INTERCEPT PHARMACEUTICALS INC
Form 10-K
February 29, 2016

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, 2015

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, 2015 was approximately $3,860,970,135. As of January 31, 2016, there were 24,405,977 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 2016 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 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, which may be affected by the reimbursement that our products receive from payors;

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 collaborators election to pursue research, development and commercialization activities;
our ability to attract collaborators with development, regulatory and commercialization expertise;
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 cash and short term investments; 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 non-viral, progressive liver diseases. 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 Phase 3 clinical trial in patients with primary biliary cirrhosis, recently renamed primary biliary cholangitis, 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 addition, in October 2015, we announced results from a Phase 2 dose ranging trial of OCA in 200 patients with NASH in Japan conducted by our collaborator, Sumitomo Dainippon Pharma Co., Ltd., or Sumitomo Dainippon.

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, Europe, Australia and Canada.

In June 2015, we completed our filings for marketing approval of OCA in PBC in the United States under the FDA s accelerated approval pathway. In August 2015, the FDA accepted for review our New Drug Application, or NDA, and granted Priority Review for OCA for the treatment of PBC. The FDA set a target date of May 29, 2016 to take action under the Prescription Drug User Fee Act, or PDUFA, after giving effect to a 90 day extension. The FDA has also publicly announced a planned advisory committee meeting date of April 7, 2016. If we receive marketing approval from the FDA on the PDUFA date, we plan to initiate the commercial launch of OCA in PBC in the United States in June 2016.

In June 2015, we also received notice of the acceptance of the Marketing Authorization Application, or MAA, for

review by the European Medicines Agency, or EMA, for use of OCA in PBC. If we are successful in the EMA review process, we anticipate receiving marketing approval in late 2016, with planned commercial launches thereafter in certain European countries. We also plan to apply for marketing approval of OCA in PBC in other markets across the world such as Australia and Canada.

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 initiated our Phase 3 clinical trial in non-cirrhotic NASH patients with liver fibrosis, known as the REGENERATE trial, in September 2015. In December 2015, we initiated a Phase 2 clinical trial, known as the CONTROL trial, to characterize the lipid metabolic effects of OCA and cholesterol management effects of concomitant statin administration in NASH patients.

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In addition to PBC and NASH, we plan to continue our research on OCA in patient populations suffering from other liver diseases, as we believe that FXR has broad therapeutic potential. In December 2014, we initiated an international Phase 2 clinical trial, known as the AESOP trial, in patients with PSC to evaluate the effects of 24 weeks of treatment with varying doses of OCA compared to placebo. In October 2015, we initiated a Phase 2 clinical trial, known as the CARE trial, of OCA in pediatric patients with biliary atresia. This trial will evaluate the effects of 11 weeks of OCA treatment where patients with biliary atresia will be randomized to varying doses of OCA or a control group receiving only their current treatment. As part of our development program, in November 2015, we initiated a Phase 1 clinical trial of our second product candidate to enter clinical development, called INT-767, a dual FXR and TGR5 agonist, in healthy volunteers. We are currently evaluating our future development strategy for OCA in other indications, for INT-767 and for our pre-clinical candidates. The following chart shows the current stage of development of OCA in different patient populations and the preclinical programs for our other product candidates.

Pipeline Focused on Liver Diseases with Limited/No Approved Therapies

Our current patents for OCA are scheduled to expire at various times through 2033. 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. Starting with OCA and its underlying patents, which were assigned to us under our agreements with Professor Roberto Pellicciari, Ph.D., one of our co-founders, other researchers and the University of Perugia, our collaboration has resulted in a pipeline of bile acid analogs in addition to OCA, such as INT-767 and INT-777. Through our collaboration with Professor Pellicciari and TES Pharma Srl, we are continuing our research to rationally design compounds that bind selectively and potently to FXR and other bile acid receptors.

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Our Strategy

Our strategy is to develop and commercialize novel therapeutics for patients with non-viral, progressive liver 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, Europe and other countries;
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 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 liver 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 longer-term 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; Renamed Primary Biliary Cholangitis)

Our current clinical focus is on the development of OCA, a novel, orally administered 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.

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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.

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, 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.

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Our PBC Opportunity

While ursodiol is the established standard of care for PBC, a majority of patients while on therapy remain at ALP levels above the upper limit of normal, or ULN. According to our analysis of industry data in PBC, approximately 70% of patients treated with ursodiol experience elevated ALP levels, with 35% of patients experiencing ALP levels greater than 1.67 times ULN. In addition, a small minority of PBC patients (estimated at approximately 3%) are intolerant to ursodiol therapy. Patients with the greatest elevations in ALP despite therapy and those intolerant to ursodiol represent a significant unmet medical need for second line therapy. Based on our Phase 3 POISE results, which evaluated OCA in these patient groups, we believe represent patients with these characteristics would be eligible for OCA as a novel therapy.

According to our analysis of industry data, there are approximately 290,000 people with PBC in our target markets consisting of the United States, certain European countries, Canada and Australia, of whom we believe approximately 110,000 have been diagnosed and are under the care of a physician for PBC. Although difficult to precisely estimate, based on our analysis of this data, we believe there are approximately 34,000 diagnosed PBC patients who still have an ALP level greater than 1.67 times ULN after treatment on ursodiol who may currently be eligible for treatment with OCA. Of those 34,000 PBC patients, approximately 15,000 are estimated to be in the United States and 19,000 in our target countries outside of the United States. We believe there are an additional 32,000 patients who have an elevated ALP between ULN and 1.67 times ULN in these target countries. Our estimates of the potential market opportunity for OCA for the treatment of PBC include a number of key assumptions related to prevalence rates, patients access to healthcare, diagnosis rates and patients response to or tolerance of OCA, which are based on available literature and epidemiology research in PBC, our industry knowledge gained through market research and other methods, industry publications, third-party research reports and other surveys.

Our Solution: OCA for PBC

Overview

Our lead product candidate, OCA, is a bile acid analog and an 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. OCA, if approved, would represent the first potent FXR agonist to market for the treatment of PBC, and represents a distinct mechanism of action relative to ursodiol, which has no known FXR effects.

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.

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.

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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 interleukin 12, or IL-12, tumor necrosis factor alpha, or TNF-a, 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.

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. Except for a small number of patients who were intolerant of ursodiol, the patients in the placebo and OCA dosing groups received standard of care ursodiol treatment throughout the trial.

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 ULN, 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 observational meta-analyses to have a significantly lower risk of progressing to liver transplant and death. The percentage 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

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In addition, both OCA dose groups met pre-specified secondary endpoints of improving other clinically relevant liver enzymes. Reductions in gamma glutamyl transferase, or 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, generally mild to moderate, was the most frequently reported adverse event associated with OCA treatment and was observed in 38% of patients on placebo, 70% 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. Pruritus has also been observed in other clinical trials 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. A majority of the pruritus events were found to be transient in nature, starting within the first month of dosing and decreasing in severity over time with continued treatment.

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.

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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 the FDA on a rolling basis as they are completed. In June 2015, we completed our filings for marketing approval of OCA in PBC in the United States under the FDA s accelerated approval pathway. In August 2015, the FDA accepted for review our NDA and granted Priority Review for OCA for the treatment of PBC. The FDA set a target date of May 29, 2016 to take action under PDUFA, after giving effect to a 90 day extension. The FDA has also publicly announced a planned advisory committee meeting date of April 7, 2016. If we receive marketing approval from the FDA on the PDUFA date, we plan to initiate the commercial launch of OCA in PBC in the United States in June 2016.

In June 2015, we also received notice of the acceptance of the MAA for review by the EMA for use of OCA in PBC. If we are successful in the EMA review process, we anticipate receiving marketing approval in late 2016, with planned commercial launches thereafter in certain European countries. We also plan to apply for marketing approval of OCA in PBC in other markets across the world such as Australia and Canada.

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 and EMA s potential acceptance of our POISE trial primary endpoint as a basis for accelerated approval will be the result of meta-analyses of 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 ULN best predicted patient outcome but not significantly better than other lower ALP thresholds such as 1.67 times ULN. 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.

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Ongoing Confirmatory Clinical Outcomes Trial: The COBALT Trial

As part of our strategy for filing the NDA for OCA under the accelerated approval pathway, in December 2014 we initiated our COBALT 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 currently enrolling patients and is expected to be completed on a post-marketing basis.

COBALT is designed 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 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. 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 a more serious form of NAFLD. Although difficult to precisely estimate, we believe that roughly one quarter of the total U.S. population and roughly 20% of the total population in France, Germany, Italy, Spain and the United Kingdom, or the EU5 countries, has NAFLD. Of the NASH population in both the United States and the EU5 countries, more than 15% of patients are believed to have fibrosis of stage 2 or greater. We believe that similar prevalence will be found in other European countries, Japan and other developed countries. Additionally, NASH has become a highly prevalent liver disease in developing countries such as India and China. 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.

Other common co-existing conditions such as obesity and type 2 diabetes, which are present in the majority of all NASH patients, are important risk factors. NASH 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. More than 20% of NASH patients progress to cirrhosis within a decade of diagnosis. Owing to 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. 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.

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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. NASH diagnosis rates in the United States and the EU5 countries are very low, driven by a lack of approved treatment options and a lack of non-invasive diagnosis options. We believe the availability of novel therapeutics and non-invasive technologies will be critical to increase diagnosis rates.

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 and those with a high risk of disease progression due to other co-morbidities such as type 2 diabetes.

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 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:

Pharmacological Activity. In addition to achieving the primary endpoint in the Phase 2b FLINT trial in NASH patients, a significantly greater number of OCA-treated patients 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. 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.

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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 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 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.

a. 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*.

a. Primary Endpoint

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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.*

b. 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.

c. 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.

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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.

d. 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 ALT (p < 0.0001), AST (p = 0.0001) and 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 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)

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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).

A post-hoc analysis showed OCA-treated patients who initiated statins during the FLINT trial (n=26) experienced a rapid reversal of their observed mean LDL-C increase to below baseline levels, with a mean decrease after 72 weeks of treatment of -18.9 mg/dL. In contrast, other OCA-treated patients with no reported initiation or change in statin therapy experienced an increase in LDL-C that peaked at week 12 and was sustained over the 72 week treatment period. Patients treated with statins at baseline who maintained statin treatment over the duration of the study (n=50) experienced a mean LDL-C increase of 8.7 mg/dL at 72 weeks. Patients not treated with statins during the study (n=65) experienced a mean LDL-C increase of 16.0 mg/dL. Treatment related LDL-C increases in all groups reversed with treatment discontinuation. This analysis suggests that the OCA-associated LDL-C increase reaches a maximum peak and plateaus soon after initiation of therapy and that concomitant statin use in NASH patients receiving OCA may mitigate treatment-related LDL-C increases.

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.

e. 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 October 2015, we announced the results of a 72-week Phase 2 dose ranging trial of OCA in 200 adult patients with NASH in Japan. The trial was conducted by our collaborator, Sumitomo Dainippon. In this trial, 202 Japanese biopsy-proven NASH patients (NAS of 5-8) were randomized into one of four arms to receive either a 10 mg, 20 mg or 40 mg dose of OCA, or placebo, and 200 of these patients 50 per group initiated treatment for a 72-week double-blind treatment phase, followed by a 24-week off treatment phase. The primary endpoint was histologic improvement defined as at least a two point improvement in NAS with no worsening of fibrosis.

The primary efficacy analysis was conducted on an intention to treat, or ITT, basis, testing the dose dependent effects of once daily OCA (10 mg, 20 mg and 40 mg) versus placebo on the primary endpoint. The ITT analysis included all randomized patients who received treatment (50 per group), and patients who discontinued or did not have a repeat biopsy were treated as non-responders. A pre-specified completer analysis was conducted on the patients who had biopsies at both baseline and 72 weeks (45, 44, 44 and 37 patients in the placebo, 10 mg, 20 mg and 40 mg OCA groups, respectively).

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This trial did not meet its primary endpoint with statistical significance. The ITT results in the table below show a dose dependent increase in the percentage of OCA treated patients compared to placebo who achieved the primary endpoint (p=0.053, not significant). The 40 mg OCA dose group achieved statistical significance on the primary endpoint compared to placebo (p=0.0496). Dose-dependent trends not reaching statistical significance were also observed for several other pre-specified histologic endpoints, including the percentage of patients with steatosis and inflammation improvement, ballooning resolution and NASH resolution. No difference was seen in fibrosis improvement in the OCA groups compared to placebo.

ITT Results	Placebo N=50	10 mg N=50	20 mg N=50	40 mg N=50	
NAS improvement ≥ 2 points with no worsening of fibrosis	10 (20%)	11 (22%) p=0.8070**	14 (28%) p=0.3378**	19 (38%) p=0.0496**	p=0.053*

* Primary efficacy analysis is a stratified Cochran-Armitage test with multiple contrast coefficients. Statistical significance is based on a p-value < 0.05.

** The secondary efficacy analysis is a CMH (Cochran-Mantel-Haenszel) test stratified by baseline fibrosis stage for pairwise comparison of each OCA group compared to the placebo group. The multiplicity was not adjusted.

In the completer analysis, similar dose dependent effects were observed, with 51% of patients in the 40 mg dose group compared to 22% in the placebo group meeting the primary endpoint (p=0.0061).

With the exception of dose dependent pruritus, OCA appeared to be generally safe and well tolerated. The number of pruritus associated discontinuations were 0, 0, 2 and 5 patients in the placebo, 10 mg, 20 mg and 40 mg OCA groups, respectively. Changes in lipid parameters, including LDL-C, HDL-C and triglycerides, appeared to be consistent with previously reported lipid changes in Western NASH patients. No other meaningful differences in the rate of adverse events between the OCA and placebo groups were noted.

We have been informed by Sumitomo Dainippon that it is exploring the initiation of a Phase 3 clinical trial for OCA in NASH patients intended to support the registration of this indication in Japan.

REGENERATE: Phase 3 Trial in NASH with Advanced Liver Fibrosis

In September 2015, we initiated the previously announced international Phase 3 trial of OCA in patients with non-cirrhotic NASH with advanced liver fibrosis, known as the REGENERATE trial, which is currently enrolling patients. The REGENERATE trial was designed following discussions with the FDA and EMA. The study population is expected to primarily be comprised of Western NASH patients with histologic evidence of stage 2 or stage 3 liver fibrosis. In addition, the trial will include an exploratory cohort of NASH patients with histologic evidence of early stage 1 liver fibrosis and concomitant diabetes, obesity or elevated ALT, who are at increased risk of progression to cirrhosis. These patients with early stage 1 liver fibrosis will not be included in the primary endpoint analysis.

REGENERATE is designed as a double-blind, placebo-controlled Phase 3 clinical trial and is expected to enroll approximately 2,000 NASH patients at up to 300 qualified centers worldwide and assess the potential benefits of OCA treatment on liver-related and other clinical outcomes. Patients are being randomized into one of three groups receiving a once-daily dose of placebo, 10 mg OCA or 25 mg OCA. The trial will include a pre-planned interim histology analysis after 72 weeks of treatment in 1,400 patients, which if successful is intended to serve as the basis for seeking initial U.S. and international marketing approvals of OCA for the treatment of NASH patients with liver fibrosis. The REGENERATE trial will remain blinded after the interim analysis and continue to follow patients until

the occurrence of a pre-specified number of adverse liver-related clinical events, including progression to cirrhosis, to confirm clinical benefit on a post-marketing basis.

Two co-primary endpoints will be assessed in the interim analysis: (i) the proportion of OCA-treated patients relative to placebo achieving at least one stage of liver fibrosis improvement with no worsening of NASH and (ii) the proportion of OCA-treated patients relative to placebo achieving NASH resolution with no worsening of liver fibrosis. The REGENERATE trial will also assess secondary outcome measures such as improvement of both fibrosis and NASH and the resolution of fibrosis.

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Additional NASH Clinical Programs

In December 2015, we initiated a Phase 2 clinical trial, known as the CONTROL trial, to characterize the lipid metabolic effects of OCA and cholesterol management effects of concomitant statin administration in NASH patients. CONTROL is expected to enroll 80 NASH patients who are naïve to statin therapy or have undergone a statin washout, and will include a 16-week double-blind phase followed by an optional two year long term safety extension phase.

We intend to complete our planning for a Phase 2 program in NASH patients with cirrhosis in 2016. The objectives of this trial are to understand the safety and tolerability of OCA in NASH patients with cirrhosis and portal hypertension and to evaluate the effect of OCA in reducing portal pressure as assessed by hepatic venous pressure gradient, or HVPG.

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.

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 AESOP Trial: OCA as Therapy in PSC

In December 2014, we initiated an international Phase 2 clinical trial, referred to as the AESOP 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

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approximately 75 patients in the United States 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.

Phase 2 CARE Trial: OCA as Therapy in Biliary Atresia

In October 2015, we initiated a Phase 2 clinical trial of OCA, referred to as the CARE trial, in pediatric patients with biliary atresia. The CARE trial will evaluate the effects of 11 weeks of OCA treatment where patients with biliary atresia will be randomized to varying doses of OCA or a control group receiving only their current treatment. The primary endpoint is to evaluate the pharmacokinetics and the safety and tolerability of OCA treatment. In addition, OCA s effect on hepatobiliary indices and biomarkers will be assessed. This trial is anticipated to enroll approximately 60 patients in the United States and Europe. All patients will be given the option to enroll in an open-label long-term safety and efficacy extension trial. In addition to studying the effects of OCA treatment in biliary atresia, this trial is a part of the approved Paediatric Investigation Plan, or PIP, in support of the MAA for OCA in PBC in the European Union.

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 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.

In November 2015, we announced the initiation of a Phase 1 clinical trial of INT-767 in healthy volunteers. The goal of the Phase 1 trial is to assess safety and pharmacokinetics in a single ascending dose escalation phase followed by a multiple ascending dose phase in healthy volunteers.

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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. By virtue of the patent assignments we have received and other contractual obligations owed to us, we believe we are the exclusive owner of the INT-777 patent portfolio.

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 an 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 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

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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

In anticipation of the potential marketing authorization of OCA in PBC in the United States and Europe in 2016, we are in the final 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 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, certain European countries, Canada and Australia if it is approved. We anticipate that our commercialization efforts will include our internal commercial organization, sales people and other specialists, and contracted outside resources. Outside of the United States, Europe, Canada and Australia, subject to obtaining necessary marketing approvals, we likely will seek to commercialize OCA through distribution or other collaboration arrangements. We believe that the build out of our U.S. commercial infrastructure is mostly complete with the recent hiring of the U.S. territory business managers and other field personnel in October 2015. We also significantly expanded our commercial and other infrastructure

internationally in 2015, and plan on making additional investments over 2016 should key regulatory milestones be achieved on a timely basis.

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 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 that these activities have

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provided us with a growing knowledge of the physicians we plan to target for the commercial launch of OCA for PBC in the United States and Europe, subject to the receipt of applicable marketing approvals. 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 an FXR agonist currently being developed to treat non-viral, progressive liver diseases. We are aware of other companies, including Novartis International AG, Gilead Sciences, Inc., Enanta Pharmaceuticals, Inc., Eli Lilly, Co., ENYO Pharma SAS, Exelixis, Inc. and Akarna Therapeutics Ltd. 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.

OCA is currently being developed as a second line treatment for PBC where ursodiol is the only therapy that is approved for treatment and is generically available at a significantly lower cost than branded products. While fibrates are not approved for use in PBC, off-label use of fibrate drugs has been reported, though many fibrates are specifically contraindicated for use in PBC due to potential concerns over acute and long-term safety in this patient population. Ongoing Phase 3 clinical trials for the treatment of PBC include an investigator-sponsored trial of bezafibrate, a fibrate that has not been approved for commercialization by the FDA and is only available outside of the United States, and a combination of ursodiol and budesonide, a steroid, sponsored by Dr. Falk Pharma GmbH. We are aware of several other companies that have product candidates in Phase 2 or earlier clinical or preclinical development for the treatment of PBC, including FXR agonists from Novartis International AG (LJN452) and Enanta Pharmaceuticals, Inc. (EDP-305), Bristol-Myers Squibb s marketed anti-CTL4 fusion protein (abatacept) and FF Pharmaceuticals anti-CD40 monoclonal antibody (FFP104). Additionally, several companies have product candidates aimed at the cholestatic-induced pruritus associated with PBC, including apical sodium dependent bile acid transport inhibitors being developed by GlaxoSmithKline (GSK2330672) and Albireo (A4250).

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. Genfit SA has an ongoing Phase 3 clinical trial of GFT505, a dual PPAR alpha/delta agonist. Gilead Sciences, Inc. is conducting multiple Phase 2 clinical trials in NASH patients of various disease severity with both simtuzumab, an anti-body against the lysyl oxidase-like 2 enzyme, and GS-4997, an inhibitor of the apoptosis signal-regulating kinase 1. Gilead Sciences, Inc. is also studying an FXR agonist (GS-9674) for the treatment of NASH. We are aware of several other companies that have product candidates in Phase 2 clinical or earlier clinical or preclinical development for the treatment of NASH, including Novo Nordisk A/S, Conatus Pharmaceuticals

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Inc., Nitto Denko Corporation, Tobira Therapeutics, Inc., Cempra Pharmaceuticals, Islet Sciences, Inc., Galectin Therapeutics Inc., Zydus Pharmaceuticals Inc., NGM Biopharmaceuticals Inc., Galmed Medical Research Ltd., Bristol-Myers Squibb, MediciNova, Inc., FibroGen, Inc., Genkyotex SA, Viking Therapeutics, Inc., AstraZeneca plc, Enanta Pharmaceuticals, Inc., Durect Corporation, Immuron Ltd., Boehringer Ingelheim GmbH, MiNA Therapeutics, NuSirt Biopharma, Inc., Protalix Biotherapeutics, and Medivation, Inc. 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 clinical or preclinical development for the treatment of PSC, including Tobira Therapeutics, Inc., Biotie Therapies Corp. (acquired by Acorda Therapeutics, Inc.), 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. NASH is a complex disease and it is unlikely that any one therapeutic option will be optimal for every NASH patient. 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 (lead product candidate; 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, 2015, we owned seven U.S. patents, seven pending U.S. patent applications, and corresponding foreign patents and patent applications. Foreign patents have been granted in 31 European countries as well as Australia, Canada, China, Israel, Japan, and Macao. In January 2016, we received notification of grant of additional OCA composition of matter patents. We expect the composition of matter patents, if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2022 (worldwide) at the soonest and 2033 at the latest. It is possible that the 2022 expiration date of the composition of matter patent in the United States may be extended up to five