine: (a) the number of performance obligations based on the determination under step (ii) above and (b) the transaction price under step (iii) above. The Company uses judgment to determine whether milestones or other variable consideration, except for royalties, should be included in the transaction price as described further below. The transaction price is allocated to each performance obligation on a relative stand-alone selling price basis, for which the Company recognizes revenue as or when the performance obligations under the contract are satisfied.

Amounts received prior to revenue recognition are recorded as deferred revenue. Amounts expected to be recognized as revenue within the 12 months following the balance sheet date are classified as current portion of deferred revenue in the accompanying consolidated balance sheets. Amounts not expected to be recognized as revenue within the 12 months following the balance sheet date are classified as deferred revenue, net of current portion.

Exclusive Licenses

If the license to the Company's intellectual property is determined to be distinct from the other promises or performance obligations identified in the arrangement, the Company recognizes revenue from non-refundable, upfront fees allocated to the license when the license is transferred to the customer and the customer is able to use and benefit from the license. In assessing whether a promise or performance obligation is distinct from the other promises, the Company considers factors such as the research, development, manufacturing and commercialization capabilities of the collaboration partner and the availability of the associated expertise in the general marketplace. In addition, the Company considers whether the collaboration partner can benefit from a promise for its intended purpose without the receipt of the remaining promise, whether the value of the promise is dependent on the unsatisfied promise, whether there are other vendors that could provide the remaining promise, and whether it is separately identifiable from the remaining promise. For licenses that are combined with other promises, the Company utilizes judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue. The Company evaluates the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition. The measure of progress, and thereby periods over which revenue should be recognized, are subject to estimates by management and may change over the course of the research and development and licensing agreement. Such a change could have a material impact on the amount of revenue the Company records in future periods.

Milestone Payments

At the inception of each arrangement that includes development milestone payments, the Company evaluates whether the milestones are considered probable of being achieved and estimates the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within the control of the Company or the licensee, such as regulatory approvals, are not considered probable of being achieved until those approvals are received. The Company evaluates factors such as the scientific, clinical, regulatory, commercial, and other risks that must be overcome to achieve the particular milestone in making this assessment. There is considerable judgment involved in determining whether it is probable that a significant revenue reversal would not occur. At the end of each subsequent reporting period, the Company reevaluates the probability of achievement of all milestones subject to constraint and, if necessary, adjusts its estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect revenues and earnings in the period of adjustment.

Royalties

For arrangements that include sales-based royalties, including milestone payments based on a level of sales, and the license is deemed to be the predominant item to which the royalties relate, the Company recognizes revenue at the later of (i) when the related sales occur, or (ii) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied).

In 2012, the Company entered into a license agreement (the Agreement) with EA Pharma Co., Ltd. (EA Pharma, formerly Ajinomoto Pharmaceuticals Co., Ltd.) to develop a select product candidate (elobixibat) for registration and subsequent commercialization in select markets. In conjunction with the Agreement, the Company granted EA Pharma an exclusive license to its intellectual property for development and commercialization activities in the designated field and territories. The Company is entitled to payments resulting from pharmaceutical ingredient or related procurement services if provided as part of a development plan. Revenue related to these payments is recorded on a net basis; in this instance, the Company acts as an agent, as it does not have discretion to change suppliers and does not perform any part of the services or manufacture of the subject pharmaceutical ingredients. The costs associated with these activities are netted against the related revenue in the condensed consolidated statements of operations.

In 2012, EA Pharma made an upfront cash payment to the Company of €10.0 million under the Agreement. The parties amended the agreement in April 2016, pursuant to which EA Pharma made an additional cash payment to the

Company of $8.0 million. As of December 31, 2018, the Company is eligible to receive an additional regulatory-based milestone payment under the Agreement of €4.3 million ($4.9 million based on the Euro to USD exchange rate as of December 31, 2018) if a specified regulatory event is achieved for elobixibat. The cash payments and any other payments for milestones and royalties from EA Pharma are non-refundable, non-creditable and not subject to set-off.

The Agreement will continue until the last royalty period for any product in the territory, which is defined as the period when there are no remaining patent rights or regulatory exclusivity in place for any products subject to royalties. EA Pharma may terminate the Agreement at will upon 180 days' prior written notice to the Company. Either party may terminate the Agreement for the other party's uncured material breach or insolvency and in certain other circumstances agreed to by the parties.

The Company assessed this arrangement in accordance with Accounting Standards Codification (ASC) Topic 606, *Revenue from Contracts with Customers* (ASC 606), and concluded that the contract counterparty, EA Pharma, is a customer. The Company identified the following material promises under the arrangement: (1) a sub-licensable and exclusive license to use the Company's intellectual property and collaboration compounds to conduct development and commercialization activities in the designated fields and territories and (2) the technology transfer of the Albireo intellectual property and compound. Participation on the joint development committee ("JDC") and joint commercialization committee ("JCC") was determined to be quantitatively and qualitatively immaterial and therefore is excluded from the performance obligations. The license was determined to not be distinct from the technology transfer; as such, the Company determined that these promises should be combined into a single performance obligation.

Under the Agreement, in order to evaluate the appropriate transaction price, the Company determined that the upfront amount constituted the entirety of the consideration to be included in the transaction price as of the outset of the arrangement, which was allocated to the single performance obligation. At the outset of the arrangement, the transaction price included only the €10.0 million upfront consideration received and was increased to include the $8.0 million received in conjunction with the 2016 amendment. The potential milestone payments were excluded from the transaction price, as all milestone amounts were either fully constrained or related to future sales-based royalties. In April 2013, December 2015, and October 2016, various development milestone events were achieved, and the Company recognized revenue related to these events; because the Company previously satisfied its performance obligation to deliver the license, the Company recorded these milestone payments as received. The Company will reevaluate the transaction price at the end of each reporting period and as other uncertain events are resolved or other changes in circumstances occur, and, if necessary, adjust its estimate of the transaction price.

In January 2018, the Japanese Ministry of Health Labour and Welfare (MHLW) approved a new drug application filed by EA Pharma for elobixibat for the treatment of chronic constipation, for which the Company received a milestone payment of $11.2 million. Based on the regulatory approval, the Company determined that the milestone was no longer at risk of significant reversal. As such, because the single performance obligation had previously been satisfied, the Company recognized this amount in full in the first quarter of 2018 and there was no deferred revenue or contract asset as of December 31, 2018. The Company recognizes the royalty revenue based on the estimated qualifying sales by EA Pharma each period.

Monetization of Future Royalties

In December 2017, the Company executed the RIAA with HCR pursuant to which it sold to HCR the right to receive all royalties from sales in Japan and sales milestones achieved from any covered territory potentially payable to the Company under the Agreement, up to a specified maximum "cap" amount of $78.8 million, based on the funds the Company received from HCR to date. The Company received $44.5 million from HCR, net of certain transaction expenses, under the RIAA and the Company is eligible to receive an additional $15.0 million under the RIAA if a specified sales milestone is achieved for elobixibat in Japan. If the cap amount is reached, the Company will again become eligible to retain royalties from Japanese sales and sales milestones from covered territories for elobixibat from EA Pharma under the Agreement. The Company is obligated to make royalty interest payments to HCR under the RIAA only to the extent it receives future Japanese royalties, sales milestones or other specified payments from EA Pharma. Although the Company sold its rights to receive royalties from the sales of elobixibat in Japan, as a result of its ongoing

involvement in the cash flows related to these royalties, the Company will continue to account for these royalties as revenue. The Company recorded the $44.5 million as a liability related to sale of future royalties (royalty obligation). The royalty obligation will be amortized using the effective interest rate method, based on the Company's best estimate of the time it will take to reach the capped amount. The following table shows the activity within the liability account for the year ending December 31, 2018:

	December 31, 2018 (in thousands)
Liability related to sale of future royalties—beginning balance	$ —
Proceeds from sale of future royalties, net	44,525
Unrealized foreign currency (gain)/loss on remeasurement of the liability	3,241
Foreign currency translation (gain)/loss in other comprehensive income/(loss)	(3,271)
Accretion of interest expense on liability related to royalty monetization	6,975
Repayment of the liability	(924)
Liability related to sale of future royalties—ending balance	$ 50,546
Less current portion classified within other current liabilities	(577)
Net ending liability related to sale of future royalties	$ 49,969

The Company records estimated royalties due for the current period in accrued other until the payment is received from EA Pharma at which time the Company then remits payment to HCR. As royalties are remitted to HCR, the balance of the royalty obligation will be effectively repaid over the life of the RIAA. In order to determine the amortization of the royalty obligation, the Company is required to estimate the total amount of future royalty payments to be received and submitted to HCR, as noted above, based on the Company's best estimate of the time it will take to reach the cap amount and when milestones will be received. The sum of these amounts less the $44.5 million proceeds the Company received will be recorded as interest expense over the life of the royalty obligation. Since inception, the Company's estimate of its total interest expense resulted in a quarterly effective interest rate of approximately 4.27%. The Company periodically assesses the estimated royalty payments to HCR and to the extent such payments are greater or less than its initial estimates or the timing of such payments is materially different than its original estimates, the Company will prospectively adjust the accretion of interest on the royalty obligation. There are a number of factors that could materially affect the amount and the timing of royalty payments, most of which are not within the Company's control. Such factors include, but are not limited to, the rate of elobixibat prescriptions, the number of doses administered, the introduction of competing products, manufacturing or other delays, patent protection, adverse events that result in governmental health authority imposed restrictions on the use of the drug products, significant changes in foreign exchange rates as the royalties remitted to HCR are in U.S. dollars while sales of elobixibat are in Japanese yen, and sales never achieving forecasted numbers, which would result in reduced royalty payments and reduced non-cash interest expense over the life of the royalty obligation. To the extent future royalties result in an amount less than the liability, the Company is not obligated to fund any such shortfall.

Stock-based compensation

The Company accounts for stock-based compensation awards in accordance with FASB ASC Topic 718, *Compensation—Stock Compensation* (ASC 718). ASC 718 requires all stock-based payments, including grants of stock options, to be recognized in the consolidated statements of operations based on their respective fair values.

The fair value of the Company's stock options has been determined using the Black-Scholes option pricing model, which requires the input of subjective assumptions, including (i) the expected stock price volatility, (ii) the expected term of the award, (iii) the risk-free interest rate and (iv) expected dividends. For the years ended December 31, 2018 and December 31, 2017, due to the lack of historical and implied volatility data of the Company's common stock and equivalents, the expected volatility has been estimated based on the historical volatilities of peer companies in the Company's industry that are publicly traded. The Company selected companies that it considers to have comparable characteristics to the Company, including enterprise value, risk profiles and position within the industry and with historical share price information sufficient to meet the expected term of the stock options. The historical volatility data has been computed using the daily closing prices for the selected companies.

Due to the lack of sufficient historical data, the Company used the "simplified" method, whereby the expected term equals the arithmetic average of the vesting term and the original contractual term of the award, to determine the expected term of stock options.

The Company records compensation expense for service-based awards over the vesting period of the award on a straight-line basis. For awards with service and performance based conditions, compensation related to the performance-based vesting conditions is recognized when achievement of the performance condition is considered probable and the compensation expense related to the service condition is recorded using the accelerated method.

Modifications to stock-based awards are treated as an exchange of the original award for a new award with total compensation equal to the grant-date fair value of the original award plus any incremental value of the modification. The incremental value is based on the excess of the fair value of the modified award over the fair value of the original award immediately before the modification.

The Company has early adopted ASC 2018-07 "*Improvement to Nonemployee Share-based Payment Accounting"* standard as of July 1, 2018, which allows the Company to continue to recognize the expense of stock options to former employees as current employees, provided that the non-employee is required to continue to provide services to the employer. Once these services are not substantive, the Company will account for the transaction as a severance arrangement with no future service requirement; therefore, any related compensation cost would be recognized immediately.

Employee benefits

Pension obligations

The Company has defined contribution plans for its Sweden-based employees whereby the Company pays contributions to employee benefit or insurance plans on a mandatory, contractual or voluntary basis. The Company has no legal or constructive obligations to pay further contributions if the fund does not hold sufficient assets to pay all employees the benefits relating to employee service in the current and prior periods.

The Company has no further payment obligations once the contributions have been paid. The contributions are recognized as employee benefit expense when they are due. Prepaid contributions are recognized as an asset to the extent that a cash refund or a reduction in the future payments is available. The Company paid $352,000 and $317,000 to the plans for the years ended December 31, 2018 and 2017, respectively.

401(k)

The Company has a 401(k) retirement plan in which all U.S.-based employees are eligible to participate. The Company contributed $164,600 and $70,200 to the plan for the years ended December 31, 2018 and 2017, respectively. The Company matches employee contributions to the plan, on a per employee basis, up to 4% of each employee's wages for the years ended December 31, 2018 and 2017.

Loss contingencies

Loss contingencies are recorded as liabilities when it is probable that a liability has occurred and the amount of loss is reasonably estimable. Disclosure is required when there is a reasonable possibility that an ultimate loss will be material. Contingent liabilities are often resolved over long periods of time. Estimating probable losses requires analysis that often depends on judgments about potential actions by third parties, such as regulators.

Income taxes

The Company accounts for income taxes in accordance with ASC 740, *Income Taxes* (ASC 740). Deferred income taxes are recorded for the expected tax consequences of temporary differences between the tax basis of assets and

liabilities for financial reporting purposes and amounts recognized for income tax purposes. The Company records a valuation allowance to reduce its deferred tax assets to the amount of future tax benefit that is more likely than not to be realized.

Income tax expense consists of taxes currently payable and changes in deferred tax assets and liabilities calculated according to local tax rules. Deferred tax assets and liabilities are based on temporary differences that arise between carrying values used for financial reporting purposes and amounts used for taxation purposes of assets and liabilities and the future tax benefits of tax loss carry forwards. A deferred tax asset is recognized only to the extent that it is more likely than not that future taxable profits will be available against which the asset can be utilized.

Significant judgment is required in determining any valuation allowance recorded against deferred tax assets. In assessing the need for a valuation allowance, the Company considers all available evidence for each jurisdiction including past operating results, estimates of future taxable income and the feasibility of ongoing tax planning strategies. In the event that the Company changes its determination as to the amount of deferred tax assets that can be realized, the Company will adjust its valuation allowance with a corresponding impact to income tax expense in the period in which such determination is made.

The amount of deferred tax provided is calculated using tax rates in effect at the balance sheet date. The impact of tax law changes is recognized in periods when the change is enacted.

A two-step approach is applied pursuant to ASC 740 in the recognition and measurement of uncertain tax positions taken or expected to be taken in a tax return. The first step is to determine if the weight of available evidence indicates that it is more likely than not that the tax position will be sustained in an audit, including resolution of any related appeals or litigation processes. The second step is to measure the tax benefit as the largest amount that is more than 50% likely to be realized upon ultimate settlement.

The Company's policy is to recognize interest and penalty expenses associated with uncertain tax positions as a component of income tax expense in the Consolidated Statements of Operations. As of the years ended December 31, 2018 and 2017, the Company had no accrued interest or penalties related to uncertain tax positions and no amounts have been recognized in the Consolidated Statements of Operations.

Net loss per share

Basic net loss per share is calculated by dividing the net loss attributable to holders of common stock by the weighted average number of shares of common stock outstanding. Diluted net loss per share is calculated by dividing the net loss attributable to holders of common stock by the weighted-average number of shares of common stock outstanding. If the Company were in a net income position, diluted net income per share would be calculated by dividing the net income attributable to holders of common stock by the weighted-average number of shares of common stock plus dilutive common stock equivalents outstanding, including any dilutive effect from such shares.

Goodwill and long-lived assets

Goodwill is the excess of the purchase price in a business combination over the fair value of identifiable net assets acquired. Goodwill and certain other intangible assets having indefinite lives are not amortized to earnings, but instead are subject to periodic testing for impairment.

Goodwill and indefinite-lived intangible assets are assessed at least annually, but also whenever events or changes in circumstances indicate the carrying values may not be recoverable. Factors that could trigger an impairment review, include: (a) significant underperformance relative to historical or projected future operating results; (b) significant changes in the manner of or use of the acquired assets or the strategy for the Company's overall business; (c) significant negative industry or economic trends; (d) significant decline in the Company's stock price for a sustained period; and (e) a decline in the Company's market capitalization below net book value.

The Company conducts an impairment assessment on October 1 each year taking a qualitative evaluation approach to determine if there are any adverse market factors or changes in circumstances indicating that the carrying value of goodwill may not be recoverable. If it is more likely than not that an impairment exists, the Company performs a quantitative test which compares the fair value to the net carrying value, and records an impairment of goodwill to the extent that the net carrying value exceeds the fair value.

Assessment for possible impairment of long-lived assets is based on the Company's ability to recover the carrying value of the long-lived asset from the expected future pre-tax cash flows. The expected future pre-tax cash flows are estimated based on historical experience, knowledge and market data. Estimates of future cash flows require the Company to make assumptions and to apply judgment, including forecasting future sales and expenses and estimating the useful lives of assets. If the expected future cash flows related to a long-lived asset are less than the asset's carrying value, an impairment charge is recognized for the difference between the estimated fair value and the carrying value.

Gain on Sale of IPR&D

In October 2017, the Company entered into an asset purchase agreement pursuant to which it sold IPR&D for $4.5 million, which resulted in a gain recorded in other operating income.

Recently adopted accounting pronouncements

In June 2018, the FASB issued, ASC 2018-07 "*Improvement to Nonemployee Share-based Payment Accounting".* Under the new standard, companies are no longer required to value non-employee awards differently from employee awards. This standard is effective for fiscal years beginning after December 15, 2018, including interim periods within that fiscal year. The Company has early adopted this standard as of July 1, 2018 and determined there was no impact on the date of adoption to the Company's condensed consolidated financial statements.

Effective January 1, 2018, the Company adopted ASC Topic 606, *Revenue from Contracts with Customers*, using the modified retrospective transition method. Under this method, results for reporting periods beginning after January 1, 2018 are presented under ASC 606, while prior period amounts are not adjusted and continue to be reported in accordance with ASC 605. This standard applies to all contracts with customers, except for contracts that are within the scope of other standards, such as leases, insurance, collaboration arrangements and financial instruments. Under ASC 606, an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration which the entity expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that an entity determines are within the scope of ASC 606, the entity performs the following five step analysis (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) the entity satisfies a performance obligation. The Company only applies the five-step analysis to contracts when it is probable that the entity will collect the consideration it is entitled to in exchange for the goods or services it transfers to the customer. At contract inception, once the contract is determined to be within the scope of ASC 606, the Company assesses the goods or services promised within each contract, determines those that are performance obligations, and assesses whether each promised good or service is distinct. The Company then recognizes as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) the performance obligation is satisfied. As a result of adopting ASC 606 on January 1, 2018, the Company did not record any cumulative changes in the current period, as the performance obligation related to the Agreement with EA Pharma was fully satisfied in 2012.

In September 2016, the FASB issued ASU 2016-15, *"Statement of Cash Flows (Topic 230): Classification of Certain Cash Receipts and Cash Payments (a consensus of the Emerging Issues Task Force),"* which changes how certain cash receipts and cash payments are presented and classified in the statement of cash flows. The new standard is effective for fiscal years beginning after December 15, 2017 and for interim periods therein. The Company has adopted this standard as of January 1, 2018 and determined there is no impact of this standard on the Company's consolidated financial statements as of the date of the adoption.

In May 2017, the FASB issued ASU 2017-09, "*Compensation – Stock Compensation (Topic 718), Scope of Modification Accounting,"* (ASC 718), which amends the scope of modification accounting for share-based payment arrangements and provides guidance on the types of changes to the terms or conditions of share-based payment awards to which an entity would be required to apply modification accounting under ASC 718. The new standard is effective for fiscal years beginning after December 15, 2017 and for interim periods therein. The Company has adopted this standard as of January 1, 2018 and determined there is minimal impact on the Company's consolidated financial statements

Accounting pronouncements issued but not yet adopted

In February 2016, the FASB issued ASU 2016-02, "*Leases (Topic 842)*." The new standard establishes a right-of-use (ROU) model that requires a lessee to record a ROU asset and a lease liability on the balance sheet for all leases with terms longer than 12 months. Leases will be classified as either finance or operating, with classification affecting the pattern of expense recognition in the income statement. The new standard is effective for fiscal years beginning after December 15, 2018, including interim periods within those fiscal years. A modified retrospective transition approach is required for lessees for capital and operating leases existing at, or entered into after, the beginning of the earliest comparative period presented in the financial statements. In August, another method of adoption was issued which provides an alternative to the modified retrospective transition method and allows companies to forgo the retrospective reporting requirements by recognizing a cumulative effect adjustment to the opening balance of retained earnings upon adoption in 2019. The Company will adopt the standard using the additional transition method introduced by ASU 2018-11. The Company completed its scoping assessment and determined that there are a limited number of leases that will be impacted by the new standard. While the Company is still in the process of determining the effect that the new standard will have on its consolidated financial statements and related disclosures based on our existing operating lease portfolio, the Company will be recognizing additional assets and corresponding liabilities on its consolidated balance sheet.

2. Fair value of financial instruments

In measuring fair value, the Company evaluates valuation techniques such as the market approach, the income approach and the cost approach. A three-level valuation hierarchy, which prioritizes the inputs to valuation techniques that are used to measure fair value, is based upon whether such inputs are observable or unobservable.

Observable inputs reflect market data obtained from independent sources, while unobservable inputs reflect market assumptions made by the reporting entity. The three-level hierarchy for the inputs to valuation techniques is briefly summarized as follows:

Level 1—Observable inputs such as quoted prices (unadjusted) for *identical* instruments in active markets;

Level 2—Observable inputs such as quoted prices for *similar* instruments in active markets, quoted prices for identical or similar instruments in markets that are not active, or model-derived valuations whose significant inputs are observable for substantially the full term of the assets or liabilities; and

Level 3—Unobservable inputs that reflect the reporting entity's estimate of assumptions that market participants would use in pricing the asset or liability.

3. Equipment, net

Equipment, net consisted of the following (in thousands):

	December 31, 2018	December 31, 2017
Cost:		
Equipment cost as of January 1,.	$ 334	$ 143
Additions	58	190
Exchange differences	(2)	1
Equipment cost as of period end	390	334
Less:		
Accumulated depreciation as of January 1	(156)	(122)
Depreciation for the period.	(45)	(35)
Exchange differences	(2)	1
Accumulated depreciation as of period end	(203)	(156)
Total equipment, net	$ 187	$ 178

Depreciation expense for the years ended December 31, 2018 and 2017 was $47,000 and $34,000, respectively.

4. Accrued expenses

Accrued expenses consisted of the following (in thousands):

	December 31, 2018	December 31, 2017
Accrued bonuses	$ 2,295	$ 1,717
Accrued vacation pay	435	464
Accrued social security pay	214	217
Accrued professional fees.	131	470
Accrued development costs	3,257	1,747
Accrued severance	356	152
Accrued other	1,477	1,338
Total accrued expenses.	$ 8,165	$ 6,105

5. Commitments and contingencies

Operating lease commitments

Parent is a party to an Office Lease Agreement with SHIGO 10 PO Owner LLC for approximately 5,116 rentable square feet in the building located at 10 Post Office Square, Boston, Massachusetts, which serves as Parent's corporate headquarters. The initial term of the lease is 62 months beginning on March 1, 2017. Parent has the option to extend the lease one time for an additional 5-year period. Following an initial two-month rent abatement period, Parent is obligated to make monthly rent payments in an amount that began at $20,997 and escalates by approximately 2% annually for the term of the lease. In addition, Parent is responsible under the lease for specified costs and charges, including certain operating expense, utilities, taxes and insurance.

Albireo AB is a party to a 36-month building lease for approximately 5,100 square feet of office space in Gothenburg, Sweden. The lease does not have stated escalating rent clauses, except for changes in the Swedish Consumer Price Index (CPI). The current quarterly payment under the lease is SEK 329,358 ($36,780 based on the SEK to USD exchange rate as of December 31, 2018). The current term of the lease expires in February 2022, but renews automatically thereafter for consecutive three-year terms unless notice of nonrenewal is given by either party at least nine months prior to the end of the current term and subject to Albireo AB's right to terminate the lease at any time upon

six months' notice. Subsequent to year end, the lease was renewed for an additional three year period (through November 2022), with quarterly payments of SEK 329,358 ($36,780 based on the SEK to USD exchange rate as of December 31, 2018).

As of December 31, 2018, future minimum commitments under facility operating leases were $961,000.

Year ended December 31,	(in thousands)
2019	$ 333
2020	266
2021	271
2022	91
Total Minimum Commitments	$ 961

Rent expense recognized under the Company's operating leases was $403,000 and $394,000 for the years ended December 31, 2018 and 2017, respectively.

Agreements with CROs

As of December 31, 2018, the Company had various agreements with CROs for the conduct of specified research and development activities and, based on the terms of the respective agreements, may be required to make future payments of up to $24.3 million upon the completion of contracted work.

Legal Contingency

On February 19, 2019, we filed a complaint for breach of contract and breach of implied covenant of good faith and fair dealing against Ferring International Center S.A. (the "Respondent") in the United States District Court for the Southern District of New York. In the complaint, we are seeking, among other things, compensatory damages of at least € 37 million.

We have retained outside counsel under a contingency fee arrangement, and as a result, we will not incur attorneys' fees for litigating the matter, but counsel will receive a contingent fee of 33 1/3% of the net recovery (after deduction of expenses) in the event a recovery is received.

Due to their nature, it is difficult to predict the outcome, or the costs involved in any litigation. Furthermore, the Respondent may have significant resources and interest to litigate and therefore, although we have a contingency fee arrangement, this litigation could be protracted and may ultimately involve significant legal expenses.

Other Commitments

In connection with the spin-off of Albireo Limited from AstraZeneca in 2008 and associated transfer agreements, the Company became party to an assignment agreement between AstraZeneca and a named inventor on a patent related to elobixibat. In connection with this agreement, in April 2018, the Company was required to pay a one-time "launch fee" payment of $457,000.

6. Goodwill

The following table summarizes the Company's goodwill activity:

	(in thousands)
Goodwill at December 31, 2016	$ 18,110
Purchasing accounting adjustment	(850)
Goodwill at December 31, 2017	$ 17,260
Purchasing accounting adjustment	—
Goodwill at December 31, 2018	$ 17,260

7. Net loss per share

Basic net loss per share, or Basic EPS, is calculated by dividing the net loss attributable to holders of common stock by the weighted average number of shares of common stock outstanding. Diluted net loss per share, or Diluted EPS, is calculated by dividing the net loss attributable to holders of common stock by the weighted-average number of common stock outstanding. If the Company were in a net income position, Diluted EPS would be calculated by dividing the net income attributable to holders of common stock by the weighted-average number of common stock plus dilutive common stock equivalents outstanding.

The following table sets forth the computation of Basic EPS and Diluted EPS (in thousands, except for share and per share data):

	December 31,	
	2018	2017
Basic and Diluted EPS:		
Numerator		
Net loss	$ (46,111)	$ (24,414)
Denominator		
Weighted average number of shares outstanding	11,702,785	7,819,302
Basic and Diluted EPS	$ (3.94)	$ (3.12)

The following weighted-average outstanding common stock equivalents were excluded from the computation of Diluted EPS for the periods presented because including them would have been anti-dilutive:

	Year Ended	
	2018	2017
Options to purchase common stock and RSUs	696,710	889,934

8. Income taxes

Effects of the Tax Cuts and Job Act

On December 22, 2017, The Tax Cuts and Job Act (the Tax Act) was signed into U.S. law. The Tax Act significantly changes the Internal Revenue Code of 1986, as amended (the Code). Changes under the new tax law include a reduction in the federal corporate tax rate from 34% to 21%, limitations or eliminations to certain tax deductions, and usage of tax benefits in the future.

In December 2017, the SEC staff issued SAB 118 to address the application of GAAP in situations when a registrant does not have the necessary information available, prepared, or analyzed (including computations) in reasonable detail to complete the accounting for certain income tax effects of H.R.1. The Company recognized the provisional tax impacts related to deemed repatriated earnings and the revaluation of deferred tax assets and liabilities and included these amounts in its consolidated financial statements for the year ended December 31, 2017. The

Company did not record any adjustments in the year ended December 31, 2018 to these provisional amounts that were material to its financial statements. As of December 31, 2018, the Company's accounting treatment is complete.

The Company has had an overall net operating loss position since its inception.

For the years ended December 31, 2018 and 2017, the components of loss before income taxes were as follows (in thousands):

	Year Ended December 31,	
	2018	2017
U.S.	$ (13,951)	$ (2,031)
Foreign	(32,140)	(22,171)
Total	$ (46,091)	$ (24,202)

The components of income tax (benefit) for the years ended December 31, 2018 and 2017 were as follows (in thousands):

	Year Ended December 31,	
	2018	2017
Current tax expense:		
Federal	$ —	$ (1)
State	21	(12)
Foreign	(1)	225
Total	$ 20	$ 212
Deferred tax benefit:		
Federal	$ —	$ —
State	—	—
Foreign	—	—
Total	$ —	$ —
Total provision for income taxes	$ 20	$ 212

A reconciliation of the U.S. statutory income tax rate to the consolidated effective income tax rate was as follows:

	Year ended December 31,	
	2018	2017
U.S. statutory income tax rate	21 %	34 %
Non-deductible interest expense	—	—
Stock compensation	(2)	(2)
U.S. taxation of foreign earnings	(10)	—
State taxes, net of federal tax effect	2	—
Change in valuation allowance	(13)	125
Write off of disallowed recognized built in loss	—	(143)
Change in U.S. tax rate	—	(4)
Foreign tax rate differences	1	(11)
Other items	1	1
Effective income tax rate	0.0 %	0.0 %

Deferred taxes are recognized for temporary differences between the bases of assets and liabilities for financial statement and income tax purposes. The tax effect of temporary differences that give rise to significant portions of the deferred tax assets are as follows (in thousands):

	Year Ended December 31,	
	2018	2017
Deferred tax assets:		
Tax loss carryforwards	$ 26,280	$ 21,653
Capitalized expenses		—
Research and development credits	200	127
Accrued expenses	520	295
Stock compensation	1,400	825
Interest carryforwards	100	—
Other	50	35
Total gross deferred tax assets	28,550	22,935
Valuation allowance	(28,520)	(22,910)
Total deferred tax assets	$ 30	$ 25
Deferred tax liabilities:		
Intangible assets	$ (30)	$ 25
Temporary difference on financial instruments		—
Total deferred tax liabilities	(30)	25
Net deferred tax assets	$ —	$ —

A valuation allowance is recorded against deferred tax assets if it is more likely than not that some or all of the deferred tax assets will not be realized. Due to the uncertainty surrounding the realization of the favorable tax attributes in future returns, the Company has reserved against its deferred tax assets at December 31, 2018 and 2017. The Company had approximately $28.5 million and $22.9 million in valuation allowances recorded against its deferred tax assets as of December 31, 2018 and 2017, respectively. The Company recorded an expense of $5.6 million for the change in valuation allowance for the year ended December 31, 2018 and a benefit of $30.2 million for the change in valuation allowance for the year ended December 31, 2017.

As of December 31, 2018, deferred tax assets related to net operating loss (NOL) carryforwards were $26.3 million, which may be used subject to certain limitations to offset future taxable income, if any. The NOL includes approximately $1.4 million for U.S. federal tax purposes and $153.9 million for U.S. state tax purposes. Losses carryforwards generated prior to December 31, 2017 expire between 2025 and 2037. As part of the changes from the Tax Cuts and Jobs Act, Federal net operating losses generated for tax years beginning after December 31, 2017 no longer have an expiration period and can be used indefinitely. Additional NOL of approximately $75.9 million were generated in various non-U.S. jurisdictions and will not expire. A valuation allowance has been established on the NOL carryforwards as it is uncertain as to whether future taxable income will be generated to utilize such NOLs.

As of December 31, 2018, the Company has federal research and development credit carryforwards of $73,000, which expire commencing in fiscal year 2028. The Company also has state research and development credit carryforwards of approximately $160,000, which expire commencing in fiscal 2022. A valuation allowance has been established on the research and development credits as it is uncertain as to whether future taxable income will be generated.

Utilization of the NOL and credit carryforwards may be subject to a substantial annual limitation due to ownership change limitations that have occurred previously or that could occur in the future as provided by Section 382 of the Code and similar state and foreign provisions. These ownership changes may limit the amount of NOL and credit carryforwards that can be utilized annually to offset future taxable income and tax, respectively. In general, an ownership change, as defined by Code Section 382, results from transactions increasing the ownership of certain shareholders or public groups in the stock of a corporation by more than 50 percentage points over a three-year period.

During 2016, the Company completed an analysis to assess and concluded that an ownership change within the meaning of Code Section 382 occurred. The analysis has not yet been updated beyond 2016.

As a result of the Tax Act, the Company has included certain foreign income related to its monetization of future royalties as taxable income in the United States. This income was offset by US net operating loss carryforwards.

The Company's policy is for any earnings of non-U.S. subsidiaries to be indefinitely invested outside the United States on the basis of estimates that future domestic cash generation will be sufficient to meet future domestic cash needs and the Company's specific plans for reinvestment of those subsidiary earnings, if any.

Uncertain tax positions

The Company accounts for uncertain tax positions under the recognition and measurement criteria of ASC 740-10. For those tax positions for which it is more likely than not that a tax benefit will be sustained, the Company records the largest amount of tax benefit with a greater than 50% likelihood of being realized upon settlement with a taxing authority that has full knowledge of all relevant information. If the Company does not believe that it is not more likely than not that a tax benefit will be sustained, no tax benefit is recognized. As of December 31, 2018 and 2017, no uncertain tax positions have been recorded. Interest and penalties related to the settlement of uncertain tax positions, if any, will be reflected in income tax expense. The Company did not recognize any interest or penalties associated with unrecognized tax benefits in the accompanying consolidated financial statements. The Company does not expect any material changes to the unrecognized benefits within 12 months of the reporting date. Due to existence of the valuation allowance, future changes in the Company's unrecognized tax benefits will not impact its effective tax rate.

The Company files U.S. federal and state tax returns and has determined that its major tax jurisdictions are the United States and Massachusetts, as well as the United Kingdom and Sweden. The Company's tax returns may be examined for certain tax jurisdictions back to December 31, 2015.

9. Stockholders' equity

Preferred Stock

As of December 31, 2018, the Company has 50,000,000 shares of preferred stock authorized. There are no shares of preferred stock issued or outstanding.

Financing

At-the-Market Sales

In October 2017, the Company entered into an at-the-market offering program Sales Agreement with Cowen and Company, LLC (Cowen) relating to the sale of shares of the Company's common stock having an aggregate offering price of up to $50.0 million from time to time through Cowen, acting as its agent. In February 2018, the Company sold an aggregate of 728,862 shares of common stock pursuant to the Sales Agreement and received proceeds, net of offering expenses, of approximately $24.2 million.

January 2018 Underwritten Public Offering

On January 29, 2018, the Company completed an underwritten public offering of 2,265,500 shares of its common stock, at a price to the public of $33.00 per share. The Company received net proceeds from this offering of $69.9 million, after deducting underwriting discounts, commission and offering expenses.

May 2017 Underwritten Public Offering

On May 30, 2017, the Company completed an underwritten public offering of 2,530,000 shares of its common stock, at a price to the public of $20.50 per share. The Company received net proceeds from this offering of $48.5 million, after deducting underwriting discounts, commissions and offering expenses.

10. Stock-based Compensation

On November 3, 2016, the Albireo Pharma, Inc. 2016 Equity Incentive Plan (the 2016 Equity Plan) was approved by the Company's stockholders. The 2016 Equity Plan replaced Biodel's 2010 Stock Incentive Plan, as amended (the 2010 Plan), in connection with completion of the Biodel Transaction. The 2016 Equity Plan authorized the issuance of up to 635,000 shares, plus up to 249,059 shares issued if awards outstanding under the 2010 Plan were cancelled, forfeited or expired on or after the Biodel Transaction. All stock options outstanding under the 2010 Plan remain in full force and effect pursuant to their terms and the terms of the 2010 Plan.

On September 13, 2017, the Parent's Board of Directors adopted the Albireo Pharma, Inc. 2017 Inducement Equity Incentive Plan (the 2017 Inducement Plan) without stockholder approval pursuant to Rule 5635(c)(4) of the Nasdaq Listing Rules. Pursuant to the 2017 Inducement Plan, Parent may grant stock options, stock awards and other stock-based awards for up to a total of 150,000 shares of common stock to new employees of the Company.

On June 8, 2018, the Albireo Pharma, Inc. 2018 Equity Incentive Plan (the 2018 Equity Plan) was approved by the Company's stockholders. The 2018 Equity Plan replaced the 2016 Equity Plan. The 2018 Equity Plan authorized the issuance of up to 1,200,000 shares, plus up to 1,078,870 shares issued if awards outstanding under the 2010 Plan, the 2016 Equity Plan, or 2017 Inducement Plan were cancelled, forfeited or expired. All stock options outstanding under the 2010 Plan, 2016 Equity Plan, or 2017 Inducement Plan remain in full force and effect pursuant to their terms and the terms of their respective plan.

The Company recognized stock-based compensation expense in the accompanying Consolidated Statements of Operations as follows (in thousands):

	Year Ended December 31,	
	2018	2017
General and administrative	$ 3,735	$ 3,406
Research and development	1,811	294
Total stock-based compensation	$ 5,546	$ 3,700

A summary of the outstanding stock options as of December 31, 2018 is as follows:

	Stock Options Outstanding			
	Number of Shares	Weighted-Average Exercise Price Per Share	Weighted-Average Remaining Contractual Term (Years)	Aggregate Intrinsic Value (in thousands)
Outstanding—December 31, 2017	1,035,361	$ 17.78	8.71	$ 11,896
Granted	608,750	$ 30.92		
Expirations/forfeitures	(201,825)	$ 28.53		
Exercises	(72,782)	$ 6.96		
Outstanding—December 31, 2018	1,369,504	$ 22.34	8.06	$ 8,421
Exercisable—December 31, 2018	545,151	$ 15.54	6.71	$ 6,596
Vested or expected to vest at—December 31, 2018	1,350,082	$ 22.65	8.07	$ 7,964

Aggregate intrinsic value represents the difference between the fair value of the underlying common stock and the exercise price of outstanding, in-the-money options.

Options to purchase 19,422 shares of common stock are performance based and vest upon the date the Company files a drug approval application for A4250 for any orphan indication, if such filing occurs prior to a specified date. This unvested performance-based option is excluded from the vested or expected to vest balance as of December 31, 2018.

As of December 31, 2018, the total unrecognized compensation expense related to unvested options was $14.1 million, which the Company expects to recognize over a weighted average vesting period of 2.6 years.

In determining the estimated fair value of the stock-based awards, the Company uses the Black-Scholes option pricing model and assumptions discussed below. Each of these inputs is subjective and generally requires significant judgment to determine.

The fair value of share option awards was estimated with the following assumptions:

	As of December 31, 2018	As of December 31, 2017
Price per share of common stock	$ 26.27- 33.61	$ 17.05- 26.12
Expected term (in years)	5.5 - 6.0	5.2 - 6.9
Risk-free interest rate	2.6 - 3.1 %	1.9 - 2.3 %
Expected volatility	84.4 - 89.9 %	69.5 - 78.4 %
Dividend rate	0 %	0 %

The Company recorded additional stock-based compensation expense of $788,000 in general and administrative expenses in its consolidated statement of operations for the year ended December 31, 2017. The additional expense was attributable to the correction of an understatement of expense recorded for the year ended December 31, 2016 due to the use of incorrect service periods for stock options.

Restricted Stock Units

The Company grants restricted stock units ("RSUs") to executive officers and employees from time to time. There is no direct cost to the recipients of RSUs, except for any applicable taxes.

Each RSU award represents one share of common stock and each award vests 25% on the first anniversary and in equal quarterly installments thereafter. The costs of the awards, determined as the fair market value of the shares on the grant date, are expensed on a straight lined basis over the length of the award.

A summary of outstanding RSU as of December 31, 2018 is as follows:

	Shares	Weighted Average Grant-Date Fair Value
Non-vested and outstanding balance at December 31, 2017	—	$ —
Changes during the period:		
RSUs granted	5,000	27.98
Non-vested and outstanding RSU balance at December 31, 2018	5,000	$ 27.98

Employee Stock Purchase Plan

In June of 2018, the Company's Board of Directors adopted the 2018 Employee Stock Purchase Plan (the Plan) that allows eligible employees to purchase shares of its common stock at a discount through payroll deductions. The Plan was subsequently approved by shareholders, with 300,000 shares being available to be issued under the Plan.

The Plan terms state implementation will be by a series of six-month offering periods, with a new offering period commencing on June 1 and December 1 of each year or the first business day thereafter. The initial Offering Period under the Plan began on December 1, 2018 and will close on May 31, 2019. The Plan is intended to qualify under the Internal Revenue Code of 1986, Section 423.

11. Long-term debt

Loan Facility

The Company (in particular, Albireo Limited) executed a loan agreement (Loan Facility) with Kreos Capital IV (UK) Limited (Kreos UK) in December 2014. The Company paid $178,000 in interest on the Loan Facility for the year ended December 31, 2017. The debt was paid in full during 2017 and therefore there was no remaining debt discount as of December 31, 2017. Interest expense included $161,000 of discount accretion for the years ended December 31, 2017 respectively.

In May 2017, Kreos Capital exercised the Replacement Kreos Warrants in full on a "cashless" basis. The number of shares of the Company's common stock issued in the cashless exercise, 29,831 shares, was determined by a formula specified in the warrant document.

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Directors

David Chiswell, Ph.D.
Chairman of the Board of Directors, Albireo Pharma
Non-Executive Chairman, IGEM Therapeutics Ltd.
Non-Executive Director, Avillion LLP

Ronald H.W. Cooper
President and Chief Executive Officer, Albireo Pharma

Michael Gutch, Ph.D.
Chief Business Officer and Chief Financial Officer, Entasis Therapeutics

Roger A. Jeffs, Ph.D.
Co-Founder and Co-Owner of Bull City Select Investments

Anne Klibanski, M.D.
Interim President and Chief Executive Officer, Chief Academic Officer, Partners Healthcare

Stephanie S. Okey, M.S.
Former Senior Vice President, Head of North America, Rare Diseases, Genzyme, a Sanofi company

Davey S. Scoon
Chair of the Board of Trustees, Allianz Global Investors

Executive Officers

Ronald H.W. Cooper
President and Chief Executive Officer

Jan P. Mattsson, Ph.D.
Chief Scientific Officer

Simon N.R. Harford
Chief Financial Officer and Treasurer

Patrick T. Horn, M.D., Ph.D.
Chief Medical Officer

Martha J. Carter
Chief Regulatory Officer

Pamela Stephenson
Chief Commercial Officer

Jason G. Duncan
General Counsel and Secretary

Stockholders and Stock Listing

Our common stock is traded on The Nasdaq Capital Market under the symbol ALBO. On March 29, 2019, the closing price of our common stock was $32.21 per share and our common stock was held by 28 stockholders of record.

Investor Information

You may obtain a copy of any of the exhibits to our Annual Report on Form 10-K free of charge. These documents are available on our website at www.albireopharma.com or by contacting Investor Relations at Albireo Pharma, Inc.

Requests for information about Albireo Pharma, Inc. should be directed to:

Investor Relations
Albireo Pharma, Inc.
10 Post Office Square, Suite 502 South
Boston, Massachusetts 02109
Telephone: (857) 254-5555

Annual Meeting

The annual meeting of stockholders will be held at the time and location stated below.

Friday, June 14, 2019
8:30 a.m. ET

10 Post Office Square, Suite 502 South
Boston, Massachusetts 02109

Internet Website

www.albireopharma.com

Legal Counsel

Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C.
Boston, Massachusetts

Independent Registered Public Accounting Firm

Ernst & Young LLP
Boston, Massachusetts

Transfer Agent and Registrar

Continental Stock Transfer & Trust Company
1 State Street, 30th Floor
New York, NY 10004-1561

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