INTERCEPT PHARMACEUTICALS INC
Form 10-K
March 02, 2015

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2014

OR

o **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: 001-35668

Intercept Pharmaceuticals, Inc.

(Exact Name of Registrant as Specified in its Charter)

Delaware (State or Other Jurisdiction of Incorporation or Organization)	22-3868459 (I.R.S. Employer Identification No.)
450 West 15th Street, Suite 505 New York, NY (Address of Principal Executive Offices)	10011 (Zip Code)

(646) 747-1000

(Registrant s Telephone Number, Including Area Code)

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

Title of each class	Name of each exchange on which registered
Common Stock, $0.001 par value	**NASDAQ Global Select 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 x No o

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

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 x No o

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files).Yes x No o

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

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

Large accelerated filer x Accelerated filer o Non-accelerated filer o Smaller reporting company o (Do not check if a smaller reporting company)

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

The aggregate market value of the registrant s voting and non-voting common stock held by non-affiliates of the registrant (without admitting that any person whose shares are not included in such calculation is an affiliate) computed by reference to the price at which the common stock was last sold on June 30, 2014 was approximately $2,970,850,843. As of February 15, 2015, there were 22,635,857 shares of common stock, $0.001 par value per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

The registrant intends to file a definitive proxy statement pursuant to Regulation 14A in connection with its 2015 Annual Meeting of Stockholders. Portions of such proxy statement are incorporated by reference into Part III of this Annual Report on Form 10-K.

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Forward-Looking Statements

This Annual Report on Form 10-K contains forward-looking statements that involve substantial risks and uncertainties. All statements other than statements of historical facts contained in this Annual Report on Form 10-K, including statements regarding our strategy, future operations, future financial position, future revenue, projected costs, prospects, plans, objectives of management and expected market growth, are forward-looking statements. These statements involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements.

The words anticipate, believe, estimate, expect, intend, may, plan, predict, project, target, poten should, continue, and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. These forward-looking statements include, among other things, statements about:

the initiation, cost, timing, progress and results of our development activities, preclinical studies and clinical trials;
the timing of and our ability to obtain and maintain regulatory approval of obeticholic acid, or OCA, and any other product candidates we may develop, particularly the possibility that regulatory authorities may require clinical outcomes data (and not just results based on achievement of a surrogate endpoint) as a condition to any marketing approval for OCA, and any related restrictions, limitations and/or warnings in the label of any approved product candidates;

our plans to research, develop and commercialize our product candidates;
our collaborators election to pursue research, development and commercialization activities;
our ability to attract collaborators with development, regulatory and commercialization expertise;
our ability to obtain and maintain intellectual property protection for our product candidates;
our ability to successfully commercialize our product candidates;
the size and growth of the markets for our product candidates and our ability to serve those markets;
the rate and degree of market acceptance of any future products;
the success of competing drugs that are or become available;
regulatory developments in the United States and other countries;
the performance of our third-party suppliers and manufacturers;
our need for and ability to obtain additional financing;
our estimates regarding expenses, future revenues and capital requirements and the accuracy thereof;
our use of the proceeds from our initial public offering in October 2012 and our follow-on public offerings in June 2013, April 2014 and February 2015; and
our ability to attract and retain key scientific or management personnel.

These forward-looking statements are only predictions and we may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, so you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have based these forward-looking statements largely on our current expectations and projections about future events and trends that we believe may affect our business, financial condition and operating results. We have included important factors in the cautionary statements included in this Annual Report on Form 10-K, particularly in Item 1.A. Risk Factors, that could cause actual future results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments we may make.

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You should read this Annual Report on Form 10-K and the documents that we have filed as exhibits to the Annual Report on Form 10-K with the understanding that our actual future results may be materially different from what we expect. We do not assume any obligation to update any forward-looking statements whether as a result of new information, future events or otherwise, except as required by applicable law.

Non-GAAP Financial Measures

This Annual Report on Form 10-K presents projected adjusted operating expense, which is a financial measure not calculated in accordance with U.S. generally accepted accounting principles, or GAAP, and should be considered in addition to, but not as a substitute for, operating expense that we prepare and announce in accordance with GAAP. We exclude certain items from adjusted operating expense, such as stock-based compensation and other non-cash items, that management does not believe affect our basic operations and that do not meet the GAAP definition of unusual or non-recurring items. We anticipate that stock-based compensation expense will represent the most significant non-cash item that is excluded in adjusted operating expenses as compared to operating expenses under GAAP. A reconciliation of projected non-GAAP adjusted operating expense to operating expense calculated in accordance with GAAP is not available on a forward-looking basis without unreasonable effort due to an inability to make accurate projections and estimates related to certain information needed to calculate, for example, future stock-based compensation expense. Management also uses adjusted operating expense to establish budgets and operational goals and to manage our company s business. Other companies may define this measure in different ways. We believe this presentation provides investors and management with supplemental information relating to operating performance and trends that facilitate comparisons between periods and with respect to projected information.

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Part I

All brand names or trademarks appearing in this Annual Report on Form 10-K are the property of their respective holders. Unless the context requires otherwise, references in this Annual Report on Form 10-K to Intercept, the Company, we, us, and our refer to Intercept Pharmaceuticals, Inc. and its consolidated subsidiaries.

Item 1. Business

Overview

We are a biopharmaceutical company focused on the development and commercialization of novel therapeutics to treat chronic liver diseases with high unmet medical need utilizing our proprietary bile acid chemistry. Our product candidates have the potential to treat orphan and more prevalent liver diseases for which there currently are limited therapeutic solutions.

Our lead product candidate, obeticholic acid, or OCA, is a bile acid analog, a chemical substance that has a structure based on a naturally occurring human bile acid, that selectively binds to and activates the farnesoid X receptor, or FXR, which we believe has broad liver-protective properties. OCA has been tested in five placebo-controlled clinical trials, including a recently completed Phase 3 clinical trial in patients with primary biliary cirrhosis, or PBC, and two Phase 2 clinical trials in patients with nonalcoholic fatty liver disease, or NAFLD, and nonalcoholic steatohepatitis, or NASH. OCA met the primary efficacy endpoint in each of these trials with statistical significance.

In January 2015, OCA received breakthrough therapy designation from the U.S. Food and Drug Administration, or FDA, for the treatment of NASH patients with liver fibrosis. OCA has also been granted fast track designation by the FDA for the treatment of patients with PBC who have an inadequate response to or are intolerant of ursodiol. OCA has received orphan drug designation in the United States and the European Union for the treatment of PBC and primary sclerosing cholangitis, or PSC.

Our most advanced development program for OCA is for PBC as a second line treatment for patients who have an inadequate response to or who are unable to tolerate standard of care therapy and therefore need additional treatment. PBC is a chronic autoimmune liver disease that, if inadequately treated, may eventually lead to cirrhosis, liver failure and death. In March 2014, we completed a Phase 3 clinical trial, known as the POISE trial, in which OCA achieved the primary endpoint for the treatment of PBC. We intend to use these results, along with two previously completed randomized Phase 2 clinical trials of OCA in PBC, as the basis for seeking the first regulatory approvals to market OCA in the United States and Europe. We initiated a rolling New Drug Application, or NDA, submission with the FDA for OCA in PBC in December 2014 under the FDA s accelerated approval pathway. We also plan to submit an application for marketing approval for OCA in PBC in Europe. We plan to complete our filings for marketing approval of OCA in PBC in the United States and Europe during the first half of 2015. If we receive marketing approval from regulatory authorities based on these applications, we plan to initiate the commercial launch of OCA in PBC in the United States and certain European countries in 2016.

OCA achieved the primary endpoint in a Phase 2b clinical trial for the treatment of NASH, known as the FLINT trial, which was sponsored by the U.S. National Institute of Diabetes and Digestive and Kidney Diseases, or NIDDK, a part of the National Institutes of Health. The FLINT trial was completed in late July 2014. We are planning to finalize the design of our Phase 3 clinical program in NASH in the second quarter of 2015, subject to the completion of our regulatory discussions with the FDA and the European Medicines Agency, or EMA, and then initiate the clinical

program. We also intend to initiate a clinical trial in 2015 characterizing the lipid metabolic effects of OCA and cholesterol management effects of concomitant statin administration in NASH patients. Our collaborator, Sumitomo Dainippon Pharma Co. Ltd., or Sumitomo Dainippon, has completed enrollment in a 200-patient Phase 2 NASH clinical trial of OCA in Japan with a primary efficacy endpoint similar to that used in our Phase 2b FLINT trial, which is anticipated to be completed by the end of 2015.

In addition to PBC and NASH, we plan to continue our research on OCA in other patient populations suffering from liver and non-liver related diseases, as we believe that FXR has broad therapeutic potential. In December 2014, we initiated an international Phase 2 clinical trial in patients with PSC to evaluate the effects

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of 24 weeks of treatment with varying doses of OCA compared to placebo. We are currently evaluating our future development strategy for OCA in other indications and for our pre-clinical candidates. As part of our development program, we plan to complete investigational new drug enabling studies for our next potential development compound, INT-767, and initiate a Phase 1 trial around year-end 2015. The following chart shows the current stage of development of OCA in different patient populations and the preclinical programs for our other product candidates.

Intercept Pipeline Focused on Neglected Liver Diseases

Our current patents for OCA are scheduled to expire at various times through 2028. We believe that coverage could be extended into 2033 based on our additional pending composition-of-matter and process patent applications. Our current plan is to commercialize OCA ourselves in the United States and Europe for the treatment of PBC, NASH and other indications primarily by targeting physicians who specialize in the treatment of liver and intestinal diseases, including both hepatologists and gastroenterologists. We own worldwide rights to OCA outside of Japan, China and Korea, where we have exclusively licensed OCA to Sumitomo Dainippon along with an option to exclusively license OCA in certain other Asian countries.

By virtue of our patent portfolio and the proprietary know-how of our employees and our collaborators at the University of Perugia, we believe that we hold a leading position in the fields of bile acid chemistry and therapeutics. Through collaboration with Professor Roberto Pellicciari, Ph.D., one of our co-founders, and TES Pharma Srl, we are continuing to our research to rationally design compounds that bind selectively and potently to FXR and other bile acid receptors. Starting with OCA and its underlying patents, which were assigned to us under our agreements with Professor Pellicciari, other researchers and the University of Perugia, our collaboration has resulted in a pipeline of bile acid analogs in addition to OCA, which target both FXR and a second dedicated bile acid receptor called TGR5, a target of interest for the treatment of type 2 diabetes and other gastrointestinal diseases.

Our Strategy

Our strategy is to develop and commercialize novel therapeutics for patients with chronic liver and other diseases, beginning with OCA for the treatment of PBC, NASH and other follow-on indications that we believe are underserved by existing marketed therapies. The key elements of our strategy are to:

obtain marketing approval of OCA for the treatment of PBC in the United States, the European Union and other countries;

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commercialize OCA in the United States, Europe and other countries, initially for the treatment of PBC;
continue to develop OCA for the treatment of NASH and seek regulatory approval of OCA in this indication;
continue to develop OCA in other orphan and more prevalent liver and other diseases; and
advance the development of earlier-stage product candidates in our pipeline.

In order to achieve our strategic objectives, we have, and will remain, focused on hiring and retaining a highly skilled management team and employee base with extensive experience and specific skill sets relating to the selection, development and commercialization of therapies for diseases with high unmet medical need. We anticipate that we will continue to increase our product development, scientific, commercial and administrative personnel significantly in the United States and abroad as part of our growth strategy.

Overview of Liver Function, Bile Acids and Chronic Liver Diseases

The liver performs many functions that are crucial for survival, including the regulation of bile acid metabolism. Bile acids are natural detergent-like emulsifying agents that are released from the gallbladder into the intestine when food is ingested, and are essential for the absorption of dietary cholesterol and other nutrients. Cholesterol bound by bile acids is taken up by the liver, where the cholesterol is then converted into one of two primary bile acids. The bile acids are then actively secreted into bile ducts, which eventually empty into the gallbladder. This digestive cycle of bile flow from gallbladder to intestine to liver and back is called the enterohepatic recirculation of bile.

In addition to facilitating nutrient absorption, bile acids have a much broader role than previously realized in regulating multiple biological functions. They are also complex signaling molecules that integrate metabolic and immune pathways involved in the healthy functioning of various tissues and organs. For example, the actions of bile acids in the liver, intestine and kidney regulate repair mechanisms that modulate inflammation and fibrosis, or scarring, which can lead to progressive organ damage.

The biological effects of bile acids are mediated through dedicated receptors. The best understood is the farnesoid X receptor, a nuclear receptor that regulates bile acid synthesis and clearance from the liver, thereby preventing excessive bile acid build-up in the liver, which may be toxic. As a result, FXR is a target for the treatment of liver diseases such as PBC and PSC that involve impaired bile flow, a condition called cholestasis, in which the liver is exposed to higher than normal levels of bile acids, causing significant damage over time due to the detergent effects of bile acids. In addition, bile acid activation of FXR induces anti-fibrotic, anti-inflammatory, anti-steatotic and other mechanisms that are necessary for the normal regeneration of the liver and may play a role in the treatment of more prevalent liver diseases such as NASH and alcoholic hepatitis. Based on the discovery of similar FXR-mediated protective mechanisms in other organs exposed to bile acids, we believe that FXR may also be a potential target for the treatment of a number of intestinal, kidney and other diseases.

Our Lead Product Candidate: Obeticholic Acid (OCA)

Primary Biliary Cirrhosis (PBC)

Our current clinical focus is on the development of OCA, a novel, orally administered, first-in-class FXR agonist that we believe has broad liver-protective properties and may effectively counter a variety of chronic insults to the liver that cause fibrosis, which can eventually lead to cirrhosis, liver transplant and death. Our first targeted disease is PBC, an orphan indication with a significant unmet medical need.

PBC is a rare liver disease that primarily results from autoimmune destruction of the bile ducts that transport bile acids out of the liver, resulting in cholestasis. As the disease progresses, persistent toxic build-up of bile acids causes progressive liver damage marked by chronic inflammation and fibrosis. In response to the bile acid mediated toxicity seen in PBC, liver cells release alkaline phosphatase, or ALP, a liver enzyme that is a key biomarker of the disease pathology. Elevated blood levels of ALP are used as the primary means of diagnosis of PBC and are closely monitored in patients as the most important indicator of treatment response and prognosis.

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While PBC is rare, it is the most common cholestatic liver disease. An estimated 90% of patients are women, with approximately one in 1,000 women over the age of 40 afflicted by the disease. The mean age of diagnosis is about 40 years and the typical initial presentation occurs between the ages of 30 and 65 years. In the United States, the disease is currently the second leading indication for liver transplant among women. A majority of PBC patients are asymptomatic at the time of initial diagnosis, but most develop symptoms over time. Fatigue and pruritus, or itching, are the most common symptoms in PBC patients. Less common symptoms include dry eyes and mouth, as well as jaundice, which can be seen in more advanced disease. Based on the guidelines of the American Association for the Study of Liver Disease, or AASLD, and the European Association for the Study of the Liver, or EASL, the clinical diagnosis of PBC is established based on the presence of (i) a positive anti-mitochondrial antibody, or AMA, a marker of this autoimmune disease seen in up to 95% of PBC patients, and (ii) elevated serum levels of ALP. In the earlier stages of PBC, ALP is often the only abnormally elevated liver enzyme, rising to between two to ten times higher than normal values. Bilirubin is a marker of liver function and is also monitored in PBC to provide an indication of how well the liver is functioning. Liver biopsy can be used to confirm the diagnosis of PBC, but is not required and is becoming less-frequently performed.

Disease progression in PBC varies significantly but usually is relatively slow, with median survival in untreated patients of 7.5 years if symptomatic at diagnosis and up to 16 years if asymptomatic at diagnosis. PBC patients whose disease is progressing have persistently elevated levels of ALP and other liver enzymes, with abnormal bilirubin levels heralding more advanced disease. Data from published long-term studies demonstrate that a significant portion of such patients with advancing disease progress to liver failure, transplant or death within five to ten years, despite receiving ursodiol, the standard of care therapy.

Currently Available Treatment Options for PBC

The only approved drug for the treatment of PBC is ursodeoxycholic acid, available generically as ursodiol, which is the standard initial course of therapy for all PBC patients. Ursodiol is a naturally occurring bile acid found in small quantities in humans and it is the least detergent of the various types of bile acids that make up the bile pool. In PBC patients, the typical daily dose of ursodiol of approximately one gram represents more than one-fifth of the entire bile pool and, after ongoing therapy, it will comprise at least half of the entire bile pool. It is believed that ursodiol treatment results in the bile pool being less toxic to the liver due to ursodiol s dilution of other more detergent bile acids.

In patients for whom ursodiol is effective, the treatment slows the progression of PBC, reducing the likelihood of liver failure and the need for transplant. As shown in numerous clinical trials of ursodiol treatment, a positive therapeutic response is primarily determined by sustained reduction of ALP levels, along with maintenance of normal bilirubin levels, indicating adequately compensated liver function. This biochemical improvement has been shown to correlate well with improved clinical outcomes such as transplant-free survival.

The outlook and treatment options for end-stage PBC patients who fail to respond to ursodiol are limited. Although other drugs such as colchicine, budesonide, methotrexate and others have been tested as treatments in PBC, none has been shown to be both effective and safe in altering the course of the disease. While a liver transplant may be curative, many patients fail to receive a donor organ in time, and for those who do receive an organ, there are very significant clinical risks such as infection and organ rejection, as well as significant costs. In addition, the disease recurrence rate is as high as 18% at five years and up to 30% at ten years after liver transplant.

Our PBC Opportunity

While ursodiol s mechanism of action at therapeutic doses is to dilute more detergent bile acids, it has no known pharmacological effects mediated by FXR or other bile acid receptors. Although ursodiol is the established standard of care for the treatment of PBC, studies have shown that up to 50% of PBC patients fail to respond adequately to treatment. Patients typically need to take approximately one gram of ursodiol daily in divided doses, which we believe presents a compliance challenge for some patients.

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According to industry data, there are approximately 300,000 people with PBC in developed countries, of whom we believe approximately 60,000 have been diagnosed and are being treated with ursodiol. Based on this estimate, we believe there are up to 30,000 diagnosed PBC patients who may currently be eligible for treatment with OCA, representing a significant unmet medical need for a second line therapy. With increasing identification of PBC through routine liver function testing in primary care, we believe that there may be significantly more patients who will potentially be eligible for, and be interested in, receiving a new therapy if it becomes available on the market. While ursodiol is the standard of care for the treatment of PBC, given the limitations of its efficacy and the compliance challenges with the dosing regimen discussed above, we believe that there is a significant unmet need for a novel second line therapy in PBC.

Our Solution: OCA for PBC

Overview

Our lead product candidate, OCA, is a bile acid analog and first-in-class FXR agonist derived from the primary human bile acid chenodeoxycholic acid, or CDCA. CDCA, a natural FXR agonist, has historically been used safely as a chronic therapy for cholesterol gallstone disease. OCA has received orphan drug designation in the United States and Europe for the treatment of PBC and PSC.

We have completed three double-blind, placebo-controlled trials of OCA in PBC patients, all of which met their primary and secondary endpoints. We believe that the results of our POISE trial of OCA in PBC and our long-term safety extension trials in PBC patients, which include a small group of patients who have been on OCA therapy for more than four years, demonstrate that OCA produces a durable therapeutic response.

We have also completed two randomized, placebo-controlled Phase 2 trials of OCA in PBC patients, one with OCA in combination with ursodiol and one with OCA as monotherapy, and our POISE trial. We intend to use the POISE trial results, along with two previously completed randomized Phase 2 clinical trials of OCA in PBC, as the basis for seeking the first regulatory approvals to market OCA in the United States and Europe.

OCA was granted Fast Track designation by FDA in May 2014 for the treatment of patients with PBC who have an inadequate response to or are intolerant of ursodiol. The Fast Track process allows a company to submit individual sections of its NDA for review by FDA on a rolling basis as they are completed. We initiated a rolling NDA submission with the FDA for OCA in PBC in December 2014 under the FDA s accelerated approval pathway. We also plan to submit an application for marketing approval for OCA in PBC in Europe. We plan to complete our filings for marketing approval of OCA in PBC in the United States and Europe during the first half of 2015. If we receive marketing approval from regulatory authorities, we plan to initiate the commercial launch of OCA in PBC in the United States and certain European countries in 2016.

We own worldwide rights to OCA outside of Japan, China and Korea, where we have exclusively licensed OCA to Sumitomo Dainippon along with an option to exclusively license OCA in certain other Asian countries.

OCA Benefits in PBC

We believe that OCA has the potential to provide the following benefits in the treatment of PBC:

Efficacy. In addition to achieving the primary endpoint in our Phase 2 and Phase 3 trials, 80% of OCA-treated patients across each of our Phase 2 and Phase 3 trials experienced a reduction in ALP levels of at least 10%, which we

consider to be a clinically meaningful improvement, as compared to 13% of placebo treated patients.

Pharmacological Activity. Unlike ursodiol, which has no FXR-agonist activity, OCA is approximately 100-times more potent than CDCA in activating the FXR receptor. In numerous animal models, sustained FXR activation with OCA treatment has resulted in the prevention, and even reversal, of liver fibrosis. In our clinical trials, patients taking OCA also have experienced significant reductions in common indicators of autoimmune activity such as gamma-glutamyl transferase, or GGT, immunoglobulin M, or IgM, and C-reactive protein, or CRP. We believe that these observations demonstrate potential disease-modifying therapeutic activity directly addressing the underlying autoimmune pathology.

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Ease of Use. We anticipate seeking approval of OCA for the treatment of PBC with the administration of a single tablet each day. With proposed tablets containing 5 mg or 10 mg of OCA, any of these doses is a small fraction of the amount of ursodiol that a PBC patient is typically prescribed.

Phase 3 PBC Program for OCA

Completed Phase 3 Trial: OCA as Combination Therapy in PBC Patients (POISE)

In March 2014, we announced that the primary endpoint was achieved in our international POISE trial studying the safety and efficacy of once-daily treatment with OCA in PBC patients with an inadequate therapeutic response to, or who are unable to tolerate, ursodiol. In the trial, 217 patients were randomized to one of three groups: placebo, 10 mg OCA or 5 mg OCA for six months titrated to 10 mg OCA based on clinical response.

The POISE data showed that OCA, at both a 10 mg dose and a 5 mg dose titrated to 10 mg, met the trial s primary endpoint of achieving a reduction in serum ALP, to below a threshold of 1.67 times upper limit normal, with a minimum of 15% reduction in ALP level from baseline, and a normal bilirubin level after 12 months of therapy. Patients with ALP and bilirubin levels below the thresholds set forth in the POISE trial primary endpoint have been shown in long-term clinical studies to have a significantly lower risk of progressing to liver transplant and death. The proportion of patients meeting the POISE trial primary endpoint was 10% in the placebo group, 47% in the 10 mg OCA group and 46% in the OCA titration group (both dose groups $p < 0.0001$ as compared to placebo) in an intention-to-treat analysis. The placebo group experienced a mean decrease in ALP from baseline of 5%, compared to a significant mean decrease of 39% in the 10 mg OCA dose group and 33% in the OCA titration group (both dose groups $p < 0.0001$ as compared to placebo). OCA treated patients achieved highly statistically significant reductions in ALP beginning as early as two weeks after initiation of treatment, with a peak effect achieved by six months.

POISE Trial: Primary Endpoint

In addition, both OCA dose groups met pre-specified secondary endpoints of improving other clinically relevant liver enzymes. Reductions in GGT of 64% in the 10 mg OCA dose group and 50% in the OCA titration group, alanine transaminase, or ALT, of 42% in the 10 mg OCA dose group and 36% in the OCA titration group, and aspartate transaminase, or AST, of 24% in the 10 mg OCA dose group and 22% in the OCA titration group, were observed, respectively (both OCA dose groups $p < 0.0005$ as compared to placebo). PBC patients typically have dyslipidemia with unique features, characterized by significantly elevated levels of high-density lipoprotein cholesterol, or HDL-C, and modestly or significantly elevated levels of low-density lipoprotein cholesterol, or LDL-C. OCA treatment led to a rapid and sustained dose-dependent decrease in HDL-C levels, similar to those seen in the prior PBC clinical trials, with most patients experiencing HDL-C within normal levels. No meaningful sustained changes in LDL-C were observed in this setting.

Pruritus, or itching, generally mild to moderate, was the most frequently reported adverse event associated with OCA treatment and was observed in 38% of patients on placebo, 68% of patients in the 10 mg OCA group and 56% of patients in the OCA titration group. Eight patients discontinued due to pruritus, of whom none were in the placebo group, seven (10%) patients were in the 10 mg OCA group and one (1%) patient was in the OCA titration group (in a patient who had titrated up to 10 mg). Pruritus has also been observed in other clinical trials

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of OCA. As shown in the graph below, patient-reported pruritus severity, as measured by the visual analog score, or VAS, was not different between OCA and placebo groups at the end of the study.

POISE Trial: Pruritus Scores

Apart from pruritus, the incidence of adverse events was generally similar across both OCA and placebo groups (placebo: 90%, OCA 10 mg: 86%, OCA titration: 89%). Overall, serious adverse events, or SAEs, occurred in 22 (10%) of the patients and, although there were more SAEs in the OCA treatment groups, none were considered drug-related and there were no apparent patterns in the SAEs.

Ongoing Open-Label Long-Term Safety Extension of the POISE Trial

Following the completion of the double-blind portion of the POISE trial described above, patients were given the option to enroll in an open-label long-term safety and efficacy extension trial, or the POISE LTSE. The POISE LTSE is currently ongoing. Patients continue to receive open-label OCA in this phase, and have been increased from a starting dose of 5 mg to as high as 25 mg, as clinically indicated. Of the 198 patients who completed the double-blind phase of the POISE trial, more than 95% continued in the LTSE phase of the trial.

Regulatory Pathway

OCA was granted Fast Track designation by FDA in May 2014 for the treatment of patients with PBC who have an inadequate response to or are intolerant of ursodiol. The Fast Track process allows a company to submit individual sections of its NDA for review by FDA on a rolling basis as they are completed. We initiated a rolling NDA submission with the FDA for OCA in PBC in December 2014 under the FDA s accelerated approval pathway. We also plan to submit an application for marketing approval for OCA in PBC in Europe. We plan to complete our filings for marketing approval of OCA in PBC in the United States and Europe within the first half of 2015. As part of our strategy for filing the NDA under the accelerated approval pathway, we initiated a clinical outcomes confirmatory trial for OCA in PBC in December 2014, following discussions with both the FDA and EMA. We do not expect completion of this trial to be a condition to the receipt of marketing approval and, as a result, plan to complete the trial following our receipt of marketing approval. If we receive marketing approval from regulatory authorities based on these applications, we plan to initiate the commercial launch of OCA in PBC in the United States and certain European countries in 2016.

A number of published clinical studies have demonstrated that lower levels of ALP, both independently or in conjunction with normal bilirubin levels, correlate with a significant reduction in adverse clinical outcomes such as liver transplant and death. We believe that one of the key factors in the FDA s potential acceptance of our POISE trial primary endpoint as a basis for accelerated approval will be the result of

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PBC clinical outcomes data of more than 6,000 PBC patients from 15 academic centers in eight countries that have been compiled by the Global PBC Study Group, which we sponsored, as well as a dataset of over 6,000 PBC patients across the United Kingdom compiled by the UK PBC Group. These represent the largest prospective PBC clinical datasets assembled to analyze the correlation of biochemical therapeutic response with clinical outcomes in PBC patients.

In the largest meta-analysis of individual PBC patient data conducted to date, published in the December 2014 issue of *Gastroenterology*, the Global PBC Study Group researchers confirmed that levels of ALP and bilirubin correlated with clinical outcomes of patients with PBC. Of the 4,845 patients included in the analysis, 1,118 reached a clinical outcome defined as liver transplantation or death. The researchers reported an association between ALP values and liver transplant-free survival, with higher ALP values associated with worse prognosis. At one year after study enrollment, an ALP level of two times upper limit of normal, or ULN, best predicted patient outcome but not significantly better than other lower ALP thresholds such as 1.67 times ULN. As shown in the graph below, among patients with ALP levels less than or equal to two times ULN, 84% survived for at least a ten year follow-up period compared with 62% of those with levels exceeding two times ULN ($p < 0.0001$). Elevated bilirubin levels were strongly correlated with worse prognosis and only 41% of such patients had not had a liver transplant or died over the subsequent 10 years compared with 86% of patients with normal bilirubin levels ($p < 0.0001$). We believe that these results, along with the published results of the UK PBC Group, show that the achievement of an ALP level of less than 1.67 times ULN, together with a normal bilirubin level, correlates with a highly statistically significant reduction of risk and adverse clinical outcomes such as liver transplant and death in PBC patients.

Ongoing Confirmatory Clinical Outcomes Trial

As part of our strategy for filing the NDA for OCA under the accelerated approval pathway, in December 2014 we initiated a confirmatory clinical outcomes trial in PBC, as required under FDA guidelines for accelerated approval, with detailed input on the trial design from both FDA and EMA. The goal of the trial is to confirm that reduction of ALP with OCA treatment is associated with a longer term benefit on liver-related clinical outcomes. This trial is expected to be completed on a post-marketing basis.

We designed our confirmatory clinical outcomes trial to assess the effect of a once-daily dose of 5 mg or 10 mg of OCA in approximately 350 PBC patients with an inadequate therapeutic response to ursodiol or who are unable to tolerate ursodiol. In this trial, eligible patients with PBC continue their ursodiol treatment, except for those patients unable to tolerate ursodiol, and are being randomized into one of two arms of approximately 175 patients each. Patients receive, in addition to ursodiol, either placebo or 5 mg of OCA increasing over the course of the trial to 10 mg of OCA based on tolerability. The primary endpoint of the trial is based on clinical outcomes as measured by time to first occurrence of any of the following adjudicated events: death (all-cause), liver transplant, Model of End stage Liver Disease, or MELD, score greater than 15, hospitalization due to variceal bleeding, encephalopathy or spontaneous bacterial peritonitis, uncontrolled ascites or hepatocellular carcinoma.

Nonalcoholic Steatohepatitis (NASH)

NASH is a common and serious chronic liver disease that develops in approximately one-third of NAFLD patients who have excessive fat accumulation in the liver, referred to as steatosis. In NASH patients, for reasons that are as yet not completely understood, steatosis and other factors such as insulin resistance induce chronic inflammation in the liver and may lead to progressive fibrosis and cirrhosis, followed by eventual liver failure and death. NASH is believed to be one of the most common chronic liver diseases worldwide, with an estimated prevalence of more than 10% of the general adult population in the United States, with similar prevalence estimated in Europe, Japan and other

developed countries. Additionally, NASH has become a highly prevalent liver disease in developing countries such as India and China. According to recent epidemiological studies, it is estimated that more than 10% of the U.S. adult population has NASH, with more than 60% of patients (potentially more than 14 million in total) believed to have liver fibrosis or cirrhosis due to progression of the disease. Although the prevalence of NASH is lower in children, it has also become a serious disease burden in the pediatric population. There are currently no drugs approved for the treatment of NASH.

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NASH is caused by excessive fat accumulation in the liver, or steatosis, that induces inflammation and may lead to progressive fibrosis and cirrhosis, followed by eventual liver failure and death. Additionally, NASH is now considered to be the leading, and a rapidly increasing, cause of hepatocellular carcinoma, or primary liver cancer, of which up to 40% of cases in NASH patients develop prior to developing cirrhosis. Other common co-existing conditions such as obesity and type 2 diabetes, which afflict up to half of all NASH patients, are important risk factors in NASH.

While NASH is commonly associated with obesity, it can also occur in non-obese patients and has been linked in both developed and developing countries to the adoption of a Western diet, with increased consumption of processed foods containing polyunsaturated fatty acids and fructose. Cardiovascular disease, cancer and liver failure are the most common causes of death in NASH patients. More than 20% of NASH patients progress to cirrhosis within a decade of diagnosis and, with the rapidly increasing prevalence of the disease, NASH has become the second most common reason for liver transplant in the United States and is projected to become the leading indication for transplant in the next few years, overtaking both chronic hepatitis C infection and alcoholic liver disease. NASH patients have a ten-fold greater risk of liver-related mortality as compared to the general population and a six-fold greater risk of liver-related mortality as compared to patients with less severe NAFLD. The presence of type 2 diabetes in the broader NAFLD population is associated with a much greater mortality risk, with a 23-fold higher rate of liver-related mortality as compared to non-diabetic NAFLD patients.

Currently, a definitive diagnosis of NASH is based on a histologic assessment of a liver biopsy for several key features associated with NASH, including, but not limited to, steatosis, lobular inflammation and hepatocyte ballooning. However, non-invasive methods of diagnosis are being explored, including transient elastography (an ultrasound technology approved in Europe and more recently in the United States for the measurement of liver fibrosis), magnetic resonance imaging and serum biomarkers. We believe that further validation and approval of non-invasive diagnostic and disease staging methods, as well as the anticipated future regulatory approval of novel NASH therapies, will lead to a significant increase in diagnosis and treatment of patients with NASH.

Currently Available Treatment Options for NASH

There are currently no drugs approved for the treatment of NAFLD or NASH. However, various therapeutics are 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 ursodiol. 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, but have not conclusively been shown to prevent disease progression.

NASH Unmet Medical Need

Although some of the off-label treatments described above have been studied as possible treatments for NASH, none has been approved by the FDA or EMA as a treatment for this disease. Currently, the outlook and treatment options for end-stage NASH patients are limited. Although liver transplant can be curative, many patients fail to receive a donor organ in time, and for those who do, there are very significant clinical risks, such as infection and organ rejection, as well as significant costs. In addition, the post-transplant recurrence rate of NASH has been shown to be as high as 25% at 18 months. Given the lack of available treatment options, we believe that there is a significant unmet need for a novel therapy for NASH, particularly in those patients with advanced fibrosis and cirrhosis.

Our Solution: OCA for NASH

OCA s Potential Benefits in NASH

FXR activation has been shown to play a key role in the regulation of the metabolic pathways relevant to NASH, highlighting FXR as a potential drug target for treatment of the disease. Given the significant unmet medical need of patients with NASH, we believe that the potent ability of OCA to activate FXR could result

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in a major clinical benefit through potential amelioration or reversal of liver fibrosis, inflammation, steatosis, and insulin resistance. We believe that OCA has the potential to provide the following benefits in the treatment of NASH:

Efficacy. In addition to achieving the primary endpoint in the Phase 2b FLINT trial in NASH patients, in an earlier 6-week Phase 2 trial in diabetic NAFLD patients, OCA also demonstrated an approximately 24.5% mean increase from baseline in insulin sensitivity, compared to a 5.5% mean decrease in insulin sensitivity in the placebo group, and statistically significant weight loss from baseline.

Pharmacological Activity. In animal models, sustained FXR activation with OCA treatment has resulted in the reversal of liver fibrosis, the reversal of portal hypertension, the prevention of atherosclerosis, and improvements in triglycerides, inflammation, steatosis and insulin sensitivity. Mice that lack functional FXR (so-called knockout mice) spontaneously develop NASH accompanied by hypertriglyceridemia and insulin resistance, and go on to develop hepatocellular carcinoma, or primary liver cancer. We believe that the combined mechanisms of FXR activation, coupled with the occurrence of NASH in animals lacking FXR, support the potential disease-modifying therapeutic potential of OCA in directly addressing the underlying disease pathology in NASH.

Ease of Use. We anticipate seeking approval of OCA for the treatment of NASH at a single daily dose.

Phase 2 NASH Program for OCA

Phase 2 Trial: OCA as Therapy in Type 2 Diabetic Patients with NAFLD

We previously completed a double-blind, placebo-controlled Phase 2 clinical trial of OCA in 64 type 2 diabetic patients with NAFLD. We believe that a majority of the patients in this trial were likely to have had NASH and, not simple steatosis, given the disease s association with obesity and diabetes and based upon an evaluation of serum fibrosis biomarkers from trial participants. In this trial, OCA therapy significantly improved insulin sensitivity both in the liver and peripheral tissues, thereby meeting the primary endpoint in the trial with a mean improvement in liver insulin sensitization from baseline of approximately 24.5% in the combined OCA dose groups, as compared to a worsening of approximately 5.5% in the placebo group ($p = 0.011$). Insulin resistance, particularly in the liver, is considered to be an important contributor to NASH disease pathology. In this trial, significant improvements in weight loss were also noted in patients receiving OCA therapy, along with improvements in liver enzymes such as GGT and AST.

OCA was generally well-tolerated by the trial patients, with side effects in the treatment groups not meaningfully different than those reported on placebo (apart from mild constipation in the 50 mg group). Consistent with anticipated FXR-related lipid metabolic effects starting with the clearance of excess lipid load from the liver, there were changes in mean serum lipid profiles observed in the OCA treatment groups compared with the placebo group that included decreased concentrations of triglycerides, increased concentrations of LDL-C and slightly decreased concentrations of HDL-C from baseline. In our publication of the results, we observed that once-daily treatment for six weeks at the 25 mg OCA dose, which we subsequently selected to advance in our NASH development program, led to an approximately 12% decrease in mean triglycerides to 170 mg/dL from a baseline mean level of 193 mg/dL, an approximately 22% increase in mean LDL cholesterol to 120 mg/dL from a baseline mean level of 98 mg/dL, and an approximately 5% decrease in mean HDL cholesterol to 35 mg/dL from a baseline mean level of 37 mg/dL.

Phase 2b FLINT Trial for NASH

OCA achieved the primary endpoint in the Phase 2b trial for the treatment of NASH, known as the FLINT trial, which was sponsored by the NIDDK, a part of the National Institutes of Health. A significantly greater number of OCA-treated patients also achieved an improvement of at least one fibrosis stage (35% vs 19%, $p = 0.004$), with OCA showing greater response rates as compared to placebo across all stages of fibrosis. After FLINT was completed in

late July 2014, we disclosed top-line results from FLINT in our Quarterly Report on Form 10-Q for the quarter ended June 30, 2014 and the results were subsequently published online in the *Lancet* in November 2014. The summary of the FLINT trial results described below

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are based on information and data provided to us by the NIDDK. This trial was a double-blind, placebo-controlled trial of a once-daily dose of 25 mg of OCA or placebo given for 72 weeks in 283 patients with biopsy-proven NASH.

Primary Endpoint

The percentage of patients meeting the FLINT primary histological endpoint, defined as a decrease in the NAFLD Activity Score, or NAS, of at least two points with no increase in the fibrosis score following 72 weeks of treatment, was 45% in the OCA treatment group and 21% in the placebo group ($p = 0.0002$, $n = 219$). The mean pre-treatment baseline NAS for patients in the OCA treatment group was 5.3 of a total possible score of eight (comprised of hepatocellular ballooning 0 2, lobular inflammation 0 3 and steatosis 0 3). Subgroup analyses showed significant response rates in the OCA treatment group in patients with risk factors for disease progression, including baseline fibrosis stage, co-morbid type 2 diabetes mellitus, ALT, insulin resistance and severe obesity (each factor $p < 0.05$ for OCA compared to placebo based on 95% confidence interval of published odds ratios). The graph below shows the results of the primary endpoint in the FLINT trial and the improvements in NAS for various subgroups published in the *Lancet*.

Primary Endpoint: Improvement in NAS by ≥ Two Points with no Worsening of Fibrosis

* *$p < 0.05$, *** $p < 0.001$. P-values calculated with the Cochran-Mantel-Haenszel test, stratified by clinic and diabetes status.*

Secondary Efficacy Endpoint: Fibrosis Improvement

A significantly greater number of OCA-treated patients also achieved an improvement of at least one fibrosis stage (35% versus 19%, $p = 0.004$). Based on our retrospective analyses of the FLINT data, more OCA-treated patients exhibited fibrosis improvement of at least two fibrosis stages (15% versus 6%, not significant) and exhibited fibrosis improvements regardless of baseline fibrosis stage and a significantly greater number of OCA-treated patients also achieved complete resolution of fibrosis (17% versus 5%, $p = 0.0018$). Also, our retrospective analysis of the FLINT data showed that fewer OCA-treated patients progressed to bridging fibrosis (15% versus 18%, not significant) or to cirrhosis (2% versus 5%, not significant). The NASH clinical research network fibrosis staging system was used to categorize the pattern of fibrosis and architectural remodeling of the liver: no fibrosis (F0), perisinusoidal or periportal fibrosis (F1), perisinusoidal and periportal fibrosis (F2), bridging fibrosis (F3) and cirrhosis (F4). Fibrosis sub-stages 1a, 1b and 1c were considered F1 for the analysis.

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Secondary Efficacy Endpoint: NASH Resolution

The secondary endpoint of NASH resolution, based on a global histological assessment, also showed improvement, although not statistically significant (22% versus 13%, p = 0.0832, not significant). A central reading of all baseline and end-of-trial biopsies was performed at the end of the trial, based on which only 80% of patients were confirmed to have definite NASH, while the remaining 20% were diagnosed as borderline NASH (10%) or not-NASH (10%). A retrospective subgroup analysis on the completer population comprised only of definite NASH patients at baseline showed that a significantly greater number of OCA-treated patients achieved NASH resolution compared with placebo-treated patients (19% versus 8%; p = 0.0278).

The graph below shows these results from the FLINT trial for fibrosis improvement, fibrosis resolution, fibrosis progression and NASH resolution.

FLINT Trial: Improvement in Histological Endpoints

*$_{*}$p < 0.05, **p < 0.01. P-values calculated with the Cochran-Mantel-Haenszel test, stratified by clinic and diabetes status. NS indicates that the results are not significant.*

$_{\#}$Retrospective analyses after the unblinding of results can potentially introduce bias and regulatory authorities typically give greatest weight to results from pre-specified analyses as compared to retrospective analyses.

Additional Secondary Endpoints

More OCA-treated patients experienced significant improvements in the major histological features of NASH, including steatosis (61% versus 38%, p = 0.001), lobular inflammation (53% versus 35%, p = 0.006) and hepatocellular ballooning (46% versus 31%, p = 0.03), as compared to the placebo treatment group. Trends were similar between the two treatment groups for portal inflammation, which is not a component of the NAS and is typically mild in adult NASH patients.

The histological improvements observed in OCA-treated patients versus placebo were accompanied by significant reductions in relevant biochemical parameters, including the serum liver enzymes alanine aminotransferase (ALT, p < 0.0001), aspartate aminotransferase (AST, p = 0.0001), gamma-glutamyl transferase

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(GGT, $p < 0.0001$), each of which were above generally accepted normal limits at baseline, and total bilirubin ($p = 0.002$). A modest but statistically significant increase in alkaline phosphatase (ALP, $p < 0.0001$) in the OCA treatment group was also observed, but levels remained within typical normal limits.

OCA treatment was associated with serum lipid changes, including average increases in total cholesterol and LDL-C and an average decrease in HDL-C, that developed within 12 weeks of treatment initiation, then began reversing through the end of treatment and returned to baseline during the 24-week post-treatment follow-up phase. Based on these observations, lipid management was emphasized partway into the trial, using generally accepted guidelines. At 72 weeks as compared to baseline, the following effects were observed in the OCA treatment group: an increase in mean total cholesterol (0.16 mmol/L or 6 mg/dL increase OCA versus 0.19 mmol/L or 7mg/dL decrease placebo, $p < 0.0009$), an increase in mean LDL-C (0.22 mmol/L or 9 mg/dL increase OCA versus 0.22 mmol/L or 8 mg/dL decrease placebo, $p < 0.0001$), a decrease in mean HDL-C (0.02 mmol/L or 1 mg/dL decrease OCA versus 0.03 mmol/L or 1 mg/dL increase placebo, $p = 0.01$) and a decrease in triglycerides (0.22 mmol/L or 20 mg/dL decrease OCA versus 0.08 mmol/L or 7 mg/dL decrease placebo, $p = 0.88$, not significant). We intend to initiate a clinical trial in 2015 characterizing the lipid metabolic effects of OCA and cholesterol management effects of concomitant statin administration in NASH patients.

In the FLINT trial, statistically significant weight loss of an average of 2.3 kilograms was observed in OCA patients compared to no weight loss in the placebo group ($p = 0.008$), and this weight loss reverted towards baseline during the 24-week follow-up phase. A pre-specified sensitivity analysis conducted by the investigators showed that weight loss was not a driver of the primary endpoint. An increase in a marker of hepatic insulin resistance known as HOMA-IR (calculated using the product of fasting plasma insulin and glucose) was observed at 72 weeks in the OCA treatment group ($p = 0.01$). However, there was an imbalance in baseline plasma insulin levels (201 pmol/L OCA versus 138 pmol/L placebo), and an even larger relative and absolute increase in HOMA-IR was observed in the placebo group at the conclusion of the 24-week follow-up phase. This is potentially attributable to the inherent variability in HOMA-IR measurements, particularly in patients with type 2 diabetes, that have been shown to make single time-point to time-point changes of this magnitude clinically uninterpretable. There were virtually no changes in mean hemoglobin A1c, a measure of average blood sugar control over a period of approximately three months, in either OCA or placebo groups at 72 weeks. In a previous study of OCA in diabetic NAFLD patients, described in more detail above, employing the hyperinsulinemic-euglycemic insulin clamp, the gold standard for detecting changes in insulin resistance, OCA improved the glucose disposal rate consistent with reduced insulin resistance.

Safety and Tolerability

OCA was generally well tolerated in the FLINT trial. Adverse events were generally mild to moderate in severity and the incidence in the OCA and placebo treatment groups was similar for all symptoms except pruritus. Pruritus in the OCA treatment group occurred more frequently (23% versus 6%, $p < 0.0001$), at a higher grade (predominantly moderate pruritus) but resulted in only one patient discontinuation. The incidence of severe or life threatening events was not different between the two treatment groups and most of the events in both groups were deemed to be unrelated to treatment, including all severe or life threatening cardiovascular events. As previously disclosed, two deaths occurred in the OCA treatment group, but neither was considered related to OCA treatment.

Phase 2 Sumitomo Dainippon Trial for NASH

In January 2014, our collaborator Sumitomo Dainippon completed enrollment of 200 patients in a double-blind, placebo-controlled, parallel group Phase 2 NASH trial in Japan. This trial is evaluating the efficacy and safety of a once-daily 10 mg, 20 mg or 40 mg dose of OCA as compared to placebo over a period of 72 weeks. The primary

efficacy endpoint in the Sumitomo Dainippon NASH trial is the same as that used in the FLINT trial, and is based on histological improvement as measured by a two-point improvement in the NAS with no worsening in fibrosis. In addition, histological scoring based on the Matteoni scoring system, which has been shown to be correlated to clinical outcomes, is planned as a secondary endpoint. This trial is anticipated to be completed by the end of 2015.

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NASH Regulatory Pathway

In January 2015, OCA received breakthrough therapy designation from the FDA for the treatment of NASH patients with liver fibrosis. The breakthrough therapy designation was created by the FDA to speed the availability of new therapies for serious or life-threatening conditions. Drugs qualifying for this designation must show credible evidence of a substantial improvement on a clinically significant endpoint over available therapies, or over placebo if there is no available therapy. The breakthrough therapy designation constitutes one of four expedited programs for serious conditions including accelerated approval, priority review, and fast-track designation, all of which can also be granted to the same drug if relevant criteria are met. The breakthrough therapy designation confers several benefits, including intensive FDA guidance and discussion and eligibility for submission of a rolling NDA.

We are currently in discussions with regulators on a Phase 3 program for NASH. Subject to a detailed review of the FLINT trial results and completion of discussions with the FDA and EMA, we currently believe that we will conduct at least one Phase 3 clinical outcomes trial of OCA in NASH patients that would incorporate an interim surrogate endpoint and that may serve as the basis for filing for accelerated approval in the United States and approval in Europe. Patients would then be followed for confirmation of clinical benefit under accelerated approval requirements. Examples of potential surrogate endpoints include the use of histological improvement, using the NAS or another scoring system, or histological resolution of NASH, or improvements in fibrosis in pre-cirrhotic patients with NASH, and examples of potential endpoints to confirm clinical benefit include liver transplant-free survival or progression to cirrhosis. We expect to finalize the design of our Phase 3 clinical program in NASH in the second quarter of 2015, subject to the completion of our regulatory discussions with the FDA and the EMA, and then initiate the clinical program.

Primary Sclerosing Cholangitis (PSC)

PSC is a rare, serious life-threatening, chronic cholestatic liver disease characterized by progressive destruction of bile ducts with eventual onset of cirrhosis and its complications. PSC has about one-third the prevalence of PBC and more than 60% of cases occur in men.

PSC is usually diagnosed by preliminary assessment of liver biochemistry, with or without reported symptoms, and confirmed by cholangiography, typically magnetic resonance cholangiopancreatography or endoscopic retrograde cholangiopancreatography, or ERCP. ALP is elevated in most PSC patients, consistent with cholestasis, and ALT and GGT are also typically elevated, but not in all cases. Bilirubin is often normal in early-stage PSC but increases with progression of the disease. The mean age at diagnosis is 40 years. Approximately 75% of PSC patients have overlapping inflammatory bowel disease, principally ulcerative colitis.

Median survival for PSC patients has been previously estimated as 8 to 12 years from diagnosis in symptomatic patients, depending upon stage of the disease at the time of diagnosis. Complications involving the biliary tree are common and include cholangitis as well as ductal strictures and gallstones, both of which may require frequent endoscopic or surgical interventions. PSC is often complicated by the development of malignancies, with cholangiocarcinoma being the most common.

Despite evaluation of multiple treatments, liver transplant is currently the only treatment shown to improve clinical outcomes. Ursodiol is often used for the treatment of PSC due to improvements in liver biochemistry following initiation of therapy. Despite general biochemical improvement, ursodiol has not been shown to improve transplant-free survival and, at high doses, has been associated with increased risk for serious complications. However, as there are no approved drugs for the treatment of PSC, some physicians treat patients with ursodiol,

typically at a dose of 13 to 15 mg/kg/day. PSC is the fourth leading indication for liver transplant. However, the post-transplant recurrence rate of PSC has been shown to be as high as 20%.

Phase 2 Trial: OCA as Therapy in PSC

In December 2014, we initiated an international Phase 2 clinical trial to evaluate the effects of 24 weeks of treatment with varying doses of OCA compared to placebo in patients with PSC. The primary endpoint is the reduction of serum ALP levels, as compared to placebo. In addition, OCA s effect on other secondary liver function endpoints, as well as symptoms of ulcerative colitis (a disease occurring in a majority of patients with PSC), will be assessed. This trial is anticipated to enroll approximately 75 patients in the United States

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and Europe. Following the completion of the 24-week double-blind portion of the trial, patients will be given the option to enroll in an open-label long-term safety and efficacy extension trial.

Biliary Atresia

Biliary atresia is a life-threatening condition in infants in which the bile ducts inside or outside the liver do not have normal openings. With biliary atresia, bile becomes trapped, builds up, and damages the liver. The damage leads to scarring, loss of liver tissue, and cirrhosis. The two types of biliary atresia are fetal and perinatal. Fetal biliary atresia appears while the baby is in the womb. Perinatal biliary atresia is much more common and does not become evident until two to four weeks after birth. Some infants, particularly those with the fetal form, also have birth defects in the heart, spleen, or intestines. Biliary atresia is rare and only affects about one out of every 18,000 infants. The disease is more common in females, premature babies, and children of Asian or African American heritage. Biliary atresia is not an inherited disease and is most likely caused by an event in the womb or around the time of birth. No single test can definitively diagnose biliary atresia, resulting in the need for a series of tests. All infants who still have jaundice two to three weeks after birth, or who have gray or white stools after two weeks of birth, should be checked for liver damage.

Once diagnosed, biliary atresia is treated with a liver transplant or, more frequently, a surgery called the Kasai procedure, in which the bile ducts are connected directly to the small intestine. After the Kasai procedure, some infants continue to have liver problems and, even with the return of bile flow, some infants develop cirrhosis. Possible complications after the Kasai procedure include ascites, bacterial cholangitis, portal hypertension, and pruritus. Even after a successful Kasai surgery, most infants with biliary atresia slowly develop cirrhosis over the years and require a liver transplant by adulthood.

We plan to initiate a Phase 2 clinical trial in pediatric patients with biliary atresia in the second half of 2015.

Other OCA Clinical Trials

The Translational Research and Evolving Alcoholic Hepatitis Treatment, or TREAT, Consortium consisting of the Mayo Clinic Rochester, Indiana University, and Virginia Commonwealth University, in collaboration with the National Institute on Alcohol Abuse and Alcoholism, or NIAAA, have initiated a Phase 2 clinical trial of OCA for the treatment of alcoholic hepatitis. Indiana University is acting as the sponsor of the trial. The trial is a randomized, double-blind, multicenter study designed to assess the safety and efficacy of a once-daily dose of 10 mg of OCA compared to placebo over a period of six weeks in patients with moderately severe alcoholic hepatitis. The clinical trial is expected to enroll 60 patients.

The Sahlgrenska University Hospital in Sweden is sponsoring and has initiated a placebo-controlled, Phase 2a pharmacodynamic trial of OCA in patients undergoing bariatric surgery or gallstone surgery, called the OCABSGS trial. The primary purpose of the trial is to evaluate the effects of OCA on bile acid, lipid and glucose turnover in 20 morbidly obese patients and 20 gallstone patients who will be administered a 25 mg dose of OCA or placebo once daily for three weeks prior to undergoing bariatric and gallstone surgery, respectively. Biopsies of the liver and abdominal fat at surgery will determine if OCA has an effect in these patients.

Potential Future Product Candidates

In addition to OCA, we are developing other novel bile acid analog compounds targeting FXR and a second dedicated bile acid receptor called TGR5, which is a target of interest for the treatment of type 2 diabetes and other

gastrointestinal indications. We intend to continue advancing these and other product candidates as we build our pipeline.

INT-767

INT-767 is an orally administered dual FXR and TGR5 agonist that, like OCA, is derived from the primary human bile acid CDCA. This product candidate has been shown to be approximately three times more potent than OCA as an FXR agonist. In animal models of chronic liver, intestinal and kidney diseases, INT-767 has consistently demonstrated greater anti-fibrotic and anti-inflammatory effects than OCA. We own exclusive worldwide, royalty-free rights to INT-767.

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We currently plan to advance INT-767 through the preclinical studies required to support the advancement of this product candidate to an IND.

Subject to the IND becoming effective, we intend to initiate an open-label Phase 1 trial of INT-767 in healthy volunteers around the end of 2015. The trial will evaluate the safety, tolerability and pharmacokinetics of single and multiple ascending doses of INT-767.

INT-777

INT-777 is an orally administered TGR5 agonist that is derived from the primary human bile acid cholic acid. We have completed the preclinical studies necessary for the filing of an IND. We own exclusive worldwide, royalty-free rights to INT-777.

Our in vitro studies of INT-777 showed that the product candidate has the potential to selectively target TGR5, a receptor that has been shown to directly regulate the release of glucagon like peptide-1, or GLP-1, in the intestine with resulting insulin sensitizing effects. There are several important and effective marketed drugs that enhance the effects of GLP-1 through different mechanisms, but none are able to induce the endogenous production of this hormone, and we believe there is interest in the potential for a TGR5 agonist to provide additive benefits. TGR5 has also been shown in animal models to regulate other metabolic pathways in brown fat and skeletal muscle that drive energy expenditure. The receptor may also play a role in the control of inflammation, which is increased in insulin resistant diabetic conditions.

In animal models of diabetes, treatment with INT-777 induced GLP-1 secretion, with resulting insulin sensitivity and normalization of glycemic control, increased basal energy expenditure and prevention of weight gain, and a reduction in blood lipid levels together with liver steatosis and fibrosis. We believe that these preclinical results could support further development of INT-777 and our other TGR5 agonists in the treatment of type 2 diabetes, associated metabolic disorders and other gastrointestinal indications. We intend to continue development of INT-777 through potential collaborations with third parties, over the next several years.

Strategic Collaborations and Research Arrangements

Sumitomo Dainippon Pharma

On March 29, 2011, we entered into a license agreement with Sumitomo Dainippon Pharma Co. Ltd., under which we granted Sumitomo Dainippon an exclusive license to research, develop and commercialize OCA as a therapeutic for the treatment of PBC and NASH in Japan and China (excluding Taiwan). Under the terms of the agreement, Sumitomo Dainippon is required to use commercially reasonable efforts to develop and commercialize OCA in its licensed territories for the treatment of PBC and NASH, and we are obligated under the agreement to use commercially reasonable efforts to develop OCA outside of Sumitomo Dainippon s licensed territories. We are also responsible for supplying Sumitomo Dainippon with clinical and commercial supply of OCA requested by Sumitomo Dainippon pursuant to clinical and commercial supply agreements that include terms specified in the agreement. Sumitomo Dainippon has agreed during the term of the agreement to not commercialize any compound that is a FXR agonist for use in the treatment of PBC or NASH other than pursuant to the agreement.

We granted Sumitomo Dainippon an option under the agreement to obtain an exclusive license to commercialize OCA for indications other than PBC and NASH on the same terms as are set forth in the agreement. Sumitomo Dainippon may exercise this option with respect to any indication at any time during the two-year period commencing on the date

we notify Sumitomo Dainippon of the commencement of a Phase 3 clinical trial involving OCA for such indication, subject to Sumitomo Dainippon s payment of an option fee for each additional indication. No option fee is required to be paid by Sumitomo Dainippon if it exercises its option for any additional indication only in China.

In addition to Japan and China, which are the original licensed territories, we also granted Sumitomo Dainippon an option under the agreement to add Korea, Taiwan, Malaysia, Vietnam, the Philippines, Thailand, Singapore and/or Indonesia to its exclusive license on the same terms as are set forth in the agreement. Sumitomo Dainippon may exercise this option with respect to any such country at any time up until the date on which regulatory approval to commercialize OCA is granted in Japan, subject to Sumitomo Dainippon s payment of an option fee for each country. If we accept or make a bona fide offer of exclusive rights to a

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third party to develop and commercialize OCA in any of these countries, we must first notify Sumitomo Dainippon and Sumitomo Dainippon has the right to exercise its option with respect to any such country. In addition, prior to accepting or making a bona fide offer of any exclusive development and commercialization rights involving OCA in the United States and Canada to a third party, we must first engage in good faith negotiations with Sumitomo Dainippon with respect to the grant to Sumitomo Dainippon of exclusive rights to develop and commercialize OCA in such countries. In May 2014, Sumitomo Dainippon exercised its option to add Korea to its licensed territories.

Sumitomo Dainippon made up-front payments to us in the amount of $16.0 million, including $1.0 million upon the exercise of its option to add Korea to its licensed territories. In addition, Sumitomo Dainippon may be required to pay us up to an aggregate of approximately $30.0 million for the achievement of development milestones, $70.0 million for the achievement of regulatory approval milestones and $200.0 million for the achievement of sales milestones based on aggregate sales amounts. As of March 2, 2015, we have achieved $1.0 million of the development milestones. Sumitomo Dainippon is also obligated to pay us tiered royalties ranging from the tens to the twenties in percent based on net sales of OCA products in Japan and the other Asian countries covered by this agreement. The term of the agreement, and Sumitomo Dainippon s obligation to pay royalties to us for each OCA product, expires on a country-by-country basis on the later of the expiration of the exclusivity period in such country, whether through the expiration of applicable patents or the introduction of generic drugs that compete with the OCA product, or ten years after the first commercial sale of such OCA product for the first or second indication in that country. Royalty rates are subject to reduction under the agreement in specified circumstances, including, with respect to any country in the exclusive territory, if sales of generic products reach a certain threshold market share in that country over a specified period.

Sumitomo Dainippon may terminate the agreement in its entirety or on a country-by-country or indication-by-indication basis upon 90 days written notice. Either we or Sumitomo Dainippon may terminate the agreement in the event of the uncured material breach by or bankruptcy of the other party, subject to certain dispute resolution procedures. If Sumitomo Dainippon were to terminate the agreement for our material breach, it would have a perpetual license following the effective date of termination, subject to the payment by Sumitomo Dainippon of a royalty based on net sales of OCA products, the amount of which will depend on whether the effective date of termination occurs prior to or after the date of first commercial sale of an OCA product. If we were to terminate the agreement for Sumitomo Dainippon s material breach or if Sumitomo Dainippon were to voluntarily terminate the agreement, Sumitomo Dainippon s license under the agreement would terminate.

Commercialization

Given our stage of development, we are in the early stages of establishing a commercial organization and distribution capabilities. In the United States and Europe, due to the nature of chronic liver diseases and the limited options for treatment, patients suffering from diseases such as PBC and their physicians generally are well informed and often have a high degree of organization, which may make it easier to identify target populations if and when OCA is approved for PBC and subsequently for other indications. We believe that the market for the treatment of PBC, NASH and other indications is a specialty care market driven by key opinion leaders in the hepatology and gastroenterology fields. Most patients are treated by physicians who specialize in the treatment of liver disease, including hepatologists and certain gastroenterologists and endocrinologists.

Our current plan is to commercialize OCA ourselves in the United States and Europe if it is approved. We anticipate that our commercialization efforts will include our internal commercial organization, sales people and other specialists, and other contracted outside resources. Outside of the United States and Europe, subject to obtaining necessary marketing approvals, we likely will seek to commercialize OCA through distribution or other collaboration

arrangements.

If OCA is approved for the treatment of patients with PBC, we believe that it will be possible to commercialize OCA for this indication with a relatively small specialty sales organization in the United States and Europe that would target a limited and focused group of specialist physicians. As a result of our ongoing clinical work, we have been engaged in dialogue with specialists who treat patients with PBC. We believe

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that these activities have provided us with a growing knowledge of the physicians we plan to target for commercial launch of OCA for PBC, subject to marketing approval in the United States and Europe. We intend to leverage the infrastructure and capabilities of our PBC-focused specialty sales organization during our pre-commercial preparation for the commercialization of OCA in NASH and other potential indications, if approved for these indications. Though we are continuing our market research and other pre-commercial planning for OCA in NASH, we currently anticipate that we would require a larger specialty sales organization that would target a broader group of hepatologists, gastroenterologists and other specialists focused on NASH if we receive marketing approval for this indication.

We exclusively licensed rights to OCA to Sumitomo Dainippon in Japan, China and Korea, along with an option to expand this exclusive license into certain other Asian countries. We will rely on Sumitomo Dainippon to commercialize OCA in its territory.

Competition

The biopharmaceutical industry is characterized by intense competition and rapid innovation. Although we believe that we hold a leading position in bile acid chemistry, our competitors may be able to develop other compounds or drugs that are able to achieve similar or better results. Our potential competitors include major multinational pharmaceutical companies, established biotechnology companies, specialty pharmaceutical companies and universities and other research institutions. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large, established companies. We believe the key competitive factors that will affect the development and commercial success of our product candidates are efficacy, safety and tolerability profile, reliability, convenience of dosing, price, the level of generic competition and reimbursement.

Our most advanced product candidate, OCA, is currently being developed as a second line treatment for PBC. Currently, ursodiol is the only therapy that is approved for the treatment of PBC and is generically available at a significantly lower cost than branded products. Off-label use of fibrate drugs has been reported in PBC, though many fibrates are specifically contraindicated for use in primary biliary cirrhosis due to potential concerns over acute and long-term safety in this patient population. An investigator-sponsored Phase 3 clinical trial of bezafibrate, a fibrate that has not been approved for commercialization by the FDA and is only available outside of the United States, is currently ongoing. Dr. Falk Pharma GmbH, which markets ursodiol, is conducting a Phase 3 clinical trial of combination ursodiol and budesonide, a steroid, as a treatment for PBC. Bristol-Myers Squibb Company is conducting an open-label clinical trial in 20 patients of a combination of ursodiol and abatacept, an anti-CTLA4 fusion protein currently marketed for the treatment of rheumatoid arthritis, as a treatment for PBC. Shire plc is conducting a Phase 2 clinical trial in 60 patients of a combination of ursodiol and SHP625, formerly known as LUM001, an apical sodium-dependent bile acid transporter inhibitor, as a treatment for PBC. NGM Biopharmaceuticals is conducting a Phase 2 clinical trial in 45 patients of a combination of ursodiol and NGM282, an engineered analog of fibroblast growth factor 19. FF Pharmaceuticals BV is conducting a Phase 1/2 clinical trial in 24 subjects of a combination of ursodiol and FFP104, a CD40-antagonist monoclonal antibody. We are aware of several companies that have announced their intentions to develop products for the treatment of PBC including Albireo AB and Virobay, Inc.

There are currently no therapeutic products approved for the treatment of NASH, NAFLD, portal hypertension, complications of cirrhosis or alcoholic hepatitis. 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 ursodiol, but none has been clearly shown in clinical trials to show a significant reversal in liver fibrosis. Gilead Sciences, Inc. is conducting two Phase 2 clinical trials in approximately 225 patients with NASH of simtuzumab, an anti-body against the lysyl oxidase-like 2 enzyme. Genfit

SA is conducting a Phase 2 clinical trial in 275 patients with NASH of GFT505, a dual PPAR alpha/delta agonist. We are aware of several other companies that have product candidates in Phase 2 clinical or earlier stage preclinical development for the treatment of NASH, including Raptor Pharmaceutical Corp., Galmed Medical Research Ltd., Novo Nordisk A/S, Immuron Ltd., Takeda Pharmaceutical Co Ltd, Conatus Pharmaceuticals Inc., Galectin Therapeutics Inc., Genkyotex SA, Kadmon Corporation LLC, Kalypsys, Tobira Therapeutics, Inc., La Jolla Pharmaceutical Company, Madrigal Pharmaceuticals, Inc., Mochida Pharmaceutical Co., Ltd., NasVax Ltd, Shire plc, Viking Therapeutics, Inc. and Virobay, Inc.

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Although there are currently no other drugs approved for the treatment of PBC, we are aware of other companies, including Eli Lilly and Co., Exelixis, Inc. and Gilead Sciences, Inc., that have FXR agonists in Phase 2 or earlier stages of clinical or preclinical development that could be used to treat PBC, NASH and the other liver diseases we are targeting.

While there is no approved treatment for PSC, ursodiol is often prescribed off-label for PSC patients. We are aware of several companies that have product candidates in Phase 2 clinical or earlier stage preclinical development for the treatment of PSC, including Biotie Therapies Corp., Dr. Falk Pharma GmbH, Gilead Sciences, Inc. and Shire plc.

We believe that OCA offers key potential advantages over ursodiol and other products in development that could enable OCA, if approved for these indications, to capture meaningful market share. However, many of our potential competitors have substantially greater financial, technical and human resources than we do, as well as greater experience in the discovery and development of product candidates, obtaining FDA and other regulatory approvals of products and the commercialization of those products. Accordingly, our competitors may be more successful than us in obtaining approval from the FDA or from other regulators for drugs and achieving widespread market acceptance. Our competitors drugs may be more effective, or more effectively marketed and sold, than any product candidate we may commercialize and may render our product candidates obsolete or non-competitive before we can recover the expenses of their development and commercialization. We anticipate that we will face intense and increasing competition as new drugs enter the market and other advanced technologies become available. Finally, the development of new treatment methods for the diseases we are targeting could render our product candidates non-competitive or obsolete. In addition, our ability to compete may be affected because in many cases insurers or other third-party payors seek to encourage the use of generic products.

Intellectual Property

The proprietary nature of, and protection for, our product candidates and our discovery programs, processes and know-how are important to our business. We have sought patent protection in the United States and internationally for OCA, INT-767 and INT-777, and our discovery programs, and other inventions to which we have rights, where available and when appropriate. Our policy is to pursue, maintain and defend patent rights, whether developed internally or licensed from third parties, and to protect the technology, inventions and improvements that are commercially important to the development of our business. We also rely on trade secrets that may be important to the development of our business.

Our commercial success will depend in part on obtaining and maintaining patent protection and trade secret protection of our current and future product candidates and the methods used to develop and manufacture them, as well as successfully defending these patents against third-party challenges. Our ability to stop third parties from making, using, selling, offering to sell or importing our products depends on the extent to which we have rights under valid and enforceable patents or trade secrets that cover these activities. We cannot be sure that patents will be granted with respect to any of our pending patent applications or with respect to any patent applications filed by us in the future, nor can we be sure that any of our existing patents or any patents that may be granted to us in the future will be commercially useful in protecting our product candidates, discovery programs and processes. For this and more comprehensive risks related to our intellectual property, please see Item 1A. Risk Factors Risks Relating to Our Intellectual Property.

OCA (first-in-class FXR agonist)

The patent portfolio for OCA contains patents and patent applications directed to compositions of matter, manufacturing methods, and methods of use. As of December 31, 2014, we owned six U.S. patents, four pending U.S. patent applications, and corresponding foreign patents and patent applications. Foreign patents have been granted in Europe (Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Liechtenstein, Lithuania, Luxembourg, Monaco, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey and the United Kingdom), Australia, Canada, China, Israel, Japan, and Macao. We expect the composition of matter patents, if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2022 (worldwide). It is possible that the term of the composition of matter patent in the United States may be extended up to five additional years under the provisions of the Drug Price Competition

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and Patent Term Restoration Act of 1984, or the Hatch-Waxman Act. Patent term extension may be available in certain foreign countries upon regulatory approval. We expect the other patents and patent applications, if issued, in the portfolio, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire from 2022 to 2033.

INT-767 (dual FXR/TGR5 agonist)

The patent portfolio for INT-767 contains patents and patent applications directed to compositions of matter and methods of use. As of December 31, 2014, we owned two U.S. patents, two pending U.S. patent applications, and corresponding foreign patents and patent applications. Foreign patents have been granted in Australia, China, Europe (Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Liechtenstein, Lithuania, Luxembourg, Monaco, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, and the United Kingdom), Israel and Japan. We expect the issued composition of matter patent in the U.S., if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2029. It is possible that the term of the composition of matter patent in the United States may be extended up to five additional years under the provisions of the Hatch-Waxman Act. We expect the foreign composition of matter patents, if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2027. Patent term extension may be available in certain foreign countries upon regulatory approval. We expect the other patents and patent applications, if issued, in the portfolio, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire from 2027 to 2033. We have received assignments of rights to the INT-767 patent portfolio from all inventors, with the exception of one inventor. That inventor is contractually obligated to provide an assignment to us. Thus, we believe that we are the owner of the INT-767 patent portfolio by virtue of this contractual obligation and the patent assignments we have received.

INT-777 (TGR5 agonist)

The patent portfolio for INT-777 contains patents and patent applications directed to compositions of matter and methods of use. As of December 31, 2014, we owned three U.S. patents, two pending U.S. patent applications, and corresponding foreign patents and patent applications. Foreign patents have been granted in Australia, China, Eurasia (Armenia, Azerbaijan, Belarus, Kyrgyz Republic, Kazakhstan, Moldova, Russian Federation, Tajikistan and Turkmenistan), Europe (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Monaco, Netherlands, Norway, Poland, Portugal, Spain, Sweden, Switzerland, Turkey and the United Kingdom), Hong Kong, Japan, Mexico and South Africa. We expect the composition of matter patent in the United States, if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2030. It is possible that the term of the composition of matter patent in the United States may be extended up to five additional years under the provisions of the Hatch-Waxman Act. We expect the foreign composition of matter patents, if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire beginning in 2028. Patent term extension may be available in certain foreign countries upon regulatory approval. We expect the other patents and patent applications, if issued, in the portfolio, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire from 2028 to 2029.

Trade Secrets

In addition to patents, we rely on trade secrets and know-how to develop and maintain our competitive position. Trade secrets and know-how can be difficult to protect. We seek to protect our proprietary processes, in part, by confidentiality agreements and invention assignment agreements with our employees, consultants, scientific advisors, contractors and commercial partners. These agreements are designed to protect our proprietary information. We also

seek to preserve the integrity and confidentiality of our data, trade secrets and know-how by maintaining physical security of our premises and physical and electronic security of our information technology systems.

Manufacturing

We do not own or operate manufacturing facilities for the production of any of our product candidates, nor do we have plans to develop our own manufacturing operations in the foreseeable future. We currently rely on third-party contract manufacturers for all of our required raw materials, active pharmaceutical

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ingredient, or API, and finished product for clinical trials and preclinical studies that we are conducting and plan to conduct prior to and after seeking regulatory approval. We are currently seeking to contract to qualify a back-up API manufacturer. We obtain these supplies and services from each of these third parties on a purchase order basis. We do not have long-term agreements with any of these third parties. We also do not have any current contractual relationships for the manufacture of commercial supplies of any of our product candidates if they are approved. As OCA and any of our other product candidates continue to progress towards potential regulatory approval, we intend to enter into agreements with a third-party contract manufacturer and one or more back-up manufacturers for the commercial production of those products. Development and commercial quantities of any products that we develop will need to be manufactured in facilities, and by processes, that comply with the requirements of the FDA and the regulatory agencies of other jurisdictions in which we are seeking approval. We currently employ internal resources to manage our manufacturing contractors.

Government Regulation and Product Approval

Government authorities in the United States, at the federal, state and local level, and analogous authorities in other countries extensively regulate, among other things, the research, development, testing, manufacture, labeling, packaging, promotion, storage, advertising, distribution, marketing and export and import of products such as those we are developing. Our product candidates must be approved by the FDA through the NDA process before they may be legally marketed in the United States and by the EMA through the MAA process before they may be legally marketed in Europe. Our product candidates will be subject to similar requirements in other countries prior to marketing in those countries. The process of obtaining regulatory approvals and the subsequent compliance with applicable federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources.

United States Government Regulation

NDA Approval Processes

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or the FDCA, and implementing regulations. 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 indication;

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;

satisfactory completion of FDA audits of clinical trial sites to assure compliance with GCP and the integrity of the clinical data;

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 outcomes studies required by the FDA.

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Once a pharmaceutical candidate is identified for development, it enters the preclinical or nonclinical testing stage. Nonclinical tests include laboratory evaluations of product chemistry, toxicity and formulation, as well as animal studies. An IND sponsor must submit the results of the nonclinical tests, together with manufacturing information and analytical data, to the FDA as part of the IND. Some nonclinical testing may continue even after the IND is submitted. In addition to including the results of the nonclinical studies, the IND will also include a protocol detailing, among other things, the objectives of the clinical trial, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated if the first phase lends itself to an efficacy determination. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day time period, places the IND on clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can begin. A clinical hold may occur at any time during the life of an IND, and may affect one or more specific studies or all studies conducted under the IND.

All clinical trials must be conducted under the supervision of one or more qualified investigators in accordance with GCPs. They must be conducted under protocols detailing the objectives of the trial, dosing procedures, research subject selection and exclusion criteria and the safety and effectiveness criteria to be evaluated. Each protocol must be submitted to the FDA as part of the IND, and progress reports detailing the status of the clinical trials must be submitted to the FDA annually. Sponsors also must timely report to FDA serious and unexpected adverse reactions, any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigation brochure, or any findings from other studies or animal or in vitro testing that suggest a significant risk in humans exposed to the drug. An institutional review board, or IRB, at each institution participating in the clinical trial must review and approve the protocol before a clinical trial commences at that institution and must also approve the information regarding the trial and the consent form that must be provided to each research subject or the subject s legal representative, monitor the study until completed and otherwise comply with IRB regulations.

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

Phase 1. The drug is initially introduced into healthy human subjects and tested for safety, dosage tolerance, absorption, metabolism, distribution and elimination. In the case of some products for severe or life-threatening diseases, such as cancer, especially when the product may be inherently too toxic to ethically administer to healthy volunteers, the initial human testing is often conducted in patients.

Phase 2. Clinical trials are performed on a limited patient population intended to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage.

Phase 3. Clinical trials are undertaken to further evaluate dosage, clinical efficacy and safety in an expanded patient population at geographically dispersed clinical study sites. These studies are intended to establish the overall risk-benefit ratio of the product and provide an adequate basis for product labeling.

Human clinical trials are inherently uncertain and Phase 1, Phase 2 and Phase 3 testing may not be successfully completed. The FDA or the sponsor may suspend a clinical trial at any time for a variety of reasons, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB s requirements or if the drug has been associated with unexpected serious harm to patients. In some cases, clinical trials are overseen by an independent group of qualified experts organized by the trial sponsor, or the clinical monitoring board or Data Safety Monitoring Board, or DSMB. This group provides authorization for whether or not a trial may move forward at designated check points. These decisions are based on the limited access to data from the ongoing trial.

During the development of a new drug, sponsors are given opportunities to meet with the FDA at certain points. These points may be prior to the submission of an IND, at the end of Phase 2 and before an NDA is submitted. Meetings at

other times may be requested. These meetings can provide an opportunity for the sponsor to share information about the data gathered to date and for the FDA to provide advice on the next

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phase of development. Sponsors typically use the meeting at the end of Phase 2 to discuss their Phase 2 clinical results and present their plans for the pivotal Phase 3 clinical trial that they believe will support the approval of the new drug. If a Phase 2 clinical trial is the subject of discussion at the end of Phase 2 meeting with the FDA, a sponsor may be able to request a Special Protocol Assessment, or SPA, the purpose of which is to reach agreement with the FDA on the Phase 3 clinical trial protocol design and analysis that will form the primary basis of an efficacy claim.

According to published guidance on the SPA process, a sponsor which meets the prerequisites may make a specific request for a SPA and provide information regarding the design and size of the proposed clinical trial. The FDA is supposed to evaluate the protocol within 45 days of the request to assess whether the proposed trial is adequate, and that evaluation may result in discussions and a request for additional information. A SPA request must be made before the proposed trial begins, and all open issues must be resolved before the trial begins. If a written agreement is reached, it will be documented and made part of the record. The agreement will be binding on the FDA and may not be changed by the sponsor or the FDA after the trial begins except with the written agreement of the sponsor and the FDA or if the FDA determines that a substantial scientific issue essential to determining the safety or efficacy of the drug was identified after the testing began.

Concurrent with clinical trials, sponsors usually complete additional animal safety studies and also develop additional information about the chemistry and physical characteristics of the drug and finalize a process for manufacturing commercial quantities of the product in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the drug and the manufacturer must develop methods for testing the quality, purity and potency of the drug. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the drug candidate does not undergo unacceptable deterioration over its proposed shelf-life.

The results of product development, nonclinical studies and clinical trials, along with descriptions of the manufacturing process, analytical tests and other control mechanisms, proposed labeling and other relevant information are submitted to the FDA as part of an NDA requesting approval to market the product. The submission of an NDA is subject to the payment of user fees, but a waiver of such fees may be obtained under specified circumstances. The FDA reviews all NDAs submitted to ensure that they are sufficiently complete for substantive review before it accepts them for filing. It may request additional information rather than accept an NDA for filing. In this event, the NDA must be resubmitted with the additional information. The resubmitted application also is subject to review before the FDA accepts it for filing.

Once the submission is accepted for filing, the FDA begins an in-depth review. NDAs receive either standard or priority review. A drug representing a significant improvement over available therapies in treatment, prevention or diagnosis of disease may receive priority review. The FDA may refuse to approve an NDA if the applicable regulatory criteria are not satisfied or may require additional clinical or other data. Even if such data are submitted, the FDA may ultimately decide that the NDA does not satisfy the criteria for approval. The FDA reviews an NDA to determine, among other things, whether a product is safe and effective for its intended use and whether its manufacturing is cGMP-compliant. The FDA may refer the NDA to an advisory committee for review and recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendation of an advisory committee, but it generally follows such recommendations. Before approving an NDA, the FDA will inspect the facility or facilities where the product is manufactured and tested.

Fast Track, Breakthrough Therapy, Priority Review and Accelerated Approval

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

designation, breakthrough therapy designation and priority review designation.

Specifically, the FDA may designate a product for fast track review if it is intended, whether alone or in combination with one or more other drugs, for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition. For fast track products, sponsors may have greater interactions with the FDA and the FDA may initiate review of sections of a fast track product s NDA before the application is complete.

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A product may also be designated as a breakthrough therapy if it is intended, either alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The FDA may take certain actions with respect to breakthrough therapies, including holding meetings with the sponsor throughout the development process; providing timely advice to the product sponsor regarding development and approval; involving more senior staff in the review process; assigning a cross-disciplinary project lead for the review team; and taking other steps to design the clinical trials in an efficient manner. In January 2015, OCA received breakthrough therapy designation from the FDA for the treatment of NASH patients with liver fibrosis.

The FDA may also designate a product for priority review if it is a drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. The FDA determines, on a case-by-case basis, whether the proposed drug represents a significant improvement when compared with other available therapies. A priority designation is intended to direct overall attention and resources to the evaluation of such applications, and to shorten the FDA s goal for taking action on a marketing application from ten months to six months.

In addition, the FDA may grant accelerated approval to a drug for a serious or life-threatening condition that provides meaningful therapeutic advantage to patients over existing treatments based upon a determination that the drug has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. The FDA may also grant accelerated approval for such a condition when the product has an effect on an intermediate clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality, or IMM, and that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. Drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval. In the case of unprecedented accelerated approval endpoints, this determination occurs during the review of the NDA. Unless otherwise informed by the FDA, an applicant must submit to the FDA for consideration during the preapproval review period copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days following marketing approval. After 120 days following marketing approval, unless otherwise informed by the FDA, the applicant must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

We currently plan to seek accelerated approval of OCA for the treatment of PBC based on the results of our POISE trial and have initiated our rolling NDA submission, which we intend to complete within the first half of 2015. As part of our strategy for filing the NDA under the accelerated approval pathway, we initiated a clinical outcomes confirmatory trial for OCA in PBC in December 2014, following discussions with the FDA. We do not expect completion of this trial to be a condition to the receipt of marketing approval and, as a result, plan to complete the trial following our receipt of marketing approval. Approval of a drug may be withdrawn if trials fail to verify clinical benefit or do not demonstrate sufficient clinical benefit to justify the risks associated with the drug (e.g., show a significantly smaller magnitude or duration of benefit than was anticipated based on the observed effect on the surrogate).

Post-approval Requirements

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product

may result in restrictions on the product or even complete withdrawal of the product from the market. After approval, some types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further FDA review and approval. In addition, the FDA may require testing and surveillance programs to

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monitor the effect of approved products that have been commercialized, and the FDA has the power to prevent or limit further marketing of a product based on the results of these post-marketing programs.

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

Failure to comply with the applicable U.S. requirements at any time during the product development process or approval process, or after approval, may subject us to administrative or judicial sanctions, any of which could have a material adverse effect on us.

These sanctions could include:

refusal to approve pending applications;
withdrawal of an approval;
imposition of a clinical hold;
warning letters;
product seizures;
total or partial suspension of production or distribution; or
injunctions, fines, disgorgement, or civil or criminal penalties.

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

We rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of our products. Future FDA and state inspections may identify compliance issues at the facilities of our contract manufacturers that may disrupt production or distribution, or require substantial resources to correct.

From time to time, legislation is drafted, introduced and passed in Congress that could significantly change the statutory provisions governing the approval, manufacturing and marketing of products regulated by the FDA. In addition, FDA regulations and guidance are often revised or reinterpreted by the agency in ways that may significantly affect our business and our products. It is impossible to predict whether legislative changes will be enacted, or FDA regulations, guidance or interpretations changed or what the impact of such changes, if any, may be.

Patent Term Restoration and Data Exclusivity

Depending upon the timing, duration and specifics of FDA approval of the use of our drug candidates, some of our U.S. patents may be eligible for limited patent term extension 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, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product s approval date. The patent term restoration period is generally one-half the time between the

effective date of an IND, and the submission date of an NDA, plus the time between the submission date of an NDA and the approval of that application. Only one patent applicable to an approved drug is eligible for the extension and the application for extension must be made prior to expiration of the patent. The United States Patent and Trademark Office, in consultation with

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the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we intend to apply for restorations of patent term for some of our currently owned or licensed patents to add patent life beyond their current expiration date, depending on the expected length of clinical trials and other factors involved in the submission of the relevant NDA.

Data exclusivity provisions under the FDCA also can delay the submission or the approval of certain applications. The FDCA provides a five-year period of non-patent data exclusivity within the United States to the first applicant to gain approval of an NDA for a new chemical entity. A drug is a new chemical entity if the FDA has not previously approved any other new drug containing the same active moiety, which is the molecule or ion responsible for the action of the drug substance. During the exclusivity period, the FDA may not accept for review an abbreviated new drug application, or ANDA. However, an application may be submitted after four years if it contains a certification of patent invalidity or non-infringement. The FDCA also provides three years of marketing exclusivity for an NDA, 505(b)(2) NDA or supplement to an approved NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are deemed by the FDA to be essential to the approval of the application, for example, for new indications, dosages or strengths of an existing drug. This three-year exclusivity covers only the conditions associated with the new clinical investigations and does not prohibit the FDA from approving ANDAs for drugs containing the original active agent for other conditions of use. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA; however, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the preclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness.

Orphan Drug Designation

Under the Orphan Drug Act, the FDA may grant orphan drug designation to drugs intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for this type of disease or condition will be recovered from sales in the United States for that drug. Orphan drug designation must be requested before submitting an NDA. After the FDA grants orphan drug designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. Orphan drug designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

If a product that has orphan drug designation subsequently receives the first FDA approval for the disease for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications to market the same drug for the same indication, except in very limited circumstances, for seven years. Orphan drug exclusivity, however, could also block the approval of one of our products for seven years if a competitor obtains approval of the same drug as defined by the FDA or if our drug candidate is determined to be contained within the competitor s product for the same indication or disease. 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.

Pediatric Exclusivity and Pediatric Use

Under the Best Pharmaceuticals for Children Act, or BPCA, certain drugs may obtain an additional six months of exclusivity, if the sponsor submits information requested in writing by the FDA, or a Written Request, relating to the use of the active moiety of the drug in children. The FDA may not issue a Written Request for studies on unapproved

or approved indications or where it determines that information relating to the use of a drug in a pediatric population, or part of the pediatric population, may not produce health benefits in that population.

We have not received a Written Request for such pediatric studies, although we may ask the FDA to issue a Written Request for such studies in the future. To receive the six-month pediatric market exclusivity, we would have to receive a Written Request from the FDA, conduct the requested studies in accordance with a written agreement with the FDA or, if there is no written agreement, in accordance with commonly accepted scientific principles, and submit reports of the studies. A Written Request may include studies for indications

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that are not currently in the labeling if the FDA determines that such information will benefit the public health. The FDA will accept the reports upon its determination that the studies were conducted in accordance with and are responsive to the original Written Request or commonly accepted scientific principles, as appropriate, and that the reports comply with the FDA s filing requirements.

In addition, the Pediatric Research Equity Act, or PREA, requires a sponsor to conduct pediatric studies for most drugs and biologicals, for a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration. Under PREA, original NDAs, biologics license application and supplements thereto, must contain a pediatric assessment unless the sponsor has received a deferral or waiver. The required assessment must assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations and support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The sponsor or FDA may request a deferral of pediatric studies for some or all of the pediatric subpopulations. A deferral may be granted for several reasons, including a finding that the drug or biologic is ready for approval for use in adults before pediatric studies are complete or that additional safety or effectiveness data needs to be collected before the pediatric studies begin. After April 2013, the FDA must send a non-compliance letter to any sponsor that fails to submit the required assessment, keep a deferral current or fails to submit a request for approval of a pediatric formulation.

As part of the FDASIA, Congress made a few revisions to BPCA and PREA, which were slated to expire on September 30, 2012, and made both laws permanent.

Regulation Outside of the United States

In addition to regulations in the United States, we will be subject to regulations of other countries governing clinical trials and commercial sales and distribution of our products. Whether or not we obtain FDA approval for a product, we must obtain approval by the comparable regulatory authorities of countries outside of the United States before we can commence clinical trials in such countries and approval of the regulators of such countries or economic areas, such as the European Union, before we may market products in those countries or areas. The approval process and requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary greatly from place to place, and the time may be longer or shorter than that required for FDA approval.

Under European Union regulatory systems, a company may submit marketing authorization applications either under a centralized or decentralized procedure. The centralized procedure, which is compulsory for medicines produced by biotechnology or those medicines intended to treat AIDS, cancer, neurodegenerative disorders or diabetes and optional for those medicines which are highly innovative, provides for the grant of a single marketing authorization that is valid for all European Union member states. The decentralized procedure provides for mutual recognition of national approval decisions. Under this procedure, the holder of a national marketing authorization may submit an application to the remaining member states. Within 90 days of receiving the applications and assessments report, each member state must decide whether to recognize approval. If a member state does not recognize the marketing authorization, the disputed points are eventually referred to the European Commission, whose decision is binding on all member states.

As in the United States, we may apply for designation of a product as an orphan drug for the treatment of a specific indication in the European Union before the application for marketing authorization is made. Orphan drugs in Europe enjoy economic and marketing benefits, including up to ten years of market exclusivity for the approved indication unless another applicant can show that its product is safer, more effective or otherwise clinically superior to the orphan-designated product.

ATU

We may apply to make OCA available for use under a cohort Autorisation Temporaire d Utilisation, or Temporary Authorization for Use, or ATU, in France. Under an ATU, the French Health Products Safety Agency, or Afssaps, allows the use of a drug in France before marketing approval has been obtained in France in order to treat serious or rare diseases for which no other treatment is available in that country. Afssaps will only grant an ATU where the benefit of the product outweighs the risk. An ATU is granted for one year and may be renewed. If an ATU is granted for OCA, we will be required to gather and analyze data concerning OCA s use and submit a periodic report to Afssaps. We also will be responsible for submitting

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pharmacovigilance reports, as necessary. An ATU may be modified, suspended, or withdrawn for reasons of public health or if the conditions under which the ATU was granted are no longer met. We believe the granting of an ATU and subsequent use by patients in France prior to marketing approval may enable us to begin recognizing some product sales revenue for OCA prior to its approval in the United States and the remainder of the European Union.

Reimbursement

Sales of our products will depend, in part, on the extent to which the costs of our products will be covered by third-party payors, such as government health programs, commercial insurance and managed healthcare organizations. These third-party payors are increasingly challenging the prices charged for medical products and services. Additionally, the containment of healthcare costs has become a priority of federal and state governments and the prices of drugs have been a focus in this effort. The U.S. government, state legislatures and foreign governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit our net revenue and results. If these third-party payors do not consider our products to be cost-effective compared to other therapies, they may not cover our products after approved as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow us to sell our products on a profitable basis.

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the MMA, imposed new requirements for the distribution and pricing of prescription drugs for Medicare beneficiaries. Under Part D, Medicare beneficiaries may enroll in prescription drug plans offered by private entities which will provide coverage of outpatient prescription drugs. Part D plans include both stand-alone prescription drug benefit plans and prescription drug coverage as a supplement to Medicare Advantage plans. Unlike Medicare Part A and B, Part D coverage is not standardized. Part D prescription drug plan sponsors are not required to pay for all covered Part D drugs, and each drug plan can develop its own drug formulary that identifies which drugs it will cover and at what tier or level. However, Part D prescription drug formularies must include drugs within each therapeutic category and class of covered Part D drugs, though not necessarily all the drugs in each category or class. Any formulary used by a Part D prescription drug plan must be developed and reviewed by a pharmacy and therapeutic committee. Government payment for some of the costs of prescription drugs may increase demand for our products for which we receive marketing approval. However, any negotiated prices for our products covered by a Part D prescription drug plan will likely be lower than the prices we might otherwise obtain. Moreover, while the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own payment rates. Any reduction in payment that results from the MMA may result in a similar reduction in payments from non-governmental payors.

The American Recovery and Reinvestment Act of 2009 provides funding for the federal government to compare the effectiveness of different treatments for the same illness. A plan for the research will be developed by the Department of Health and Human Services, the Agency for Healthcare Research and Quality and the National Institutes for Health, and periodic reports on the status of the research and related expenditures will be made to Congress. Although the results of the comparative effectiveness studies are not intended to mandate coverage policies for public or private payors, it is not clear what effect, if any, the research will have on the sales of any product, if any such product or the condition that it is intended to treat is the subject of a study. It is also possible that comparative effectiveness research demonstrating benefits in a competitor s product could adversely affect the sales of our product candidates. If third-party payors do not consider our products to be cost-effective compared to other available therapies, they may not cover our products as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow us to sell our products on a profitable basis.

The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act of 2010, collectively referred to as the ACA, enacted in March 2010, is expected to have a significant impact on the health care industry. ACA is expected to expand coverage for the uninsured while at the same time containing overall healthcare costs. With regard to pharmaceutical products, among other things, ACA is expected to expand and increase industry rebates for drugs covered under

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Medicaid programs and make changes to the coverage requirements under the Medicare Part D program. We cannot predict the impact of ACA on pharmaceutical companies, as many of the ACA reforms require the promulgation of detailed regulations implementing the statutory provisions which has not yet occurred. In addition, although the United States Supreme Court recently upheld the constitutionality of most of the ACA, some states have indicated that they intend to not implement certain sections of the ACA, and some members of the U.S. Congress are still working to repeal parts of the ACA. These challenges add to the uncertainty of the legislative changes enacted as part of ACA.

ACA required pharmaceutical manufacturers to track certain financial arrangements with physicians and teaching hospitals, including any transfer of value made or distributed to such entities, as well as any investment interests held by physicians and their immediate family members. Manufacturers were required to begin tracking this information in 2013 and to report this information to CMS beginning in 2014.

In addition, in some non-U.S. jurisdictions, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing vary widely from country to country. For example, the European Union provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. A member state may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our products. Historically, products launched in the European Union do not follow price structures of the United States and generally tend to be significantly lower.

Employees

As of December 31, 2014, we had 136 employees, of which 92 employees were in our drug development operations, 18 employees were in our commercial group and 26 employees were in our corporate group. As of December 31, 2014, one employee was based in Europe and the rest were based in the United States. None of our employees are represented by a labor union and we consider our employee relations to be good.

Corporate Information

We were incorporated in the State of Delaware on September 4, 2002. Our principal executive offices are located at 450 West 15th Street, Suite 505, New York, NY 10011, and our telephone number is (646) 747-1000.

Our corporate website address is *www.interceptpharma.com.* Our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K, and amendments to reports filed pursuant to Sections 13(a) and 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act, are available free of charge on our website as soon as reasonably practicable after we electronically file such material with, or furnish it to, the Securities and Exchange Commission. The Securities and Exchange Commission maintains an internet site that contains our public filings with the Securities and Exchange Commission and other information regarding our company, at *www.sec.gov.* These reports and other information concerning our company may also be accessed at the Securities and Exchange Commission s Public Reference Room at 100 F Street, NE, Washington, DC 20549. The public may obtain information on the operation of the Public Reference Room by calling the Securities and Exchange Commission at 1-800-SEC-0330. The contents of these websites are not incorporated into this Annual Report. Further, our references to the URLs for these websites are intended to be inactive textual reference only.

Legal Proceedings

From time to time we are party to legal proceedings in the course of our business in addition to those described below. We do not, however, expect such other legal proceedings to have a material adverse effect on our business, financial condition or results of operations.

On February 21, 2014 and February 28, 2014, purported shareholder class actions, styled *Scot H. Atwood v. Intercept Pharmaceuticals, Inc. et al.* and *George Burton v. Intercept Pharmaceuticals, Inc. et al.*, respectively, were filed in the United States District Court for the Southern District of New York, naming us

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and certain of our officers as defendants. These lawsuits were filed by stockholders who claim to be suing on behalf of anyone who purchased or otherwise acquired our securities between January 9, 2014 and January 10, 2014. The plaintiffs seek unspecified monetary damages on behalf of the putative class and an award of costs and expenses, including attorney s fees. The lawsuits allege that we made material misrepresentations and/or omissions of material fact in our public disclosures during the period from January 9, 2014 to January 10, 2014, in violation of Sections 10(b) and 20(a) of the Securities Exchange Act of 1934, as amended, and Rule 10b-5 promulgated thereunder. The alleged improper disclosures relate to our January 9, 2014 announcement that the FLINT trial had been stopped early based on a pre-defined interim efficacy analysis. Specifically, the lawsuits claim that our January 9, 2014 announcement was misleading because it did not contain information regarding certain lipid abnormalities seen in the FLINT trial in OCA-treated patients compared to placebo. On April 22, 2014, two individuals each moved to consolidate the cases and a lead plaintiff was subsequently appointed by the Court. On June 27, 2014, the lead plaintiff filed an amended complaint on behalf of the putative class as contemplated by the order of the Court. On August 14, 2014, the defendants filed a motion to dismiss the complaint, which has been opposed by the lead plaintiff. Oral arguments on the motion to dismiss were held on February 24, 2015. No decision has been made by the Court on the motion to dismiss. The lead plaintiff seeks unspecified monetary damages on behalf of the putative class and an award of costs and expenses, including attorneys fees.

We believe that we have valid defenses to the claims in the lawsuit and intend to deny liability and defend ourselves vigorously. At this time, no assessment can be made as to the likely outcome of these lawsuits or whether the outcome will be material to us. Therefore, we have not accrued for any loss contingencies related to these lawsuits.

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Item 1A. Risk Factors

Except for the historical information contained herein, this Annual Report on Form 10-K contains forward-looking statements that involve risks and uncertainties. These statements include projections about our accounting and finances, plans and objectives for the future, future operating and economic performance and other statements regarding future performance. These statements are not guarantees of future performance or events. Our actual results could differ materially from those discussed in this Annual Report on Form 10-K. Important factors that could cause or contribute to these differences include, but are not limited to, those discussed in the following section, as well as those discussed in Part II, Item 7 entitled Management s Discussion and Analysis of Financial Condition and Results of Operations and elsewhere throughout this Annual Report on Form 10-K.

You should consider carefully the following risk factors, together with all of the other information included in this Annual Report on Form 10-K. If any of the following risks, either alone or taken together, or other risks not presently known to us or that we currently believe to not be significant, develop into actual events, then our business, financial condition, results of operations or prospects could be materially adversely affected. If that happens, the market price of our common stock could decline, and stockholders may lose all or part of their investment.

Risks Related to Our Financial Position and Need for Additional Capital

We have never been profitable. Currently, we have no products approved for commercial sale, and to date we have not generated any revenue from product sales. As a result, our ability to reduce our losses and reach profitability is unproven, and we may never achieve or sustain profitability.

We have never been profitable and do not expect to be profitable in the foreseeable future. We have not yet submitted any product candidates for approval by regulatory authorities in the United States or elsewhere for our lead indication, primary biliary cirrhosis, or PBC, or any other indication, including nonalcoholic steatohepatitis, or NASH. We have incurred net losses in each year since our inception, including net losses of $43.6 million, $67.8 million and $283.2 million for the years ended December 31, 2012, 2013 and 2014, respectively. To date, we have financed our operations primarily through private placements of our convertible preferred stock, convertible notes and warrants to purchase common stock, public offerings of our common stock and payments received under our licensing and collaboration agreements with Sumitomo Dainippon Pharma Co. Ltd., or Sumitomo Dainippon, and Les Laboratoires Servier and Institut de Recherches Servier, which are collectively referred to as Servier. At December 31, 2014, we had $239.7 million in cash, cash equivalents and investment securities. In February 2015, we completed a follow-on public offering of 1,150,000 shares at a public offering price of $176.00 per share. After underwriting discounts and commissions and estimated offering expenses, we estimate that the net proceeds from our February 2015 follow-on equity offering were approximately $191.2 million.

We have devoted substantially all of our resources to our development efforts relating to our product candidates, including conducting clinical trials of our product candidates, providing general and administrative support for these operations, protecting our intellectual property and engaging in activities to prepare for the commercialization of our product candidates. We do not have any products approved for sale and have not generated any revenues from product sales. We expect to continue to incur losses for the foreseeable future, and we expect these losses to increase as we continue our development of, and seek regulatory approvals for, obeticholic acid, or OCA, which is our lead product candidate, and our other product candidates, prepare for and begin the commercialization of any approved products,

and add infrastructure and personnel in the United States and Europe to support our product development and commercialization efforts and operations as a public company. We anticipate that any such losses could be significant for the next several years as we continue our confirmatory clinical outcomes trial of OCA in PBC, continue our long-term safety extension phases of our clinical trials of OCA in PBC, commence our Phase 3 clinical program of OCA in nonalcoholic steatohepatitis, or NASH, continue our Phase 2 clinical trial of OCA for primary sclerosing cholangitis, or PSC, and finalize other planned activities for regulatory submission and approval of OCA in PBC. We also expect that continuing the development of OCA in additional diseases, such as biliary atresia, a rare pediatric disease characterized by deficient bile duct development. We also plan on initiating a clinical trial to assess the lipid metabolic effects of OCA and the effects of concomitant statin administration in NASH patients

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during 2015. Furthermore, we plan to complete IND-enabling studies of INT-767, an earlier stage product candidate for which we plan to initiate, Phase 1 clinical trial by the end of 2015. Our expenses could increase if we are required by the U.S. Food and Drug Administration, or FDA, or the European Medicines Agency, or EMA, to perform studies or trials in addition to those currently expected, or if there are any delays in completing our clinical trials or the development of any of our product candidates. We also anticipate that we will continue to increase our product development, scientific, commercial and administrative personnel significantly and expand our facilities and infrastructure in the United States and abroad as part of our growth strategy.

Our ability to generate profits from operations and become profitable will depend on our ability to obtain marketing approval for, and commercialize, our product candidates. We do not expect to generate significant revenues unless and until we obtain marketing approval for, and commercialize, OCA for the treatment of PBC and other indications. This will require us to be successful in a range of challenging activities, including:

obtaining approval to market OCA for the treatment of PBC, NASH and other indications and patient populations;
expanding our manufacturing of commercial supply for OCA;
establishing sales, marketing and distribution capabilities to effectively market and sell OCA in the United States and Europe; and
negotiating and securing reimbursement from third-party payors for OCA.

If OCA or any of our other product candidates fails in clinical trials or does not gain regulatory approval, or if our product candidates do not achieve market acceptance, we may never become profitable. Our net losses and negative cash flows have had, and will continue to have, an adverse effect on our stockholders equity and working capital. Because of the numerous risks and uncertainties associated with pharmaceutical product development and commercialization, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able to achieve profitability. The amount of future net losses will depend, in part, on the rate of future growth of our expenses and our ability to generate revenues.

We will require substantial additional funding, which may not be available to us on acceptable terms, or at all, and, if not so available, may require us to delay, limit, reduce or cease our operations.

We are currently advancing OCA through clinical development for multiple indications and other product candidates through preclinical development. Developing pharmaceutical products, including conducting preclinical studies and clinical trials, is expensive. In December 2014, we initiated a rolling NDA submission for OCA in PBC under the FDA s accelerated approval pathway. We also plan to submit an application for marketing approval for OCA in PBC in Europe. We plan to complete our filings for marketing approval of OCA in PBC in the United States and Europe within the first half of 2015. If the FDA or EMA requires that we perform preclinical studies or clinical trials in addition to those contemplated or conducted by us, our expenses would further increase beyond what we currently expect and the anticipated timing for the completion of our potential NDA or MAA filing would likely be delayed. In addition, if we receive marketing approval from regulatory authorities, we plan to initiate the commercial launch of OCA in PBC in the United States and certain European countries in 2016. We anticipate incurring significant expenses as we prepare for the potential commercialization of OCA in PBC, including significant expenses to establish our sales, marketing and distribution capabilities and increase our drug manufacturing activities. We will require substantial additional future capital in order to complete clinical development and commercialize OCA, and to conduct the research and development and clinical and regulatory activities necessary to bring other product candidates to market. We also anticipate incurring significant expenses in connection with our planned increase in our product development, scientific, commercial and administrative personnel and expansion of our facilities and infrastructure in the United States and abroad.

As of December 31, 2014, we had $239.7 million in cash, cash equivalents and investment securities. We estimate that the net proceeds from our February 2015 follow-on equity offering were approximately $191.2 million, after underwriting discounts and commissions and estimated offering expenses. We currently project adjusted operating expenses in the range of $180 million to $200 million in the fiscal year ending December 31, 2015, which excludes stock-based compensation and other non-cash items. These expenses are

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planned to support the clinical development program for OCA in PBC, NASH and PSC, the expansion of our clinical, regulatory, medical affairs and commercial infrastructure in the United States and Europe, increased OCA manufacturing activities, as well as the continued development of INT-767 and other preclinical pipeline programs. We anticipate that stock-based compensation expense will represent the most significant non-cash item that is excluded in adjusted operating expenses as compared to operating expenses under U.S. generally accepted accounting principles, or GAAP. Adjusted operating expense is a financial measure not calculated in accordance with GAAP. See Non-GAAP Financial Measures for more information. Accordingly, we will continue to require substantial additional capital to continue our clinical development and commercialization activities. Because successful development of our product candidates is uncertain, we are unable to estimate the actual funds we will require to complete research and development and commercialize our products under development.

Due to the many variables inherent to the development and commercialization of novel therapies, such as the risks described in this Risk Factors section, and our rapid growth and expansion, we currently cannot accurately or precisely predict the duration beyond 2015 over which we expect our cash and cash equivalents (including the net proceeds from our February 2015 follow-on equity offering) to be sufficient to fund our operating expenses and capital expenditure requirements. However, we currently believe that our cash and cash equivalents, together with the net proceeds from our February 2015 follow-on equity offering, will be sufficient for us to:

expand our clinical, regulatory, medical affairs and commercial infrastructure in the United States and Europe;
continue and expand our clinical development programs for OCA in PBC, NASH and PSC, such as initiating and/or continuing, but not completing, our planned Phase 3 clinical program for OCA in NASH, our planned clinical trial characterizing lipid metabolic effects of OCA and cholesterol management effects of concomitant statin administration in NASH patients, our ongoing Phase 2 clinical trial of OCA for PSC, and our ongoing confirmatory clinical outcomes trial of OCA in PBC;
advance the continued development of INT-767, including the completion of IND-enabling preclinical studies for INT-767 and the initiation of a Phase 1 clinical trial, and other preclinical compounds;
complete the filings of our NDA and MAA for OCA in PBC, but not complete our filings for marketing authorization in any other indication;
increase OCA manufacturing activities, including investing in supply chain and product development, preparing for PBC commercial launch and planning for the continuation of our clinical program in NASH, but not manufacture the supply needed for any potential commercial launch of OCA in NASH; and
prepare for and, if we obtain marketing approval on a timely basis, initiate the commercial launch of OCA in PBC in both the United States and certain European countries in 2016, but not commercially launch OCA in PBC in other countries across the world.

Accordingly, we will continue to require substantial additional capital to continue our clinical development, commercialization and other activities. Because successful development and commercialization of our product candidates is uncertain, we are unable to estimate the actual funds we will require to complete research and development and commercialize our products under development.

The amount and timing of our future funding requirements will depend on many factors, including:

the willingness of the FDA and EMA to accept the POISE trial, which is our completed phase 3 clinical trial for PBC, as well as our other completed and planned clinical and preclinical studies and other work, as the basis for review and marketing approval of OCA for PBC;
the progress, costs, results of and timing of our recently initiated confirmatory clinical outcomes trial of OCA for the treatment of PBC, the completion of which we expect will not be a condition to the receipt of marketing approval in the United States or the European Union;

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the design of our planned Phase 3 clinical program for OCA in NASH and the progress, costs, results of and timing of the Phase 3 program and other supporting trials and studies necessary to support anticipated filings for marketing approval in NASH, including the sufficiency of one pivotal clinical trial for marketing approval or the acceptability of a surrogate endpoint for accelerated approval of OCA for the treatment of NASH;

the progress, costs, results of and timing of clinical development of OCA for other indications, including our Phase 2 trial of OCA in PSC and biliary atresia;

the significant expansion of our operations, personnel and the size of our company and our need to continue to expand;

the outcome, costs and timing of seeking and obtaining FDA, EMA and any other regulatory approvals;

the number and characteristics of product candidates that we pursue, including our product candidates in preclinical development, such as INT-767 and INT-777;

the ability of our product candidates to progress through pre-clinical and clinical development successfully and in a timely manner;

the expansion of our research and development activities;

the costs and timing of commercialization activities, including product sales, marketing and distribution, for any of our product candidates that receive marketing approval;

the costs associated with securing and establishing manufacturing capabilities and procuring the materials necessary for our product candidates;

market acceptance of our product candidates;

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

our ability to maintain, expand and defend the scope of our intellectual property portfolio, including the amount and timing of any payments we may be required to make, or that we may receive, in connection with the licensing, filing, prosecution, defense and enforcement of any patents or other intellectual property rights;

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