INTERCEPT PHARMACEUTICALS INC
Form S-1
September 04, 2012

As filed with the Securities and Exchange Commission on September 4, 2012

Registration No. 333-

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

FORM S-1

REGISTRATION STATEMENT UNDER
THE SECURITIES ACT OF 1933

INTERCEPT PHARMACEUTICALS, INC.

(Exact name of Registrant as specified in its charter)

Delaware	2834	22-3868459
(State or other jurisdiction of incorporation or organization)	(Primary Standard Industrial Classification Code Number)	(I.R.S. Employer Identification Number)

18 Desbrosses Street
New York, NY 10013
(646) 747-1000

(Address, including zip code, and telephone number,
including area code, of Registrant s principal executive offices)

Mark Pruzanski, M.D.
President and Chief Executive Officer
Intercept Pharmaceuticals, Inc.
18 Desbrosses Street
New York, NY 10013
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(Name, address, including zip code, and telephone number,
including area code, of agent for service)

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Approximate date of commencement of proposed sale to the public: As soon as practicable after the effective date of this registration statement.

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, check the following box. o

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. o

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. o

If this Form is a post-effective amendment filed pursuant to Rule 462(d) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. 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.

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

The Registrant is an emerging growth company, as defined in Section 2(a) of the Securities Act. This registration statement complies with the requirements that apply to an issuer that is an emerging growth company.

CALCULATION OF REGISTRATION FEE

Title of each class of securities to be registered	Proposed Maximum Aggregate Offering Price[1]	Amount of Registration Fee[2]
Common stock, par value $0.001 per share	$ 75,000,000	$ 8,595

(1) Estimated solely for the purpose of computing the amount of the registration fee pursuant to Rule 457(o) under the Securities Act of 1933, as amended. Includes offering price of shares that the underwriters have the option to purchase to cover over-allotments, if any.

(2) Calculated pursuant to Rule 457(o) based on an estimate of the proposed maximum aggregate offering price of the securities registered hereunder to be sold by the Registrant.

The Registrant hereby amends this registration statement on such date or dates as may be necessary to delay its effective date until the Registrant shall file a further amendment which specifically states that this registration statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933 or until the registration statement shall become effective on such date as the Commission, acting pursuant to such Section 8(a), may determine.

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The information in this preliminary prospectus is not complete and may be changed. We may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. This preliminary prospectus is not an offer to sell these securities and it is not soliciting an offer to buy these securities in any jurisdiction where the offer or sale is not permitted.

Subject to Completion
Preliminary Prospectus dated September 4, 2012

P R O S P E C T U S

Shares

Common Stock

This is Intercept Pharmaceuticals initial public offering. We are selling shares of our common stock.

We expect the initial offering price to be between $ and $ per share. Currently, no public market exists for the shares. After pricing of the offering, we expect that the shares will trade on the Nasdaq Global Market under the symbol ICPT.

We are an emerging growth company under federal securities laws and are subject to reduced public company disclosure standards. See Prospectus Summary Implications of Being an Emerging Growth Company.

Investing in our common stock involves risks that are described in the Risk Factors section beginning on page 10 of this prospectus.

	Per Share	Total
Public offering price	$	$
Underwriting discount	$	$
Proceeds, before expenses, to us	$	$

The underwriters may also exercise their option to purchase up to an additional shares from us, at the public offering price, less the underwriting discount, for 30 days after the date of this prospectus.

Certain of our existing stockholders and their affiliated entities have indicated an interest in purchasing up to approximately $ million in shares of our common stock in this offering at the initial public offering price. However, because indications of interest are not binding agreements or commitments to purchase, the underwriters could determine to sell more, less or no shares to any of these existing stockholders and any of these existing stockholders could determine to purchase more, less or no shares in this offering.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

The shares will be ready for delivery on or about , 2012.

BofA Merrill Lynch

BMO Capital Markets

Needham & Company

Wedbush PacGrow Life Sciences

ThinkEquity LLC

The date of this prospectus is , 2012.

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You should rely only on the information contained in this prospectus. We have not authorized anyone to provide you with information different from that contained in this prospectus. We are offering to sell, and seeking offers to buy, shares of common stock only in jurisdictions where offers and sales are permitted. The information contained in this prospectus is accurate only as of the date of this prospectus, regardless of the time of delivery of this prospectus or of any sale of common stock.

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PROSPECTUS SUMMARY

This summary provides an overview of selected information contained elsewhere in this prospectus and does not contain all of the information you should consider before investing in our common stock. You should carefully read this prospectus and the registration statement of which this prospectus is a part in their entirety before investing in our common stock, including the information discussed under Risk Factors and our consolidated financial statements and notes thereto that appear elsewhere in this prospectus. Unless otherwise indicated herein, the terms we, our, us, or the Company refer to Intercept Pharmaceuticals, Inc.

Overview

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

Our Lead Product Candidate

Our lead product candidate, obeticholic acid, or OCA, is a bile acid analog and first-in-class agonist of the farnesoid X receptor, or FXR, which we believe has broad liver-protective properties. We are developing OCA initially for the second line treatment of primary biliary cirrhosis, or PBC. PBC is a chronic autoimmune liver disease that, if inadequately treated, may eventually lead to cirrhosis, liver failure and death. We are conducting a Phase 3 clinical trial of OCA in PBC, which we call the POISE trial, that we anticipate will serve as the basis for seeking regulatory approval in the United States and Europe. We currently expect results from the trial to be available by mid-2014. OCA has received orphan drug designation in the United States and Europe for the treatment of PBC.

We own worldwide rights to OCA outside of Japan and China, where we have exclusively licensed the compound to Dainippon Sumitomo Pharma, or DSP, and granted it an option to exclusively license OCA in certain other Asian countries. Patents covering the composition of matter for OCA expire in 2022, before any patent term adjustments or patent term extensions. Our current plan is to commercialize OCA in the United States and Europe ourselves for the treatment of PBC by targeting a limited and focused group of specialist physicians.

The liver performs many essential functions that are crucial for survival, including the regulation of bile acid metabolism. A critical function of bile acids is to facilitate the absorption of dietary cholesterol and other nutrients by acting as natural detergent-like emulsifying agents in the intestine. In the past decade, we have learned that bile acids are also complex signaling molecules that integrate metabolic, immune and inflammatory pathways involved in the healthy functioning of various tissues and organs. The biological effects of bile acids are mediated through dedicated receptors such as FXR, which regulates bile acid synthesis and clearance from the liver, thereby preventing excessive bile acid build-up in the liver, which may be toxic. In addition, bile acid activation of FXR induces anti-fibrotic, anti-inflammatory and other mechanisms that are necessary for the normal regeneration of the liver. We believe this makes FXR an attractive drug target in a broad spectrum of chronic liver diseases. Similar FXR-mediated protective mechanisms in other organs exposed to bile acids also make it a potential target for the treatment of a number of intestinal, kidney and other diseases.

PBC is a rare liver disease that primarily results from autoimmune destruction of the bile ducts that transport bile acids out of the liver. The disease causes a toxic build-up of bile acids in the liver, resulting in progressive liver damage

marked by chronic inflammation and fibrosis, or scarring. 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.

The only approved drug for the treatment of PBC is ursodeoxycholic acid, which is available generically as ursodiol. Ursodiol is itself a bile acid that is present in small quantities in humans, and is the least detergent of the various types of bile acids that make up the bile pool. Its primary mechanism of action at

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therapeutic doses is to dilute more detergent bile acids, but it has no known pharmacological effects mediated by FXR or other bile acid receptors. Although ursodiol is the standard of care, studies have shown that up to 50% of PBC patients fail to respond adequately to treatment, meaning that they continue to be at significant risk of progressing to liver failure even with treatment. The options for end-stage PBC patients who fail to respond to ursodiol are limited, and include liver transplant, which is associated with significant complications and costs. Patients typically need to take approximately one gram of ursodiol daily in divided doses, which we believe presents a compliance challenge for some patients. Given this issue, coupled with ursodiol s limited efficacy in up to 50% of PBC patients, we believe that there is a significant unmet need for a novel second line therapy in PBC. We believe that OCA has the potential to provide significant benefits in the treatment of PBC, including efficacy, pharmacological activity and ease of use.

According to industry data, there are approximately 300,000 people with PBC in developed countries, of whom we believe approximately 60,000 have been diagnosed and are on ursodiol therapy. Based on this estimate, we believe there are up to 30,000 PBC patients who may currently be eligible for treatment with OCA. With increasing identification of PBC through routine liver function testing in primary care, we believe that there may be significantly more patients who will potentially be eligible for, and be interested in, receiving a new therapy if it becomes available on the market.

We have previously completed two randomized, placebo-controlled Phase 2 trials with OCA in PBC patients, one with OCA in combination with ursodiol and one with OCA as monotherapy. The results demonstrated that over a 12-week period single daily doses of OCA at the lowest dose of 10 milligrams (mg) met the primary endpoint in both Phase 2 trials, producing statistically significant reductions in ALP levels of greater than 20%. We consider reductions in ALP levels of greater than 10% to be a clinically meaningful improvement. Pruritus, or itching, a very common symptom in PBC patients, was the most common adverse event reported in our Phase 2 trials, with severity increasing with dose.

Our Phase 3 POISE trial has been designed to study the safety and efficacy of OCA in patients with an inadequate therapeutic response to ursodiol or who are unable to tolerate ursodiol. The primary endpoint of the 12-month double-blind portion of the POISE trial is the achievement of both an ALP level of less than 1.67 times upper limit normal, or ULN, and a minimum 15% reduction in ALP level from baseline, together with a normal bilirubin level, as compared to placebo. Patients with ALP and bilirubin levels within these thresholds have been shown in long-term studies to be at significantly lower risk of progressing to liver transplant and death.

We are advancing a once daily 10 mg dose of OCA in the POISE trial as our potential approvable dose. We recently completed an intention to treat analysis for the 10 mg dose groups in our two Phase 2 trials that was limited to those patients who would have met the POISE trial entry criteria. This analysis demonstrated that after 12 weeks of treatment approximately 40% to 45% of OCA-treated patients would have met the POISE trial primary endpoint, as compared to 5% to 9% of the placebo-treated patients. In addition, 80% of OCA-treated patients across our Phase 2 trials had a reduction in ALP levels of at least 10%, as compared to 13% of placebo-treated patients.

If the POISE trial is successful, we intend to submit a New Drug Application, or NDA, to the U.S. Food and Drug Administration, or FDA, for approval of OCA for the treatment of PBC in the United States and a Marketing Authorization Application, or MAA, to the European Medicines Agency, or EMA, for approval in Europe. Based on written scientific advice from the EMA, we believe that the EMA will accept our current clinical program as the basis for considering approval of OCA for PBC. With respect to the FDA, we intend to request that the POISE trial primary endpoint be accepted as a basis for approval of OCA under the FDA s accelerated approval regulation that enables the use of a surrogate endpoint reasonably likely to predict clinical benefit. If the FDA agrees to consider the potential approval of OCA in accordance with its accelerated approval regulation based on the POISE trial results, we will likely have to conduct a Phase 3 clinical outcomes trial to confirm the clinical benefit predicted by the biochemical

therapeutic response. This Phase 3 clinical outcomes trial would have to be substantially underway at the time of the NDA submission and would be completed after accelerated approval. We are in discussions with the FDA about the details of such a clinical trial and are planning to initiate it as early as the second half of 2013.

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A number of published clinical studies have demonstrated that, as a measure of therapeutic response, lower levels of ALP, on its own 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 acceptance of our POISE trial primary endpoint as a basis for approval will be the result of additional analysis of the already available PBC clinical outcomes data. We are sponsoring an independent study involving more than ten leading PBC centers in North America and Europe that are pooling their long-term patient data, anticipated to be from at least 4,000 patients, in order to further substantiate that our POISE trial primary endpoint is predictive of clinical benefit. We anticipate these results will be available in 2013 and will support what we believe is an emerging consensus among PBC opinion leaders concerning the clinical utility of our selected endpoint.

Additional Pipeline Opportunities Beyond OCA in PBC

In addition to PBC, we are pursuing other indications in our OCA development program, including portal hypertension, nonalcoholic steatohepatitis, or NASH, and bile acid diarrhea. The pipeline chart below shows the current stage of development of OCA for these indications, as well as the preclinical programs for our other product candidates.

* An agonist is a substance that binds to a receptor of a cell and triggers a response by that cell.

We are currently conducting an open label Phase 2a trial of OCA in patients with portal hypertension, and we anticipate receiving results from the 10 mg dose group of this trial by the end of 2012. There are currently no approved therapies for the treatment of portal hypertension, although beta blockers are commonly used to treat patients. In addition, OCA is currently being tested in a Phase 2b trial for the treatment of NASH, sponsored by the U.S. National Institute of Diabetes and Digestive and Kidney Diseases, or NIDDK, in collaboration with us. Based on the interim analysis that was completed in June 2012, the NIDDK decided to continue this Phase 2b trial and we anticipate that final results will be available in late 2014. There are currently no approved therapies for the treatment of NASH. In addition, investigators at the Imperial College of London initiated enrollment in July 2012 in an open label Phase 2a trial of OCA as a treatment for bile acid diarrhea.

By virtue of our patent portfolio and the proprietary knowhow of our employees and our collaborators at the University of Perugia, we believe that we hold a leading position in the bile acid chemistry therapeutic field. Through a longstanding exclusive collaboration with Professor Roberto Pellicciari, Ph.D., one of our co-founders, and certain scientists in the medicinal chemistry group at the University of Perugia, we have gained the capability to rationally design compounds that bind selectively and potently to FXR and other bile

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acid receptors. Starting with OCA, which was invented by Professor Pellicciari and, together with its underlying patents, was assigned to us under our agreements with him and the University of Perugia, our collaboration has resulted in a pipeline of bile acid analogs in addition to OCA, which target both FXR and a second dedicated bile acid receptor called TGR5, a target of interest for the treatment of type 2 diabetes and associated metabolic diseases. We intend to continue developing these and other product candidates as we advance our pipeline, in some cases subject to the procurement of additional funding or through strategic collaborations.

Our Strategy

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

complete the development of OCA for its lead indication, PBC;
obtain regulatory 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 in other orphan and more prevalent liver and other diseases; and
advance the earlier stage product candidates in our pipeline.

We may enter into strategic collaborations to implement our strategy.

Risks Relating to Our Business

We are a development stage biopharmaceutical company, and our business and ability to execute our business strategy are subject to a number of risks of which you should be aware before you decide to buy our common stock. In particular, you should consider the following risks, which are discussed more fully in the section entitled Risk Factors :

we have never been profitable, have no products approved for commercial sale and to date have not generated any revenue from product sales;
we will require substantial additional funding beyond this contemplated offering to complete the development and commercialization of OCA and to continue to advance the development of our other product candidates, and such funding may not be available on acceptable terms or at all;
OCA and/or our other product candidates may not receive regulatory approval in a timely manner or at all;
the FDA may not agree to our proposed surrogate endpoint for accelerated approval of OCA for the treatment of PBC, in which case we would need to complete an additional Phase 3 trial in order to seek approval in the United States;
we may be subject to delays in our clinical trials, which could result in increased costs and delays or limit our ability to obtain regulatory approval for our product candidates;
because the results of earlier studies and clinical trials of our product candidates may not be predictive of future clinical trial results, our product candidates may not have favorable results in future clinical trials, which would delay or limit their future development;
we have never commercialized any of our product candidates and our products, even if approved, may not be accepted by healthcare providers or healthcare payors;
the failure of our collaborators to perform their obligations under our collaboration agreements may delay or otherwise harm the development and commercialization of our product candidates; and
we may be unable to maintain and protect our intellectual property assets, which could impair the advancement of our pipeline and commercial opportunities.

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Implications of Being an Emerging Growth Company

We qualify as an emerging growth company as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. As an emerging growth company, we may take advantage of specified reduced disclosure and other requirements that are otherwise applicable generally to public companies. These provisions include:

only two years of audited financial statements in addition to any required unaudited interim financial statements with correspondingly reduced Management s Discussion and Analysis of Financial Condition and Results of Operations disclosure;

reduced disclosure about our executive compensation arrangements;

no non-binding advisory votes on executive compensation or golden parachute arrangements; and

exemption from the auditor attestation requirement in the assessment of our internal control over financial reporting.

We may take advantage of these exemptions for up to five years or such earlier time that we are no longer an emerging growth company. We would cease to be an emerging growth company on the date that is the earliest of (i) the last day of the fiscal year in which we have total annual gross revenues of $1 billion or more; (ii) the last day of our fiscal year following the fifth anniversary of the date of the completion of this offering; (iii) the date on which we have issued more than $1 billion in nonconvertible debt during the previous three years; or (iv) the date on which we are deemed to be a large accelerated filer under the rules of the Securities and Exchange Commission. We may choose to take advantage of some but not all of these exemptions. We have taken advantage of reduced reporting requirements in this prospectus. Accordingly, the information contained herein may be different than the information you receive from other public companies in which you hold stock.

Corporate Information

We were incorporated in the State of Delaware on September 4, 2002. Our principal executive offices are located at 18 Desbrosses Street, New York, NY 10013, and our telephone number is (646) 747-1000. We also have an office in San Diego, CA. Our website address is *www.interceptpharma.com*. The information contained on, or that can be accessed through, our website is not part of this prospectus.

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THE OFFERING

Common stock offered by us
shares

Common stock to be outstanding after this offering
shares

Over-allotment option
We have granted the underwriters an option for a period of up to 30 days to purchase up to additional shares of common stock at the initial public offering price.

Use of proceeds
We estimate that the net proceeds from this offering will be approximately $ million, or approximately $ million if the underwriters exercise their over-allotment option in full, at an assumed initial public offering price of $ per share, the midpoint of the range set forth on the cover page of this prospectus, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us. We intend to use substantially all of the net proceeds from this offering to fund (i) the continued clinical development of OCA in PBC, including our Phase 3 POISE trial and other studies and work necessary for anticipated FDA and EMA filings; (ii) the continuation of the long-term safety extension portion of our POISE trial and the Phase 3 clinical outcomes trial after the anticipated FDA and EMA filings; (iii) certain pre-commercialization activities of OCA for PBC; (iv) further preclinical development work on INT-767 and, if warranted, Phase 1 clinical trials of INT-767; and (v) if warranted, initiation of a Phase 2 clinical trial for an additional indication for OCA, such as portal hypertension. Any remaining amounts will be used for general corporate purposes, general and administrative expenses, capital expenditures, working capital and prosecution and maintenance of our intellectual property. See Use of Proceeds for a more complete description of the intended use of proceeds from this offering.

Risk factors
You should read the Risk Factors section of this prospectus beginning on page 10 for a discussion of factors to consider carefully before deciding to invest in shares of our common stock.

Proposed Nasdaq Global Market symbol
ICPT

Certain of our existing stockholders and their affiliated entities have indicated an interest in purchasing up to approximately $ million in shares of our common stock in this offering at the initial public offering price. However, because indications of interest are not binding agreements or commitments to purchase, the underwriters could determine to sell more, less or no shares to any of these existing stockholders and any of these existing stockholders could determine to purchase more, less or no shares in this offering. Any shares purchased by these existing stockholders will be subject to lock-up restrictions described in Shares Eligible for Future Sale.

The number of shares of common stock to be outstanding after this offering is based on an aggregate of 62,016,196 shares, consisting of (i) 19,238,418 shares of common stock outstanding on June 30, 2012, (ii) 27,777,778 shares of common stock into which all of our preferred stock outstanding as of June 30, 2012 will be converted upon the completion of this offering and (iii) 15,000,000 shares of common stock into which the shares of preferred stock issued on August 9, 2012 will be converted upon the completion of this offering. The number of shares of our common stock outstanding immediately after this offering excludes:

7,565,535 shares of common stock issuable upon exercise of outstanding options as of June 30, 2012, at a weighted average exercise price of $1.55 per share, of which 5,627,135 shares are vested as of such date;

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137,500 shares of common stock issuable upon exercise of options granted on July 31, 2012 under our 2003 Stock Incentive Plan, as amended, or 2003 Plan, at an exercise price of $1.61 per share, to our non-employee directors as of January 1, 2012 for service during fiscal year 2012;

3,211,554 shares of our common stock reserved for future issuance under our 2003 Plan; provided, however, that (i) immediately upon completion of this offering, our 2003 Plan will terminate so that no further awards may be granted under the 2003 Plan; (ii) all the shares of common stock reserved for future issuance under our 2003 Plan will be added to the shares to be reserved under our 2012 Equity Incentive Plan, or 2012 Plan, upon its effectiveness at the completion of this offering; and (iii) all or some of these shares added to the 2012 Plan may be granted under the 2012 Plan to our employees and directors shortly after the completion of this offering;

shares of our common stock reserved for future issuance (including the 3,211,554 shares of common stock to be added from the 2003 Plan) under our 2012 Plan, which will become effective in connection with this offering; and

7,122,889 shares of common stock issuable upon the exercise of warrants outstanding as of June 30, 2012, at a weighted average exercise price of $1.62 per share.

Except as otherwise indicated, all information in this prospectus:

gives effect to the conversion of all outstanding shares of our preferred stock into an aggregate of 42,777,778 shares of our common stock upon the completion of this offering, including the conversion of our Series A, Series B and Series C preferred stock into 13,888,889 shares, 13,888,889 shares and 15,000,000 shares of common stock, respectively;

reflects the 1-for- reverse stock split of our common stock to be effected prior to the completion of this offering;

gives effect to our restated certificate of incorporation and our restated by-laws to be adopted in connection with the completion of this offering; and

assumes no exercise by the underwriters of their option to purchase additional shares of our common stock to cover over-allotments.

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SUMMARY CONSOLIDATED FINANCIAL DATA

The summary consolidated financial data presented below for the years ended December 31, 2010 and 2011 are derived from our audited consolidated financial statements included elsewhere in this prospectus. The summary consolidated financial data presented below for the six months ended June 30, 2011 and 2012, and for the period from inception (September 4, 2002) to June 30, 2012, as we are a development stage company, are derived from our unaudited financial statements included elsewhere in this prospectus. The unaudited consolidated financial statements have been prepared on the same basis as our audited consolidated financial statements and include, in the opinion of management, all adjustments necessary for a fair presentation of the financial information set forth in those statements.

Our historical results are not necessarily indicative of future operating results. You should read this summary consolidated financial data in conjunction with the sections entitled Risk Factors, Capitalization, Selected Financial Data and Management s Discussion and Analysis of Financial Condition and Results of Operations and our consolidated financial statements and related notes, all included elsewhere in this prospectus.

	Years Ended December 31,		Six Months Ended June 30,		Period From September 4, 2002 (Inception) Through June 30, 2012
	2010	2011	2011	2012	
	(In thousands, except share and per share amounts)				
			(Unaudited)		(Unaudited)
Statement of Operations Data:					
Licensing revenues	$	$1,805	$405	$1,518	$3,323
Operating expenses:					
Research and development	12,710	11,426	4,751	8,078	63,330
General and administrative	3,644	4,209	2,020	2,003	26,424
Total operating expenses	16,354	15,635	6,771	10,081	89,754
Loss from operations	(16,354)	(13,830)	(6,366)	(8,563)	(86,431)
Total other income (expense), net	1,266	1,093	115	797	4,125
Net loss	$(15,088)	$(12,737)	$(6,251)	$(7,766)	$(82,306)
Dividend on preferred stock, not declared	(2,901)	(3,000)	(1,500)	(1,500)	(9,814)
Net loss attributable to common stockholders	$(17,989)	$(15,737)	$(7,751)	$(9,266)	$(92,120)
Net loss per share, basic and diluted	$(0.94)	$(0.82)	$(0.40)	$(0.48)	
Weighted average shares outstanding, basic and diluted	19,238,418	19,238,418	19,238,418	19,238,418	
Pro forma information[1]					
Pro forma net loss attributable to common stockholders		$(12,737)		$(7,766)	

Pro forma net loss per share, basic and diluted (unaudited)	$(0.21)	$(0.13)

(1) Pro forma net loss and pro forma net loss per share, basic and diluted have been calculated after giving effect to (i) the conversion of our preferred stock outstanding as of such dates into an aggregate of 27,777,778 shares of common stock upon the completion of this offering and (ii) the conversion of our shares of preferred stock issued on August 9, 2012 into an aggregate of 15,000,000 shares of common stock upon the completion of this offering. See *Unaudited Pro Forma Information* and *Net Loss per Share and Unaudited Pro Forma Net Loss per Share* in note 2 to our consolidated financial statements, which are included elsewhere in this prospectus.

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The following summary unaudited balance sheet data as of June 30, 2012 is presented:

on an actual basis;

on a pro forma basis after giving effect to (i) the conversion of our preferred stock outstanding as of such date into an aggregate of 27,777,778 shares of common stock upon the completion of this offering, (ii) the conversion of our shares of preferred stock issued on August 9, 2012 into an aggregate of 15,000,000 shares of common stock upon the completion of this offering, (iii) the receipt of $29.8 million of net proceeds from the issuance of preferred stock on August 9, 2012, and (iv) and the reclassification of certain warrants with registration rights upon the completion of this offering from stockholders equity to warrant liability; and

on a pro forma as adjusted basis to give further effect to our sale of shares of common stock in this offering at an assumed initial public offering price of $ per share, the midpoint of the range listed on the cover page of this prospectus, after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

The summary unaudited pro forma as adjusted balance sheet is for informational purposes only and does not purport to indicate balance sheet information as of any future date.

	As of June 30, 2012		
	Actual	Pro Forma	Pro Forma As Adjusted[1]
	(In thousands) (Unaudited)		
Balance Sheet Data:			
Cash and cash equivalents	$ 9,947	$ 39,747	
Working capital	6,104	35,904	
Total assets	12,145	41,945	
Accounts payable, accrued expenses and other liabilities	3,578	3,578	
Warrant liability	4,856	5,280	
Deferred revenue	13,091	13,091	
Common and preferred stock	47	62	
Additional paid-in capital	72,879	102,241	
Accumulated deficit during development stage	(82,306)	(82,306)	
Total stockholders equity (deficit)	(9,380)	19,997	

(1) Each $1.00 increase (decrease) in the public offering price per share would increase (decrease) each of cash and cash equivalents, total assets and total stockholders equity by approximately $, assuming that the number of shares we are offering, as set forth on the cover page of this prospectus, remains the same and that the underwriters do not exercise their over-allotment option. Depending on market conditions and other considerations at the time we price this offering, we may sell a greater or lesser number of shares than the number set forth on the cover page of this prospectus. An increase (decrease) of 1,000,000 in the number of shares we are offering would increase (decrease) each of cash and cash equivalents, total assets and total stockholders equity by approximately $, assuming the public offering price per share remains the same. An increase of 1,000,000 in the number of shares we are offering, together with a $1.00 increase in the public offering price per share, would increase each of cash and cash equivalents, total assets and total stockholders equity by approximately $. A decrease of 1,000,000 in the number of shares we are offering, together with a $1.00 decrease in the public offering price per share, would decrease each of cash and cash equivalents, total assets and total stockholders equity by approximately $.

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RISK FACTORS

Investing in our common stock involves a high degree of risk. You should carefully consider the following risk factors, as well as the other information in this prospectus, including our financial statements and related notes, before deciding whether to invest in shares of our common stock. The occurrence of any of the adverse developments described in the following risk factors could materially and adversely harm our business, financial condition, results of operations or prospects. In that case, the trading price of our common stock could decline, and you may lose all or part of your investment.

Risks Relating to Our Financial Position and Need for Additional Capital

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

We have never been profitable and do not expect to be profitable in the foreseeable future. We have not yet submitted any product candidates for approval by regulatory authorities in the United States or elsewhere for our lead indication, primary biliary cirrhosis, or PBC, or any other indication. We have incurred net losses in each year since our inception, including net losses of $15.1 million and $12.7 million for the years ended December 31, 2010 and 2011, respectively, and we incurred a net loss of $7.8 million for the six months ended June 30, 2012. We had an accumulated deficit of $82.3 million as of June 30, 2012. Our working capital and cash and cash equivalents as of June 30, 2012 were $6.1 million and $9.9 million, respectively, and, after giving effect to the receipt of $29.8 million of net proceeds from the issuance of preferred stock on August 9, 2012, our working capital and cash equivalents as of June 30, 2012 would have been $35.9 million and $39.7 million, respectively.

To date, we have devoted most of our financial resources to our corporate overhead and research and development, including our drug discovery research, preclinical development activities and clinical trials. We have not generated any revenues from product sales. We expect to continue to incur losses for the foreseeable future, and we expect these losses to increase as we continue our development of, and seek regulatory approvals for, obeticholic acid, or OCA, which is our lead product candidate, and our other product candidates, prepare for and begin the commercialization of any approved products, and add infrastructure and personnel to support our product development efforts and operations as a public company. We anticipate that any such losses could be significant for the next several years as we complete our Phase 3 clinical trial of OCA in PBC, which we call the POISE trial, and related activities required for regulatory approval of OCA and continue pursuing additional indications for OCA in clinical trials. If OCA or any of our other product candidates fails in clinical trials or does not gain regulatory approval, or if our product candidates do not achieve market acceptance, we may never become profitable. As a result of the foregoing, we expect to continue to experience net losses and negative cash flows for the foreseeable future. These net losses and negative cash flows have had, and will continue to have, an adverse effect on our stockholders equity and working capital.

Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able to achieve profitability. In addition, our expenses could increase if we are required by the U.S. Food and Drug Administration, or

FDA, or the European Medicines Agency, or EMA, to perform studies or trials in addition to those currently expected, or if there are any delays in completing our clinical trials or the development of any of our product candidates. The amount of future net losses will depend, in part, on the rate of future growth of our expenses and our ability to generate revenues.

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

We are currently advancing OCA through clinical development for multiple indications and other product candidates through preclinical development. Developing pharmaceutical products, including conducting preclinical studies and clinical trials, is expensive. We will require substantial additional future capital in order to complete clinical development and commercialize OCA, and to conduct the research and development and clinical and regulatory activities necessary to bring other product candidates to market. For instance, to

We have never been profitable. Currently, we have no products approved forcommercial sale, and to date, we have

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complete the work necessary to file a New Drug Application, or NDA, and a Marketing Authorization Application, or MAA, for OCA as a treatment for PBC, which is currently anticipated to occur in 2014, we estimate that our ongoing Phase 3 POISE trial, and our planned clinical and preclinical studies, as well as other work needed to submit OCA for the treatment of PBC for regulatory approval in the United States, Europe and other countries, will cost approximately $40.0 million, including the internal resources needed to manage the program. If the FDA or EMA requires that we perform additional preclinical studies or clinical trials, our expenses would further increase beyond what we currently expect and the anticipated timing of any potential NDA or MAA would likely be delayed.

We intend to use substantially all of the net proceeds from this offering to fund (i) the continued clinical development of OCA in PBC, including our Phase 3 POISE trial and other studies and work necessary for anticipated FDA and EMA filings; (ii) the continuation of the long-term safety extension portion of our POISE trial and the Phase 3 clinical outcomes trial after the anticipated FDA and EMA filings; (iii) certain pre-commercialization activities of OCA for PBC; (iv) further preclinical development work on INT-767 and, if warranted, potential Phase 1 clinical trials of INT-767; and (v) if warranted, initiation of a Phase 2 clinical trial for an additional indication for OCA, such as portal hypertension. Any remaining amounts will be used for general corporate purposes, general and administrative expenses, capital expenditures, working capital and prosecution and maintenance of our intellectual property. As such, the expected net proceeds from this offering will not be sufficient to complete advanced clinical development of any of our product candidates other than OCA for PBC. Accordingly, we will continue to require substantial additional capital beyond the expected proceeds of this offering to continue our clinical development and commercialization activities. Because successful development of our product candidates is uncertain, we are unable to estimate the actual funds we will require to complete research and development and commercialize our products under development.

The amount and timing of our future funding requirements will depend on many factors, including but not limited to:

the progress, costs, results of and timing of our Phase 3 POISE trial of OCA for the treatment of PBC, and the clinical development of OCA for other potential indications;

the willingness of the FDA and EMA to accept our POISE trial, as well as our other completed and planned clinical and preclinical studies and other work, as the basis for review and approval of OCA for PBC;

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

the number and characteristics of product candidates that we pursue, including our product candidates in preclinical development;

the ability of our product candidates to progress through clinical development successfully;

our need to expand our research and development activities;

the costs associated with securing and establishing commercialization and manufacturing capabilities;

market acceptance of our product candidates;

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

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

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

the effect of competing technological and market developments;

We will require substantial additional funding, which may not be available tous on acceptable terms, or at all, and, if

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our need to implement additional internal systems and infrastructure, including financial and reporting systems; and

the economic and other terms, timing of and success of our existing licensing arrangements and any collaboration, licensing or other arrangements into which we may enter in the future.

Some of these factors are outside of our control. If we successfully complete this offering, based upon our currently expected level of operating expenditures, we believe that we will be able to fund our operations through 2015. This period could be shortened if there are any significant increases in planned spending on development programs or more rapid progress of development programs than anticipated. We do not expect our existing capital resources, including $29.8 million of net proceeds received on August 9, 2012 upon the issuance of our Series C preferred stock, along with the intended net proceeds from this offering, to be sufficient to enable us to complete the commercialization of OCA, if approved, or to initiate any clinical trials or additional development work for any of our other product candidates, other than as described above. See also Use of Proceeds. Accordingly, we expect that we will need to raise additional funds in the future.

We may seek additional funding through a combination of equity offerings, debt financings, government or other third-party funding, marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements. Additional funding may not be available to us on acceptable terms or at all. In addition, the terms of any financing may adversely affect the holdings or the rights of our stockholders. In addition, the issuance of additional shares by us, or the possibility of such issuance, may cause the market price of our shares to decline.

If we are unable to obtain funding on a timely basis, we may be required to significantly curtail one or more of our research or development programs. We also could be required to seek funds through arrangements with collaborative partners or otherwise that may require us to relinquish rights to some of our technologies or product candidates or otherwise agree to terms unfavorable to us.

Our revenues to date have been generated through our collaboration agreements and we may not receive any additional revenues under such agreements.

To date, our sources of revenue have been the up-front payments received under our collaboration and license agreements with Dainippon Sumitomo Pharma Co. Ltd., or DSP, and Les Laboratoires Servier and Institut de Recherches Servier, which are collectively referred to as Servier. Additional payments under each of the DSP and Servier agreements are based on the achievement of various research, development, regulatory and commercial sales milestones and royalty payments based on the sales of the products covered by such agreements. Future payments from DSP and Servier under their respective collaboration and license agreements are uncertain because DSP or Servier, as the case may be, may choose not to continue research or development of activities for the product candidates under license in their licensed territory, the product candidates may not be approved for the proposed indications or, even if any product candidate is approved for one or more indications, it may not be commercially successful. If we are unable to develop and commercialize one or more of our product candidates, either alone or with collaborators, or if revenues from any such collaboration product candidate that receives marketing approval are insufficient, we will not achieve profitability. Even if we achieve profitability, we may not be able to sustain or increase profitability.

We have a limited operating history and we expect a number of factors to cause our operating results to fluctuate on a quarterly and annual basis, which may make it difficult to predict our future performance.

We are a development stage biopharmaceutical company with a limited operating history. Our operations to date have been limited to developing our technology and undertaking preclinical studies and clinical trials of our product candidates. We have not yet obtained regulatory approvals for any of our product candidates. Consequently, any predictions made about our future success or viability may not be as accurate as they could be if we had a longer operating history or approved products on the market. Our financial condition and operating results have varied significantly in the past and are expected to continue to significantly fluctuate from quarter-to-quarter or year-to-year due to a variety of factors, many of which are beyond our control. Factors relating to our business that may contribute to these fluctuations include:

We have a limited operating history and we expect a number of factors tocause our operating results to fluctuate on

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any delays in regulatory review and approval of our product candidates in clinical development, including our ability to receive approval from the FDA and the EMA for OCA for the treatment of PBC based on our Phase 3 POISE trial, and our other completed and planned clinical and preclinical studies and other work, as the basis for review and approval of OCA for PBC;

delays in the commencement, enrollment and timing of clinical trials;

difficulties in identifying and treating patients suffering from our target indications, and PBC in particular, which is considered to be a rare disease;

the success of our clinical trials through all phases of clinical development, including our POISE trial of OCA for the treatment of PBC;

potential side effects of our product candidates that could delay or prevent approval or cause an approved drug to be taken off the market;

our ability to obtain additional funding to develop our product candidates;

our ability to identify and develop additional product candidates;

market acceptance of our product candidates;

our ability to establish an effective sales and marketing infrastructure directly or through collaborations with third parties;

competition from existing products or new products that may emerge;

the ability of patients or healthcare providers to obtain coverage or sufficient reimbursement for our products;

our ability to adhere to clinical study requirements directly or with third parties such as contract research organizations, or CROs;

our dependency on third-party manufacturers to manufacture our products and key ingredients;

our ability to establish or maintain collaborations, licensing or other arrangements;

the costs to us, and our ability and our third-party collaborators ability to obtain, maintain and protect our intellectual property rights;

costs related to and outcomes of potential intellectual property litigation;

our ability to adequately support future growth;

our ability to attract and retain key personnel to manage our business effectively;

our ability to build our finance infrastructure and improve our accounting systems and controls;

potential product liability claims;

potential liabilities associated with hazardous materials; and

our ability to obtain and maintain adequate insurance coverage.

In addition, our financial results may vary due to fluctuations in our warrant liability. Accordingly, the results of any quarterly or annual periods should not be relied upon as indications of future operating performance.

Our recurring losses from operations may raise substantial doubt regarding our ability to continue as a going concern.

Our recurring losses from operations may raise substantial doubt about our ability to continue as a going concern. If in the future, our independent registered public accounting firm were to include an explanatory paragraph in its report on our consolidated financial statements stating there is substantial doubt about our ability to continue as a going concern, such an opinion could materially limit our ability to raise additional funds through the issuance of new debt or equity securities or otherwise. There is no assurance that sufficient

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financing will be available when needed to allow us to continue as a going concern. The perception that we may not be able to continue as a going concern may cause others to choose not to deal with us due to concerns about our ability to meet our contractual obligations.

Risks Relating to Regulatory Review and Approval of Our Product Candidates

We cannot be certain that OCA or any of our other product candidates will receive regulatory approval, and without regulatory approval we will not be able to market our product candidates.

We are initially developing OCA for the treatment of patients with PBC, portal hypertension, nonalcoholic steatohepatitis, or NASH, and bile acid diarrhea, and are also consulting with investigators to develop protocols for other indications. Our business currently depends entirely on the successful development and commercialization of OCA. Our ability to generate revenue related to product sales, if ever, will depend on the successful development and regulatory approval of OCA for the treatment of PBC and other indications and our other product candidates.

We currently have no products approved for sale and we cannot guarantee that we will ever have marketable products. The development of a product candidate and issues relating to its approval and marketing are subject to extensive regulation by the FDA in the United States, the EMA in Europe and regulatory authorities in other countries, with regulations differing from country to country. We are not permitted to market our product candidates in the United States or Europe until we receive approval of a NDA from the FDA or a MAA from the EMA, respectively. We have not submitted any marketing applications for any of our product candidates.

NDAs and MAAs must include extensive preclinical and clinical data and supporting information to establish the product candidate s safety and effectiveness for each desired indication. NDAs and MAAs must also include significant information regarding the chemistry, manufacturing and controls for the product. Obtaining approval of a NDA or a MAA is a lengthy, expensive and uncertain process, and we may not be successful in obtaining approval. The FDA and the EMA review processes can take years to complete and approval is never guaranteed. If we submit a NDA to the FDA, the FDA must decide whether to accept or reject the submission for filing. We cannot be certain that any submissions will be accepted for filing and review by the FDA. Regulators of other jurisdictions, such as the EMA, have their own procedures for approval of product candidates. Even if a product is approved, the FDA or the EMA, as the case may be, may limit the indications for which the product may be marketed, require extensive warnings on the product labeling or require expensive and time-consuming clinical trials or reporting as conditions of approval. Regulatory authorities in countries outside of the United States and Europe also have requirements for approval of drug candidates with which we must comply prior to marketing in those countries. Obtaining regulatory approval for marketing of a product candidate in one country does not ensure that we will be able to obtain regulatory approval in any other country. In addition, delays in approvals or rejections of marketing applications in the United States, Europe or other countries may be based upon many factors, including regulatory requests for additional analyses, reports, data, preclinical studies and clinical trials, regulatory questions regarding different interpretations of data and results, changes in regulatory policy during the period of product development and the emergence of new information regarding our product candidates or other products. Also, regulatory approval for any of our product candidates may be withdrawn.

We have completed three Phase 2 trials for OCA: two in patients with PBC and one in patients with type 2 diabetes with co-morbid nonalcoholic fatty liver disease. We are currently in the process of enrolling patients into our Phase 3 POISE trial. Before we submit a NDA to the FDA or a MAA to the EMA for OCA for the treatment of patients with PBC, we must successfully complete this trial. In addition, we must complete other preclinical and clinical studies, such as a Phase 1 clinical trial in healthy volunteers to evaluate the effect of OCA on the heart s electrical cycle, known as the QT interval, studies to evaluate the interaction of OCA with other drugs and two-year, two-species carcinogenicity studies. We cannot predict whether our future trials and studies will be successful or whether regulators will agree with our conclusions regarding the preclinical studies and clinical trials we have conducted to date.

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If we are unable to obtain approval from the FDA, the EMA or other regulatory agencies for OCA and our other product candidates, or if, subsequent to approval, we are unable to successfully commercialize OCA or our other product candidates, we will not be able to generate sufficient revenue to become profitable or to continue our operations.

We may never reach an agreement with the FDA on a surrogate endpoint for the accelerated approval of OCA for the treatment of PBC. The FDA, EMA and other regulators may require us to complete additional Phase 3 trials prior to the submission of an application for OCA for the treatment of PBC.

Typically, the FDA requires two pivotal clinical trials to approve a NDA. However, for OCA as a treatment for PBC, we currently plan to request accelerated approval from the FDA based on the Phase 3 POISE trial, the primary endpoint of which is a surrogate endpoint that we believe is reasonably likely to predict clinical benefit, therefore meeting the FDA s requirements for consideration under its accelerated approval regulation. However, the FDA has not yet provided any assurance that it will accept our approach, and we do not know if we will receive further written guidance from the FDA prior to submitting a NDA as to the acceptability of the POISE trial surrogate endpoint to support an approval of OCA for the treatment of PBC. We are currently seeking to build additional consensus regarding the clinical utility of the surrogate endpoint by working with a number of leading PBC academic centers to pool together and analyze their long-term PBC patient data. However, we may not be able to attain such consensus and, even if we do achieve such consensus, the supporting data may still not be accepted by the FDA in its consideration of the adequacy of our surrogate endpoint under a NDA for OCA for the treatment of PBC. The FDA has informed us that, in the context of considering OCA for potential accelerated approval, we will be required to conduct a Phase 3 clinical outcomes trial to confirm the clinical benefit of OCA in PBC by demonstrating the correlation of biochemical therapeutic response in patients taking OCA with a significant reduction in adverse clinical outcomes over time. We believe that this Phase 3 clinical outcomes trial will need to be substantially underway at the time we submit a NDA. It is possible that our NDA submission for regulatory approval will not be accepted by the FDA for review or, even if it is accepted for review, that there may be delays in the FDA s review process and that the FDA may determine that our NDA does not merit the approval of OCA for the treatment of PBC, in which case the FDA may require that we conduct and/or complete additional clinical trials and preclinical studies before it will reconsider our application for approval.

Because the FDA normally requires two pivotal clinical trials to approve a NDA, even if we achieve favorable results in our ongoing POISE trial, the FDA may not accept this trial as an adequate basis for approval and require that we conduct and complete a second Phase 3 clinical trial before considering a NDA for OCA for the treatment of PBC. Furthermore, the EMA and regulatory authorities in other countries in which we may seek approval for, and market, OCA, may require additional preclinical studies and/or clinical trials prior to granting approval. It may be expensive and time consuming to conduct and complete additional preclinical studies and clinical trials that the FDA, EMA and other regulatory authorities may require us to perform. As such, any requirement by the FDA, EMA or other regulatory authorities that we conduct additional preclinical studies or clinical trials could materially and adversely affect our business, financial condition and results of operations. Furthermore, even if we receive regulatory approval of OCA for the treatment of PBC, the labeling for OCA in the United States, Europe or other countries in which we seek approval may include limitations that could impact the commercial success of OCA.

Delays in the commencement, enrollment and completion of clinical trials could result in increased costs to us and delay or limit our ability to obtain regulatory approval for OCA and our other product candidates.

We may never reach an agreement with the FDA on a surrogate endpoint for the accelerated approval of OCA for t

Delays in the commencement, enrollment and completion of clinical trials could increase our product development costs or limit the regulatory approval of our product candidates. We are currently enrolling patients for our Phase 3 POISE trial. We currently expect results from the trial to be available by mid-2014. Although we anticipate that the net proceeds from this offering, together with existing cash and cash equivalents, including $29.8 million of net proceeds received on August 9, 2012 upon the issuance of our Series C preferred stock, and interest on our cash balances, will be sufficient to fund our projected operating requirements through the completion of our POISE trial, we may not be able to complete this trial on time or we may be required to conduct additional clinical trials or preclinical studies not currently planned to receive approval for OCA as a treatment for PBC, in which case we would require additional funding beyond the net

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proceeds of this offering. In addition, we do not know whether any future trials or studies of our other product candidates, including any confirmatory clinical trial of OCA, will begin on time or will be completed on schedule, if at all. The commencement, enrollment and completion of clinical trials can be delayed or suspended for a variety of reasons, including:

inability to obtain sufficient funds required for a clinical trial;

inability to reach agreements on acceptable terms with prospective CROs and trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;

clinical holds, other regulatory objections to commencing or continuing a clinical trial or the inability to obtain regulatory approval to commence a clinical trial in countries that require such approvals;

discussions with the FDA or non-U.S. regulators regarding the scope or design of our clinical trials;

inability to identify and maintain a sufficient number of trial sites, many of which may already be engaged in other clinical trial programs, including some that may be for the same indications targeted by our product candidates;

inability to obtain approval from institutional review boards, or IRBs, to conduct a clinical trial at their respective sites;

severe or unexpected drug-related adverse effects experienced by patients;

inability to timely manufacture sufficient quantities of the product candidate required for a clinical trial;

difficulty recruiting and enrolling patients to participate in clinical trials for a variety of reasons, including meeting the enrollment criteria for our study and competition from other clinical trial programs for the same indications as our product candidates; and

inability to retain enrolled patients after a clinical trial is underway.

For example, in the past, we experienced delays in our Phase 2 clinical trial of OCA given as a monotherapy to patients with PBC because we were unable to find and enroll a sufficient number of trial patients who met the specific enrollment criteria in accordance with our anticipated trial schedule.

Changes in regulatory requirements and guidance may also occur and we or any of our collaborators may need to amend clinical trial protocols to reflect these changes with appropriate regulatory authorities. Amendments may require us or any of our collaborators to resubmit clinical trial protocols to IRBs for re-examination, which may impact the costs, timing or successful completion of a clinical trial. In addition, a clinical trial may be suspended or terminated at any time by us, our current or future collaborators, the FDA or other regulatory authorities due to a number of factors, including:

our failure or the failure of our collaborators to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols;

unforeseen safety issues or any determination that a clinical trial presents unacceptable health risks;

lack of adequate funding to continue the clinical trial due to unforeseen costs or other business decisions; and

a breach of the terms of any agreement with, or for any other reason by, current or future collaborators that have responsibility for the clinical development of any of our product candidates, including DSP and Servier.

In addition, if we or any of our collaborators are required to conduct additional clinical trials or other preclinical studies of our product candidates beyond those contemplated, our ability to obtain regulatory approval of these product candidates and generate revenue from their sales would be similarly harmed.

Delays in the commencement, enrollment and completion of clinical trialscould result in increased costs to us and d

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Clinical failure can occur at any stage of clinical development and we have never conducted a Phase 3 trial or submitted a NDA or MAA before. The results of earlier clinical trials are not necessarily predictive of future results and any product candidate we, DSP, Servier or our potential future collaborators advance through clinical trials may not have favorable results in later clinical trials or receive regulatory approval.

Clinical failure can occur at any stage of our clinical development. Clinical trials may produce negative or inconclusive results, and we or our collaborators may decide, or regulators may require us, to conduct additional clinical trials or preclinical studies. In addition, data obtained from trials and studies are susceptible to varying interpretations, and regulators may not interpret our data as favorably as we do, which may delay, limit or prevent regulatory approval. Success in preclinical studies and early clinical trials does not ensure that subsequent clinical trials will generate the same or similar results or otherwise provide adequate data to demonstrate the efficacy and safety of a product candidate. A number of companies in the pharmaceutical industry, including those with greater resources and experience than us, have suffered significant setbacks in Phase 3 clinical trials, even after seeing promising results in earlier clinical trials.

Both of our Phase 2 clinical trials of OCA in PBC patients showed statistically significant results against a primary endpoint that is similar to the endpoint of our Phase 3 POISE trial protocol currently underway. However, in our Phase 2 PBC trials, the primary endpoint was a reduction in alkaline phosphatase, or ALP, to a threshold below 1.5 times upper limit normal, or ULN, compared to placebo after 12 weeks of treatment, but the primary endpoint for our POISE trial is both a reduction in ALP to below a threshold of 1.67 times ULN, with a minimum of 15% reduction in ALP from baseline, and a normal bilirubin level, compared to placebo after 12 months of therapy. We cannot assure you that our POISE trial will achieve positive results. Moreover, the fact that a retrospective analysis of the data from our Phase 2 PBC trials appears to demonstrate that the defined endpoint in our POISE trial was achieved based on the Phase 2 data does not mean that this endpoint will be successfully achieved in the POISE trial.

In addition, the design of a clinical trial can determine whether its results will support approval of a product and flaws in the design of a clinical trial may not become apparent until the clinical trial is well-advanced. We have limited experience in designing clinical trials and may be unable to design and execute a clinical trial to support regulatory approval. Further, clinical trials of potential products often reveal that it is not practical or feasible to continue development efforts.

If OCA or our other product candidates are found to be unsafe or lack efficacy, we will not be able to obtain regulatory approval for them and our business would be harmed. For example, if the results of our Phase 3 POISE trial of OCA do not achieve the primary efficacy endpoints or demonstrate expected safety, the prospects for approval of OCA would be materially and adversely affected.

In some instances, there can be significant variability in safety and/or efficacy results between different trials of the same product candidate due to numerous factors, including changes in trial protocols, differences in composition of the patient populations, adherence to the dosing regimen and other trial protocols and the rate of dropout among clinical trial participants. We do not know whether any Phase 2, Phase 3 or other clinical trials we or any of our collaborators may conduct will demonstrate consistent or adequate efficacy and safety to obtain regulatory approval to market our product candidates. If we are unable to bring any of our current or future product candidates to market, or to acquire any marketed, previously approved products, our ability to create long-term stockholder value will be limited.

Our product candidates may have undesirable side effects which may delay or prevent marketing approval, or, if approval is received, require them to be taken off the market, require them to include safety warnings or otherwise limit their sales.

A substance that binds to a receptor of a cell and triggers a response by that cell is called an agonist. OCA has been shown to be a potent agonist of the farnesoid X receptor, or FXR. With the exception of the bile acid CDCA, which has been approved to treat cholesterol gallstone dissolution and a rare lipid storage disease, there are no approved FXR agonists and the adverse effects from long-term exposure to this drug class are unknown. Unforeseen side effects from any of our product candidates could arise either during clinical development or, if approved, after the approved product has been marketed. The most common side effects observed in clinical trials of OCA were pruritus, or itching, headaches, fatigue, nausea, constipation and diarrhea. In our Phase 2 PBC clinical trial of OCA in combination with ursodiol, approximately 8% of the

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patients enrolled in the 10 milligram (mg) and 25 mg dose groups withdrew from the trial due to severe pruritus. At the 50 mg dose, approximately 25% of the patients withdrew from the trial due to severe pruritus. Additional or unforeseen side effects from these or any of our other product candidates could arise either during clinical development or, if approved, after the approved product has been marketed.

The range and potential severity of possible side effects from systemic therapies is significant. The results of future clinical trials may show that our product candidates cause undesirable or unacceptable side effects, which could interrupt, delay or halt clinical trials, and result in delay of, or failure to obtain, marketing approval from the FDA and other regulatory authorities, or result in marketing approval from the FDA and other regulatory authorities with restrictive label warnings.

If any of our product candidates receives marketing approval and we or others later identify undesirable or unacceptable side effects caused by such products:

regulatory authorities may require the addition of labeling statements, specific warnings, a contraindication or field alerts to physicians and pharmacies;
we may be required to change instructions regarding the way the product is administered, conduct additional clinical trials or change the labeling of the product;
we may be subject to limitations on how we may promote the product;
sales of the product may decrease significantly;
regulatory authorities may require us to take our approved product off the market;
we may be subject to litigation or product liability claims; and
our reputation may suffer.

Any of these events could prevent us, DSP, Servier or our potential future collaborators from achieving or maintaining market acceptance of the affected product or could substantially increase commercialization costs and expenses, which in turn could delay or prevent us from generating significant revenues from the sale of our products.

Reimbursement decisions by third-party payors may have an adverse effect on pricing and market acceptance. If there is not sufficient reimbursement for our products, it is less likely that they will be widely used.

Market acceptance and sales of OCA or any other product candidates that we develop, if approved, will depend on reimbursement policies and may be affected by future healthcare reform measures. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which drugs they will cover and establish payment levels. We cannot be certain that reimbursement will be available for OCA or any other product candidates that we develop. Also, we cannot be certain that reimbursement policies will not reduce the demand for, or the price paid for, our products. If reimbursement is not available or is available on a limited basis, we may not be able to successfully commercialize OCA or any other product candidates that we develop.

In the United States, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or MMA, changed the way Medicare covers and pays for pharmaceutical products. The legislation established Medicare Part D, which expanded Medicare coverage for outpatient prescription drug purchases by the elderly but provided authority for limiting the number of drugs that will be covered in any therapeutic class. The MMA also introduced a new reimbursement methodology based on average sales prices for physician- administered drugs. Any negotiated prices for our products covered by a Part D prescription drug plan will likely be lower than the prices we might otherwise obtain. Moreover, while the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own payment rates. Any reduction in

payment that results from the MMA may result in a similar reduction in payments from non-governmental payors.

The United States and several other jurisdictions are considering, or have already enacted, a number of legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to

Reimbursement decisions by third-party payors may have an adverse effect on pricing and market acceptance. If th

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sell our products profitably. Among policy makers and payors in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and/or expanding access to healthcare. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives. We expect to experience pricing pressures in connection with the sale of OCA and any other products that we develop, due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative proposals.

In March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act, or collectively, ACA, became law in the United States. The goal of ACA is to reduce the cost of health care and substantially change the way health care is financed by both governmental and private insurers. While we cannot predict what impact on federal reimbursement policies this legislation will have in general or on our business specifically, the ACA may result in downward pressure on pharmaceutical reimbursement, which could negatively affect market acceptance of OCA or any future product candidates. In addition, some members of the U.S. Congress have been seeking to overturn at least portions of the legislation and we expect they will continue to review and assess this legislation and alternative health care reform proposals. We cannot predict whether new proposals will be made or adopted, when they may be adopted or what impact they may have on us if they are adopted.

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

Depending upon the timing, duration and specifics of FDA marketing approval of OCA and our other product candidates, if any, one or more of our U.S. patents may be eligible for limited patent term restoration under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Act. The Hatch-Waxman Act permits a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, we may not be granted an extension because of, for example, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents or otherwise failing to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we are unable to obtain patent term extension or restoration or the term of any such extension is less than we request, the period during which we will have the right to exclusively market our product will be shortened and our competitors may obtain approval of competing products following our patent expiration, and our revenue could be reduced, possibly materially. In the event that we are unable to obtain any patent term extensions, the issued composition of matter patents for OCA are expected to expire in 2022 assuming they withstand any challenge. We expect that the other patents and patent applications for the OCA portfolio, if issued, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, would expire from 2022 to 2028.

If we market products in a manner that violates healthcare fraud and abuse laws, or if we violate government price reporting laws, we may be subject to civil or criminal penalties.

In addition to FDA restrictions on marketing of pharmaceutical products, several other types of state and federal healthcare laws, commonly referred to as fraud and abuse laws, have been applied in recent years to restrict certain marketing practices in the pharmaceutical industry. Other jurisdictions such as Europe have similar laws. These laws

include false claims and anti-kickback statutes. If we market our products and our products are paid for by governmental programs, it is possible that some of our business activities could be subject to challenge under one or more of these laws.

Federal false claims laws prohibit any person from knowingly presenting, or causing to be presented, a false claim for payment to the federal government or knowingly making, or causing to be made, a false statement to get a false claim paid. The federal healthcare program anti-kickback statute prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration to induce, or in return for, purchasing, leasing, ordering or arranging for the purchase, lease or order of any healthcare item or service covered by Medicare, Medicaid or other federally financed healthcare programs. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers,

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purchasers or formulary managers on the other. Although there are several statutory exemptions and regulatory safe harbors protecting certain common activities from prosecution, the exemptions and safe harbors are drawn narrowly, and practices that involve remuneration intended to induce prescribing, purchasing or recommending may be subject to scrutiny if they do not qualify for an exemption or safe harbor. Most states also have statutes or regulations similar to the federal anti-kickback law and federal false claims laws, which apply to items and services covered by Medicaid and other state programs, or, in several states, apply regardless of the payor. Administrative, civil and criminal sanctions may be imposed under these federal and state laws.

Over the past few years, a number of pharmaceutical and other healthcare companies have been prosecuted under these laws for a variety of promotional and marketing activities, such as: providing free trips, free goods, sham consulting fees and grants and other monetary benefits to prescribers; reporting inflated average wholesale prices that were then used by federal programs to set reimbursement rates; engaging in off-label promotion; and submitting inflated best price information to the Medicaid Rebate Program to reduce liability for Medicaid rebates.

If the FDA and EMA and other regulatory agencies do not approve the manufacturing facilities of our future contract manufacturers for commercial production, we may not be able to commercialize any of our product candidates.

We do not intend to manufacture the pharmaceutical products that we plan to sell. We currently have agreements with contract manufacturers for the production of the active pharmaceutical ingredients and the formulation of sufficient quantities of drug product for our Phase 3 POISE trial of OCA for the treatment of PBC and the other trials and preclinical studies that we believe we will need to conduct prior to seeking regulatory approval. However, we do not have agreements for commercial supplies of OCA or any of our other product candidates and we may not be able to reach agreements with these or other contract manufacturers for sufficient supplies to commercialize OCA if it is approved. Additionally, the facilities used by any contract manufacturer to manufacture OCA or any of our other product candidates must be the subject of a satisfactory inspection before the FDA or the regulators in other jurisdictions approve the product candidate manufactured at that facility. We are completely dependent on these third-party manufacturers for compliance with the requirements of U.S. and non-U.S. regulators for the manufacture of our finished products. If our manufacturers cannot successfully manufacture material that conform to our specifications and current good manufacturing practice requirements of any governmental agency whose jurisdiction to which we are subject, our product candidates will not be approved or, if already approved, may be subject to recalls. Reliance on third-party manufacturers entails risks to which we would not be subject if we manufactured the product candidates, including:

the possibility that we are unable to enter into a manufacturing agreement with a third party to manufacture our product candidates;
the possible breach of the manufacturing agreements by the third parties because of factors beyond our control; and
the possibility of termination or nonrenewal of the agreements by the third parties before we are able to arrange for a qualified replacement third-party manufacturer.

Any of these factors could cause the delay of approval or commercialization of our product candidates, cause us to incur higher costs or prevent us from commercializing our product candidates successfully. Furthermore, if any of our product candidates are approved and contract manufacturers fail to deliver the required commercial quantities of finished product on a timely basis and at commercially reasonable prices and we are unable to find one or more replacement manufacturers capable of production at a substantially equivalent cost, in substantially equivalent volumes and quality and on a timely basis, we would likely be unable to meet demand for our products and could lose potential revenue. It may take several years to establish an alternative source of supply for our product candidates and

to have any such new source approved by the government agencies that regulate our products.

If the FDA and EMA and other regulatory agencies do not approve the manufacturing facilities of our future contract

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Even if our product candidates receive regulatory approval, we may still face future development and regulatory difficulties.

Our product candidates, if approved, will also be subject to ongoing regulatory requirements for labeling, packaging, storage, advertising, promotion, record-keeping and submission of safety and other post-market information. In addition, approved products, manufacturers and manufacturers facilities are required to comply with extensive FDA and EMA requirements and requirements of other similar agencies, including ensuring that quality control and manufacturing procedures conform to current Good Manufacturing Practices, or cGMPs. As such, we and our contract manufacturers are subject to continual review and periodic inspections to assess compliance with cGMPs. Accordingly, we and others with whom we work must continue to expend time, money and effort in all areas of regulatory compliance, including manufacturing, production and quality control. We will also be required to report certain adverse reactions and production problems, if any, to the FDA and EMA and other similar agencies and to comply with certain requirements concerning advertising and promotion for our products. Promotional communications with respect to prescription drugs are subject to a variety of legal and regulatory restrictions and must be consistent with the information in the product s approved label. Accordingly, we may not promote our approved products, if any, for indications or uses for which they are not approved.

If a regulatory agency discovers previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured, or disagrees with the promotion, marketing or labeling of a product, it may impose restrictions on that product or us, including requiring withdrawal of the product from the market. If our product candidates fail to comply with applicable regulatory requirements, a regulatory agency may:

issue warning letters;

mandate modifications to promotional materials or require us to provide corrective information to healthcare practitioners;

require us or our collaborators to enter into a consent decree or permanent injunction, which can include imposition of various fines, reimbursements for inspection costs, required due dates for specific actions and penalties for noncompliance;

impose other administrative or judicial civil or criminal penalties;

withdraw regulatory approval;

refuse to approve pending applications or supplements to approved applications filed by us, DSP, Servier or our potential future collaborators;

impose restrictions on operations, including costly new manufacturing requirements; or

seize or detain products.

Risks Relating to the Commercialization of Our Products

Even if approved, our product candidates may not achieve broad market acceptance among physicians, patients and healthcare payors, and as a result our revenues generated from their sales may be limited.

The commercial success of OCA or our other product candidates, if approved, will depend upon their acceptance among the medical community, including physicians, health care payors and patients. For PBC, the current standard of care is ursodeoxycholic acid, which is available generically as ursodiol. In order for OCA to be commercially

successful, we will need to demonstrate that it is safe and effective for the treatment of patients who have an inadequate response to or who are unable to tolerate ursodiol, referred to as second line treatment, and is more effective than any other alternatives that may be developed as a second line treatment for PBC, particularly given the planned much higher price that we anticipate charging for OCA compared to the price of generically available ursodiol. The degree of market acceptance of our product candidates will depend on a number of factors, including:

limitations or warnings contained in our product candidates FDA-approved labeling;

Even if approved, our product candidates may not achieve broad marketacceptance among physicians, patients an

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changes in the standard of care or availability of alternative therapies at similar or lower costs for the targeted indications for any of our product candidates, such as ursodiol for the treatment of PBC;

limitations in the approved clinical indications for our product candidates;

demonstrated clinical safety and efficacy compared to other products;

lack of significant adverse side effects;

sales, marketing and distribution support;

availability of reimbursement from managed care plans and other third-party payors;

timing of market introduction and perceived effectiveness of competitive products;

the degree of cost-effectiveness;

availability of alternative therapies at similar or lower cost, including generics and over-the-counter products;

the extent to which our product candidates are approved for inclusion on formularies of hospitals and managed care organizations;

whether our product candidates are designated under physician treatment guidelines for the treatment of the indications for which we have received regulatory approval;

adverse publicity about our product candidates or favorable publicity about competitive products;

convenience and ease of administration of our product candidates; and

potential product liability claims.

If our product candidates are approved, but do not achieve an adequate level of acceptance by physicians, patients, the medical community and healthcare payors, sufficient revenue may not be generated from these products and we may not become or remain profitable. In addition, efforts to educate the medical community and third-party payors on the benefits of our product candidates may require significant resources and may never be successful.

We have no sales, marketing or distribution experience and we will have to invest significant resources to develop those capabilities or enter into acceptable third-party sales and marketing arrangements.

We have no sales, marketing or distribution experience. To develop internal sales, distribution and marketing capabilities, we will have to invest significant amounts of financial and management resources, some of which will be committed prior to any confirmation that OCA or any of our other product candidates will be approved. For product candidates where we decide to perform sales, marketing and distribution functions ourselves or through third parties, we could face a number of additional risks, including:

we or our third-party sales collaborators may not be able to attract and build an effective marketing or sales force;

the cost of securing or establishing a marketing or sales force may exceed the revenues generated by any products; and

our direct sales and marketing efforts may not be successful.

We have entered into an agreement with DSP for the development and commercialization of OCA in Japan and China and other potential Asian countries, if approved, and have entered into an agreement with Servier to assist in the development and commercialization of certain of our earlier stage agonists of a dedicated bile acid receptor called TGR5 outside of the United States and Japan, if approved, and may elect to seek additional strategic collaborators for our product candidates. We may have limited or no control over the sales, marketing and distribution activities of these third parties. Our future revenues may depend heavily on the success of the efforts of these third parties.

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If any of our current strategic collaborators fails to perform its obligations or terminates its agreement with us, the development and commercialization of the product candidates under such agreement could be delayed or terminated and our business could be substantially harmed.

We currently have strategic collaborations in place relating to certain of our product candidates. We entered into an exclusive license agreement with DSP regarding the development and commercialization of OCA for PBC and NASH in Japan and China and provided DSP with an option to extend its exclusive license to different indications as well as certain other Asian countries. We entered into a strategic collaboration with Servier initially focused on the identification and optimization of novel TGR5 agonists for the treatment of type-2 diabetes and other associated disorders. These strategic collaborations may not be scientifically or commercially successful due to a number of important factors, including the following:

DSP and Servier have significant discretion in determining the efforts and resources that each will apply to their strategic collaboration with us. The timing and amount of any cash payments, milestones and royalties that we may receive under such agreements will depend on, among other things, the efforts, allocation of resources and successful development and commercialization of our product candidates by DSP and Servier under their respective agreements;
Our agreement with Servier provides it with wide discretion in deciding which novel compounds to advance through the preclinical and clinical development process. It is possible for Servier to reject certain compounds at any point in the research, development and clinical trial process without triggering a termination of their agreement with us. In the event of any such decision, our business and prospects may be adversely affected due to our inability to progress such compounds ourselves;
Our agreement with DSP restricts it from developing or commercializing any FXR agonist to treat PBC or NASH during the term of the agreement other than pursuant to the DSP agreement and our agreement with Servier restricts it from developing or commercializing any TGR5 receptor agonist during the term of the agreement other than pursuant to the Servier agreement. Subject to these restrictions, it is possible that DSP or Servier may develop and commercialize, either alone or with others, or be acquired by a company that has, products that are similar to or competitive with the product candidates that they license from us;
DSP or Servier may change the focus of their development and commercialization efforts or pursue higher-priority programs;
DSP or Servier may, under specified circumstances, terminate their strategic collaborations with us on short notice and for circumstances outside of our control, which could make it difficult for us to attract new strategic collaborators or adversely affect how we are perceived in the scientific and financial communities;
DSP and Servier have, under certain circumstances, the right to maintain or defend our intellectual property rights licensed to them in their territories, and, although we may have the right to assume the maintenance and defense of our intellectual property rights if our strategic collaborators do not, our ability to do so may be compromised by our strategic collaborators acts or omissions;
DSP or Servier may utilize our intellectual property rights in such a way as to invite litigation that could jeopardize or invalidate our intellectual property rights or expose us to potential liability; and
DSP or Servier may not comply with all applicable regulatory requirements, or fail to report safety data in accordance with all applicable regulatory requirements.

If either DSP or Servier fails to develop or effectively commercialize OCA or any TGR5 compounds, respectively, we may not be able to replace them with another collaborator. We may also be unable to obtain, on terms acceptable to us, a license from such strategic collaborator to any of its intellectual property that may be necessary or useful for us to continue to develop and commercialize a product candidate. Any of these events could have a material adverse effect on our business, results of operations and our ability to achieve future profitability, and could cause our stock price to decline.

If any of our current strategic collaborators fails to perform its obligations or terminates its agreement with us, the de

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We may not be successful in establishing and maintaining development and commercialization collaborations, which could adversely affect our ability to develop certain of our product candidates and our financial condition and operating results.

Because developing pharmaceutical products, conducting clinical trials, obtaining regulatory approval, establishing manufacturing capabilities and marketing approved products are expensive, we have entered into, and may seek to enter into, collaborations with companies that have more experience. For example, we have entered into collaborations with DSP for OCA and Servier for our earlier stage TGR5 program. We may establish additional collaborations for development and commercialization of OCA in territories outside of those licensed by DSP or for our earlier stage TGR5 program in the United States or Japan and product candidates and research programs, including INT-767 and INT-777. Additionally, if any of our product candidates receives marketing approval, we may enter into sales and marketing arrangements with third parties with respect to our unlicensed territories. If we are unable to maintain our existing arrangements or enter into any new such arrangements on acceptable terms, if at all, we may be unable to effectively market and sell our products in our target markets. We expect to face competition in seeking appropriate collaborators. Moreover, collaboration arrangements are complex and time consuming to negotiate, document and implement and they may require substantial resources to maintain. We may not be successful in our efforts to establish and implement collaborations or other alternative arrangements for the development of our product candidates.

When we collaborate with a third party for development and commercialization of a product candidate, we can expect to relinquish some or all of the control over the future success of that product candidate to the third party. For example, DSP has the exclusive rights to OCA in Japan and China and the option to exclusively license OCA in several other Asian countries. Our collaboration partner may not devote sufficient resources to the commercialization of our product candidates or may otherwise fail in their commercialization. The terms of any collaboration or other arrangement that we establish may not be favorable to us. In addition, any collaboration that we enter into, including our collaborations with DSP and Servier, may be unsuccessful in the development and commercialization of our product candidates. In some cases, we may be responsible for continuing preclinical and initial clinical development of a product candidate or research program under a collaboration arrangement, and the payment we receive from our collaboration partner may be insufficient to cover the cost of this development. If we are unable to reach agreements with suitable collaborators for our product candidates, we would face increased costs, we may be forced to limit the number of our product candidates we can commercially develop or the territories in which we commercialize them and we might fail to commercialize products or programs for which a suitable collaborator cannot be found. If we fail to achieve successful collaborations, our operating results and financial condition will be materially and adversely affected.

If we fail to develop OCA for additional indications, our commercial opportunity will be limited.

To date, we have focused the majority of our development efforts on the development of OCA for the second line treatment of PBC. One of our strategies is to pursue clinical development of OCA for other orphan and more common indications, to the extent that we have sufficient funding.

PBC is a rare disease and, as a result, the market size for treatments of PBC is limited. Furthermore, because a significant proportion of PBC patients do not exhibit any symptoms at the time of diagnosis, PBC may be left undiagnosed for a significant period of time. Due to these factors, our ability to grow revenues will be dependent on

our ability to successfully develop and commercialize OCA for the treatment of additional indications. The completion of development, securing of approval and commercialization of OCA for additional indications will require substantial additional funding beyond the net proceeds of this offering and is prone to the risks of failure inherent in drug development. We cannot provide you any assurance that we will be able to successfully advance any of these indications through the development process. Even if we receive FDA approval to market OCA for the treatment of any of these additional indications, we cannot assure you that any such additional indications will be successfully commercialized, widely accepted in the marketplace or more effective than other commercially available alternatives. If we are unable to successfully develop and commercialize OCA for these additional indications, our commercial opportunity will be limited and our business prospects will suffer.

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If serious adverse events or other undesirable side effects are identified during the development of OCA for one indication, we may need to abandon our development of OCA for other indications.

Product candidates in clinical stages of development have a high risk of failure. We cannot predict when or if OCA will prove effective or safe in humans or will receive regulatory approval. To date, the most common side effects observed in clinical trials of OCA were pruritus, headaches, fatigue, constipation and diarrhea. New side effects could, however, be identified as we expand our clinical trials for OCA to other indications. If new side effects are found during the development of OCA for any indication, if known side effects are shown to be more severe than previously observed or if OCA is found to have other unexpected characteristics, we may need to abandon our development of OCA for PBC and other potential indications. We cannot assure you that additional or more severe adverse side effects with respect to OCA will not develop in future clinical trials, which could delay or preclude regulatory approval of OCA or limit its commercial use.

Risks Relating to Our Business and Strategy

We face competition from other biotechnology and pharmaceutical companies and our operating results will suffer if we fail to compete effectively.

The biotechnology and pharmaceutical industries are intensely competitive and subject to rapid and significant technological change. We have competitors in the United States, Europe and other jurisdictions, including major multinational pharmaceutical companies, established biotechnology companies, specialty pharmaceutical and generic drug companies and universities and other research institutions. Many of our competitors have greater financial and other resources, such as larger research and development staff and more experienced marketing and manufacturing organizations. Large pharmaceutical companies, in particular, have extensive experience in clinical testing, obtaining regulatory approvals, recruiting patients and manufacturing pharmaceutical products. These companies also have significantly greater research, sales and marketing capabilities and collaborative arrangements in our target markets with leading companies and research institutions. Established pharmaceutical companies may also invest heavily to accelerate discovery and development of novel compounds or to in-license novel compounds that could make the product candidates that we develop obsolete. As a result of all of these factors, our competitors may succeed in obtaining patent protection and/or FDA approval or discovering, developing and commercializing drugs for the chronic liver and other diseases that we are targeting before we do. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large, established companies. Some of the pharmaceutical and biotechnology companies we expect to compete with include Astellas Pharma US, Inc., AstraZeneca, Dr. Falk Pharma GmbH, Eli Lilly, Exelixis, Inc., Galmed Medical Research Ltd., Immuron Ltd., Johnson & Johnson, Mochida Pharmaceutical Co., Ltd., NasVax Ltd., NovImmune SA., Phenex Pharmaceuticals AG, Raptor Pharmaceutical Corp., Salix Pharmaceuticals, Inc. and Tioga Pharmaceuticals, Inc. In addition, many universities and private and public research institutes may become active in our target disease areas. Our competitors may succeed in developing, acquiring or licensing on an exclusive basis, technologies and drug products that are more effective or less costly than OCA or any other product candidates that we are currently developing or that we may develop, which could render our products obsolete and noncompetitive.

We believe that our ability to successfully compete will depend on, among other things:

- the results of our and our strategic collaborators clinical trials and preclinical studies;
- our ability to recruit and enroll patients for our clinical trials;

the efficacy, safety and reliability of our product candidates;
the speed at which we develop our product candidates;
our ability to design and successfully execute appropriate clinical trials;
our ability to maintain a good relationship with regulatory authorities;
the timing and scope of regulatory approvals, if any;

We face competition from other biotechnology and pharmaceutical companiesand our operating results will suffer if

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our ability to commercialize and market any of our product candidates that receive regulatory approval;
the price of our products;
adequate levels of reimbursement under private and governmental health insurance plans, including Medicare;
our ability to protect intellectual property rights related to our products;
our ability to manufacture and sell commercial quantities of any approved products to the market; and
acceptance of our product candidates by physicians and other health care providers.

If our competitors market products that are more effective, safer or less expensive than our future products, if any, or that reach the market sooner than our future products, if any, we may not achieve commercial success. In addition, the biopharmaceutical industry is characterized by rapid technological change. Because our research approach integrates many technologies, it may be difficult for us to stay abreast of the rapid changes in each technology. If we fail to stay at the forefront of technological change, we may be unable to compete effectively. Technological advances or products developed by our competitors may render our technologies or product candidates obsolete, less competitive or not economical.

We depend on third-party contractors for a substantial portion of our operations and may not be able to control their work as effectively as if we performed these functions ourselves.

We outsource substantial portions of our operations to third-party service providers, including the conduct of preclinical studies and clinical trials, collection and analysis of data and manufacturing. Our agreements with third-party service providers and CROs are on a study-by-study and project-by-project basis. Typically, we may terminate the agreements with notice and are responsible for the supplier s previously incurred costs. In addition, any CRO that we retain will be subject to the FDA s and EMA s regulatory requirements and similar standards outside of the United States and Europe and we do not have control over compliance with these regulations by these providers. Consequently, if these providers do not adhere to applicable governing practices and standards, the development and commercialization of our product candidates could be delayed or stopped, which could severely harm our business and financial condition.

Because we have relied on third parties, our internal capacity to perform these functions is limited to management oversight. Outsourcing these functions involves the risk that third parties may not perform to our standards, may not produce results in a timely manner or may fail to perform at all. Several years ago, we experienced difficulties with a third-party contract manufacturer for OCA, including delays in receiving adequate clinical trial supplies as requested within the requested time periods. We subsequently replaced this manufacturer with other third-party contract manufacturers for OCA. Although we have not experienced any significant difficulties with our third-party contractors since then, it is possible that we could experience difficulties in the future. In addition, the use of third-party service providers requires us to disclose our proprietary information to these parties, which could increase the risk that this information will be misappropriated. There are a limited number of third-party service providers that specialize or have the expertise required to achieve our business objectives. Identifying, qualifying and managing performance of third-party service providers can be difficult, time consuming and cause delays in our development programs. We currently have a small number of employees, which limits the internal resources we have available to identify and monitor third-party service providers. To the extent we are unable to identify, retain and successfully manage the performance of third-party service providers in the future, our business may be adversely affected, and we may be subject to the imposition of civil or criminal penalties if their conduct of clinical trials violates applicable law.

A variety of risks associated with our planned international business relationships could materially adversely affect our business.

We have entered into an agreement with DSP for the development of OCA and with Servier for our earlier stage TGR5 program, and we may enter into agreements with other third parties for the development

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and commercialization of OCA or our other product candidates in international markets. International business relationships subject us to additional risks that may materially adversely affect our ability to attain or sustain profitable operations, including:

differing regulatory requirements for drug approvals internationally;
potentially reduced protection for intellectual property rights;
potential third-party patent rights in countries outside of the United States;
the potential for so-called parallel importing, which is what occurs when a local seller, faced with relatively high local prices, opts to import goods from another jurisdiction with relatively low prices, rather than buying them locally;
unexpected changes in tariffs, trade barriers and regulatory requirements;
economic weakness, including inflation, or political instability, particularly in non-U.S. economies and markets, including several countries in Europe;
compliance with tax, employment, immigration and labor laws for employees traveling abroad;
taxes in other countries;
foreign currency fluctuations, which could result in increased operating expenses and reduced revenue, and other obligations incident to doing business in another country;
workforce uncertainty in countries where labor unrest is more common than in the United States;
production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
business interruptions resulting from geo-political actions, including war and terrorism, or natural disasters, including earthquakes, volcanoes, typhoons, floods, hurricanes and fires.

We will need to expand our operations and increase the size of our company, and we may experience difficulties in managing growth.

As we increase the number of ongoing product development programs and advance our product candidates through preclinical studies and clinical trials, we will need to increase our product development, scientific and administrative headcount to manage these programs. In addition, to meet our obligations as a public company, we will need to increase our general and administrative capabilities. Our management, personnel and systems currently in place may not be adequate to support this future growth. Our need to effectively manage our operations, growth and various projects requires that we:

successfully attract and recruit new employees or consultants with the expertise and experience we will require;
manage our clinical programs effectively, which we anticipate being conducted at numerous clinical sites;
develop a marketing and sales infrastructure; and
continue to improve our operational, financial and management controls, reporting systems and procedures.

If we are unable to successfully manage this growth and increased complexity of operations, our business may be adversely affected.

We may not be able to manage our business effectively if we are unable to attract and retain key personnel and consultants.

We may not be able to attract or retain qualified management, finance, scientific and clinical personnel and consultants due to the intense competition for qualified personnel and consultants among biotechnology, pharmaceutical and other businesses. If we are not able to attract and retain necessary personnel and

We may not be able to manage our business effectively if we are unable toattract and retain key personnel and con

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consultants to accomplish our business objectives, we may experience constraints that will significantly impede the achievement of our development objectives, our ability to raise additional capital and our ability to implement our business strategy.

Our industry has experienced a high rate of turnover of management personnel in recent years. We are highly dependent on the development, regulatory, commercialization and business development expertise of Mark Pruzanski, our co-founder and president and chief executive officer; David Shapiro, our chief medical officer; Barbara Duncan, our chief financial officer, treasurer and secretary; Luciano Adorini, our chief scientific officer; and our other key employees and consultants, such as Professor Roberto Pellicciari, our co-founder who provides ongoing consulting services to us. If we lose one or more of our executive officers or key employees or consultants, our ability to implement our business strategy successfully could be seriously harmed. Any of our executive officers or key employees or consultants may terminate their employment at any time. Replacing executive officers, key employees and consultants may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to develop, gain regulatory approval of and commercialize products successfully. Competition to hire and retain employees and consultants from this limited pool is intense, and we may be unable to hire, train, retain or motivate these additional key personnel and consultants. Our failure to retain key personnel or consultants could materially harm our business.

We have scientific and clinical advisors and consultants who assist us in formulating our research, development and clinical strategies. These advisors are not our employees and may have commitments to, or consulting or advisory contracts with, other entities that may limit their availability to us and typically they will not enter into non-compete agreements with us. If a conflict of interest arises between their work for us and their work for another entity, we may lose their services. In addition, our advisors may have arrangements with other companies to assist those companies in developing products or technologies that may compete with ours.

Failure to build our finance infrastructure and improve our accounting systems and controls could impair our ability to comply with the financial reporting and internal controls requirements for publicly traded companies.

As a public company, we will operate in an increasingly demanding regulatory environment, which requires us to comply with the Sarbanes-Oxley Act of 2002, and the related rules and regulations of the Securities and Exchange Commission, expanded disclosure requirements, accelerated reporting requirements and more complex accounting rules. Company responsibilities required by the Sarbanes-Oxley Act include establishing corporate oversight and adequate internal control over financial reporting and disclosure controls and procedures. Effective internal controls are necessary for us to produce reliable financial reports and are important to help prevent financial fraud.

We have begun implementing our system of internal controls over financial reporting and preparing the documentation necessary to perform the evaluation needed to comply with Section 404(a) of the Sarbanes-Oxley Act. However, we anticipate that we will need to retain additional finance capabilities and build our financial infrastructure as we transition to operating as a public company, including complying with the requirements of Section 404 of the Sarbanes-Oxley Act. As we begin operating as a public company following this offering, we will continue improving our financial infrastructure with the retention of additional financial and accounting capabilities, the enhancement of internal controls and additional training for our financial and accounting staff.

Section 404(a) of the Sarbanes-Oxley Act requires annual management assessments of the effectiveness of our internal control over financial reporting, starting with the second annual report that we would expect to file with the Securities and Exchange Commission. However, for as long as we remain an emerging growth company as defined in

the JOBS Act, we intend to take advantage of certain exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies including, but not limited to, not being required to comply with the auditor attestation requirements of Section 404(b) of the Sarbanes-Oxley Act. We may take advantage of these reporting exemptions until we are no longer an emerging growth company. We will remain an emerging growth company until the earliest of (i) the last day of the fiscal year in which we have total annual gross revenues

Failure to build our finance infrastructure and improve our accounting systems and controls could impair our ability t

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of $1 billion or more; (ii) the last day of our fiscal year following the fifth anniversary of the date of the completion of this offering; (iii) the date on which we have issued more than $1 billion in nonconvertible debt during the previous three years; or (iv) the date on which we are deemed to be a large accelerated filer under the rules of the Securities and Exchange Commission.

Until we are able to expand our finance and administrative capabilities and establish necessary financial reporting infrastructure, we may not be able to prepare and disclose, in a timely manner, our financial statements and other required disclosures or comply with the Sarbanes-Oxley Act or existing or new reporting requirements. If we cannot provide reliable financial reports or prevent fraud, our business and results of operations could be harmed and investors could lose confidence in our reported financial information.

Our employees may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements and insider trading, which could significantly harm our business.

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with the regulations of the FDA and non-U.S. regulators, provide accurate information to the FDA and non-U.S. regulators, comply with health care fraud and abuse laws and regulations in the United States and abroad, report financial information or data accurately or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the health care industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Employee misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. We have adopted a code of conduct, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions.

We face potential product liability exposure, and if successful claims are brought against us, we may incur substantial liability for a product candidate and may have to limit its commercialization.

The use of our product candidates in clinical trials and the sale of any products for which we may obtain marketing approval expose us to the risk of product liability claims. Product liability claims may be brought against us or our collaborators by participants enrolled in our clinical trials, patients, health care providers or others using, administering or selling our products. If we cannot successfully defend ourselves against any such claims, we would incur substantial liabilities. Regardless of merit or eventual outcome, product liability claims may result in:

withdrawal of clinical trial participants;
termination of clinical trial sites or entire trial programs;
costs of related litigation;
substantial monetary awards to patients or other claimants;
decreased demand for our product candidates and loss of revenues;

impairment of our business reputation;
diversion of management and scientific resources from our business operations; and
the inability to commercialize our product candidates.

We have obtained limited product liability insurance coverage for our clinical trials in the United States and in selected other jurisdictions where we are conducting clinical trials. Our product liability insurance coverage for clinical trials in the United States is currently limited to an aggregate of $10 million and outside of the United States we have coverage for lesser amounts that vary by country. As such, our insurance

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coverage may not reimburse us or may not be sufficient to reimburse us for any expenses or losses we may suffer. Moreover, insurance coverage is becoming increasingly expensive, and, in the future, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to product liability. We intend to expand our insurance coverage for products to include the sale of commercial products if we obtain marketing approval for our product candidates in development, but we may be unable to obtain commercially reasonable product liability insurance for any products approved for marketing. Large judgments have been awarded in class action lawsuits based on drugs that had unanticipated side effects. A successful product liability claim or series of claims brought against us, particularly if judgments exceed our insurance coverage, could decrease our cash resources and adversely affect our business.

Our insurance policies are expensive and only protect us from some business risks, which will leave us exposed to significant uninsured liabilities.

We do not carry insurance for all categories of risk that our business may encounter. Some of the policies we currently maintain include general liability, employment practices liability, property, auto, workers compensation, products liability and directors and officers insurance. We do not know, however, if we will be able to maintain insurance with adequate levels of coverage. Any significant uninsured liability may require us to pay substantial amounts, which would adversely affect our financial position and results of operations.

If we engage in an acquisition, reorganization or business combination, we will incur a variety of risks that could adversely affect our business operations or our stockholders.

From time to time we have considered, and we will continue to consider in the future, strategic business initiatives intended to further the expansion and development of our business. These initiatives may include acquiring businesses, technologies or products or entering into a business combination with another company. If we pursue such a strategy, we could, among other things:

issue equity securities that would dilute our current stockholders percentage ownership;

incur substantial debt that may place strains on our operations;

spend substantial operational, financial and management resources to integrate new businesses, technologies and products;

assume substantial actual or contingent liabilities;

reprioritize our development programs and even cease development and commercialization of our product candidates; or

merge with, or otherwise enter into a business combination with, another company in which our stockholders would receive cash and/or shares of the other company on terms that certain of our stockholders may not deem desirable.

Although we intend to evaluate and consider acquisitions, reorganizations and business combinations in the future, we have no agreements or understandings with respect to any acquisition, reorganization or business combination at this time.

Risks Relating to Our Intellectual Property

It is difficult and costly to protect our proprietary rights, and we may not be able to ensure their protection. If our patent position does not adequately protect our product candidates, others could compete against us more directly, which would harm our business, possibly materially.

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 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 product candidates is dependent upon the extent to which we have rights under valid and enforceable patents or trade secrets that cover these activities.

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The patent positions of biotechnology and pharmaceutical companies can be highly uncertain and involve complex legal and factual questions for which important legal principles remain unresolved. No consistent policy regarding the breadth of claims allowed in pharmaceutical patents has emerged to date in the United States or in many jurisdictions outside of the United States. Changes in either the patent laws or interpretations of patent laws in the United States and other countries may diminish the value of our intellectual property. Accordingly, we cannot predict the breadth of claims that may be enforced in the patents that may be issued from the applications we currently or may in the future own or license from third parties. Further, if any patents we obtain or license are deemed invalid and unenforceable, our ability to commercialize or license our technology could be adversely affected.

Others have filed, and in the future are likely to file, patent applications covering products and technologies that are similar, identical or competitive to ours or important to our business. We cannot be certain that any patent application owned by a third party will not have priority over patent applications filed or in-licensed by us, or that we or our licensors will not be involved in interference, opposition or invalidity proceedings before U.S. or non-U.S. patent offices.

The degree of future protection for our proprietary rights is uncertain because legal means afford only limited protection and may not adequately protect our rights or permit us to gain or keep our competitive advantage. For example:

others may be able to develop a platform similar to, or better than, ours in a way that is not covered by the claims of our patents;
others may be able to make compounds that are similar to our product candidates but that are not covered by the claims of our patents;
we might not have been the first to make the inventions covered by our pending patent applications;
we might not have been the first to file patent applications for these inventions;
others may independently develop similar or alternative technologies or duplicate any of our technologies;
any patents that we obtain may not provide us with any competitive advantages;
we may not develop additional proprietary technologies that are patentable; or
the patents of others may have an adverse effect on our business.

As of July 31, 2012, we were the owner of record of 45 issued or granted U.S. and non-U.S. patents relating to OCA with claims directed to pharmaceutical compounds, pharmaceutical compositions, methods of making these compounds, and methods of using these compounds in various indications. We were also the owner of record of 12 pending U.S. and non-U.S. patent applications relating to OCA in these areas.

In addition, as of July 31, 2012, we were the owner of record of issued or granted U.S. and non-U.S. patents relating to our product candidates other than OCA, with claims directed to pharmaceutical compounds, pharmaceutical compositions and methods of using these compounds in various indications. We were also the owner of record of pending U.S. and non-U.S. patent applications relating to such other product candidates in these areas.

Patents covering the composition of matter of OCA expire in 2022 if the appropriate maintenance fee renewal, annuity, or other government fees are paid. We expect that the other patents and patent applications for the OCA portfolio, if issued, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, would expire from 2022 to 2028. We expect the issued INT-767 composition of matter patent in the United States, if the appropriate maintenance fee, renewal, annuity, or other governmental fees are paid, to expire in 2029. We expect the other pending patent applications in the INT-767 portfolio, if issued, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire in 2027. We expect the issued INT-777 composition of matter patent in the United States, if the appropriate maintenance fee, renewal, annuity, or other governmental fees are paid, to expire in 2030. We expect the other pending patent

It is difficult and costly to protect our proprietary rights, and we may not be able to ensure their protection. Our pat

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applications in the INT-777 portfolio, if issued, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, to expire from 2028 to 2029.

Without patent protection on the composition of matter of our product candidates, our ability to assert our patents to stop others from using or selling our product candidates in a non-pharmaceutically acceptable formulation may be limited.

Due to the patent laws of a country, or the decisions of a patent examiner in a country, or our own filing strategies, we may not obtain patent coverage for all of our product candidates or methods involving these candidates in the parent patent application. We plan to pursue divisional patent applications or continuation patent applications in the United States and other countries to obtain claim coverage for inventions which were disclosed but not claimed in the parent patent application.

We may also rely on trade secrets to protect our technology, especially where we do not believe patent protection is appropriate or feasible. However, trade secrets are difficult to protect. Although we use reasonable efforts to protect our trade secrets, our employees, consultants, contractors, outside scientific collaborators and other advisors may unintentionally or willfully disclose our information to competitors. Enforcing a claim that a third party illegally obtained and is using any of our trade secrets is expensive and time consuming, and the outcome is unpredictable. In addition, courts outside the United States are sometimes less willing to protect trade secrets. Moreover, our competitors may independently develop equivalent knowledge, methods and know-how.

We may incur substantial costs as a result of litigation or other proceedings relating to patent and other intellectual property rights.

If we choose to go to court to stop another party from using the inventions claimed in any patents we obtain, that individual or company has the right to ask the court to rule that such patents are invalid or should not be enforced against that third party. These lawsuits are expensive and would consume time and resources and divert the attention of managerial and scientific personnel even if we were successful in stopping the infringement of such patents. In addition, there is a risk that the court will decide that such patents are not valid and that we do not have the right to stop the other party from using the inventions. There is also the risk that, even if the validity of such patents is upheld, the court will refuse to stop the other party on the ground that such other party s activities do not infringe our rights to such patents. In addition, the U.S. Supreme Court has recently modified some tests used by the U.S. Patent and Trademark Office, or USPTO, in granting patents over the past 20 years, which may decrease the likelihood that we will be able to obtain patents and increase the likelihood of challenge of any patents we obtain or license.

We may infringe the intellectual property rights of others, which may prevent or delay our product development efforts and stop us from commercializing or increase the costs of commercializing our product candidates.

Our success will depend in part on our ability to operate without infringing the proprietary rights of third parties. We cannot guarantee that our products, or manufacture or use of our product candidates, will not infringe third-party patents. Furthermore, a third party may claim that we or our manufacturing or commercialization collaborators are using inventions covered by the third party s patent rights and may go to court to stop us from engaging in our normal operations and activities, including making or selling our product candidates. These lawsuits are costly and could affect our results of operations and divert the attention of managerial and scientific personnel. There is a risk that a court would decide that we or our commercialization collaborators are infringing the third party s patents and would

order us or our collaborators to stop the activities covered by the patents. In that event, we or our commercialization collaborators may not have a viable way around the patent and may need to halt commercialization of the relevant product. In addition, there is a risk that a court will order us or our collaborators to pay the other party damages for having violated the other party s patents. In the future, we may agree to indemnify our commercial collaborators against certain intellectual property infringement claims brought by third parties. The pharmaceutical and biotechnology industries have produced a proliferation of patents, and it is not always clear to industry participants, including us, which patents cover various types of products or methods of use. The coverage of patents is subject to interpretation by the courts, and the interpretation is not always uniform.

We may infringe the intellectual property rights of others, which may preventor delay our product development effor

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If we are sued for patent infringement, we would need to demonstrate that our products or methods either do not infringe the patent claims of the relevant patent or that the patent claims are invalid, and we may not be able to do this. Proving invalidity is difficult. For example, in the United States, proving invalidity requires a showing of clear and convincing evidence to overcome the presumption of validity enjoyed by issued patents. Even if we are successful in these proceedings, we may incur substantial costs and divert management s time and attention in pursuing these proceedings, which could have a material adverse effect on us. If we are unable to avoid infringing the patent rights of others, we may be required to seek a license, which may not be available, defend an infringement action or challenge the validity of the patents in court. Patent litigation is costly and time consuming. We may not have sufficient resources to bring these actions to a successful conclusion. In addition, if we do not obtain a license, develop or obtain non-infringing technology, fail to defend an infringement action successfully or have infringed patents declared invalid, we may incur substantial monetary damages, encounter significant delays in bringing our product candidates to market and be precluded from manufacturing or selling our product candidates.

We cannot be certain that others have not filed patent applications for technology covered by our pending applications, or that we were the first to invent the technology, because:

some patent applications in the United States may be maintained in secrecy until the patents are issued;
patent applications in the United States are typically not published until 18 months after the priority date; and
publications in the scientific literature often lag behind actual discoveries.

Our competitors may have filed, and may in the future file, patent applications covering technology similar to ours. Any such patent application may have priority over our patent applications, which could further require us to obtain rights to issued patents covering such technologies. If another party has filed a U.S. patent application on inventions similar to ours, we may have to participate in an interference proceeding declared by the USPTO to determine priority of invention in the United States. The costs of these proceedings could be substantial, and it is possible that such efforts would be unsuccessful if, unbeknownst to us, the other party had independently arrived at the same or similar invention prior to our own invention, resulting in a loss of our U.S. patent position with respect to such inventions. Other countries have similar laws that permit secrecy of patent applications, and may be entitled to priority over our applications in such jurisdictions.

Some of our competitors may be able to sustain the costs of complex patent litigation more effectively than we can because they have substantially greater resources. In addition, any uncertainties resulting from the initiation and continuation of any litigation could have a material adverse effect on our ability to raise the funds necessary to continue our operations.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

Periodic maintenance fees, renewal fees, annuity fees and various other governmental fees on patents and/or applications will be due to be paid to the USPTO and various governmental patent agencies outside of the United States in several stages over the lifetime of the patents and/or applications. We have systems in place to remind us to pay these fees, and we employ an outside firm and rely on our outside counsel to pay these fees due to non-U.S. patent agencies. The USPTO and various non-U.S. governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. We employ

reputable law firms and other professionals to help us comply, and in many cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. However, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, our competitors might be able to enter the market and this circumstance would have a material adverse effect on our business.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submis

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We may be subject to claims that our employees have wrongfully used or disclosed alleged trade secrets of their former employers. If we are not able to adequately prevent disclosure of trade secrets and other proprietary information, the value of our technology and products could be significantly diminished.

As is common in the biotechnology and pharmaceutical industries, we employ individuals who were previously employed at other biotechnology or pharmaceutical companies, including our competitors or potential competitors. We may be subject to claims that these employees, or we, have inadvertently or otherwise used or disclosed trade secrets or other proprietary information of their former employers. Litigation may be necessary to defend against these claims. Even if we are successful in defending against these claims, litigation could result in substantial costs and be a distraction to management.

We rely on trade secrets to protect our proprietary technologies, especially where we do not believe patent protection is appropriate or obtainable. However, trade secrets are difficult to protect. We rely in part on confidentiality agreements with our employees, consultants, outside scientific collaborators, sponsored researchers and other advisors to protect our trade secrets and other proprietary information. These agreements may not effectively prevent disclosure of confidential information and may not provide an adequate remedy in the event of unauthorized disclosure of confidential information. In addition, others may independently discover our trade secrets and proprietary information. For example, the FDA, as part of its Transparency Initiative, is currently considering whether to make additional information publicly available on a routine basis, including information that we may consider to be trade secrets or other proprietary information, and it is not clear at the present time how the FDA s disclosure policies may change in the future, if at all. Costly and time-consuming litigation could be necessary to enforce and determine the scope of our proprietary rights, and failure to obtain or maintain trade secret protection could adversely affect our competitive business position.

We have not yet registered our trademarks and failure to secure those registrations could adversely affect our business.

If we seek to register any of our trademarks, our trademark applications may not be allowed for registration or our registered trademarks may not be maintained or enforced. During trademark registration proceedings, we may receive rejections. Although we are given an opportunity to respond to those rejections, we may be unable to overcome such rejections. In addition, in the USPTO and in comparable agencies in many other jurisdictions, third parties are given an opportunity to oppose pending trademark applications and to seek to cancel registered trademarks. Opposition or cancellation proceedings may be filed against our trademarks, and our trademarks may not survive such proceedings. If we do not secure registrations for our trademarks, we may encounter more difficulty in enforcing them against third parties than we otherwise would.

In addition, we have not yet proposed a proprietary name for any of our product candidates, including OCA, in any jurisdiction. Any proprietary name we propose to use with OCA in the United States must be approved by the FDA, regardless of whether we have registered it, or applied to register it, as a trademark. The FDA typically conducts a review of proposed product names, including an evaluation of potential for confusion with other product names. If the FDA objects to any of our proposed proprietary product names, we may be required to expend significant additional resources in an effort to identify a suitable proprietary product name that would qualify under applicable trademark laws, not infringe the existing rights of third parties and be acceptable to the FDA.

Risks Relating to Owning Our Common Stock

No public market for our common stock currently exists and an active trading market may not develop or be sustained following this offering.

Prior to this offering, there has been no public market for our common stock. An active trading market may not develop following the completion of this offering or, if developed, may not be sustained. Certain of our existing stockholders and their affiliated entities have indicated an interest in purchasing up to approximately $ million in shares of our common stock in this offering at the initial public offering price. To the extent these existing stockholders are allocated and purchase shares in this offering, such purchases would reduce the available public float for our shares because