

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  
(State or other jurisdiction of  
incorporation or organization)

2834  
(Primary Standard Industrial  
Classification Code Number)

22-3868459  
(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**  
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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. ☐

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. ☐

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. ☐

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. ☐

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

Mark Pruzanski, M.D. President and Chief Executive Officer Intercept Pharmaceuticals, Inc. 18 Desbrosses Street New York, NY 10013 (646) 747-1000

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 <sup>(1)</sup>	Amount of Registration Fee <sup>(2)</sup>
Common stock, par value \$0.001 per share	\$ 75,000,000	\$ 8,595

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**

PROSPECTUS

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.**

	<u>Per Share</u>	<u>Total</u>
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](http://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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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	
<u>Pro forma information<sup>(1)</sup></u>					
Pro forma net loss attributable to common stockholders		\$(12,737)		\$(7,766)	

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Pro forma net loss per share, basic and diluted (unaudited)	\$ (0.21 )	\$ (0.13 )
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(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		Pro Forma
	Actual	Pro Forma	As Adjusted <sup>(1)</sup>
	(In thousands)		
	(Unaudited)		
<b>Balance Sheet Data:</b>			
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	

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 (1)(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

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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;

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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:

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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.

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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.

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.

**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

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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

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

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

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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;

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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

We may not be successful in establishing and maintaining development and commercialization collaborations, which

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;

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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



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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

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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;

Our employees may engage in misconduct or other improper activities, including noncompliance with regulatory sta

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.59our 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

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

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.

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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.

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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 these existing stockholders will be

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restricted from selling the shares under the lock-up agreements described in the Shares Eligible for Future Sale section of this prospectus. As a result, the liquidity of our common stock could be significantly reduced from what it would have been if these shares had been purchased by investors that were not affiliated with us. The lack of an active market may impair your ability to sell your shares at the time you wish to sell them or at a price that you consider reasonable. The lack of an active market may also reduce the fair market value of your shares. An inactive market may also impair our ability to raise capital to continue to fund operations by selling shares and may impair our ability to acquire other companies or technologies by using our shares as consideration.

### **Our share price may be volatile, which could subject us to securities class action litigation and prevent you from being able to sell your shares at or above the offering price.**

The initial public offering price for our shares will be determined by negotiations between us and the representatives of the underwriters and may not be indicative of prices that will prevail in the trading market. The market price of shares of our common stock could be subject to wide fluctuations in response to many risk factors listed in this section, and others beyond our control, including:

- results of our clinical trials;
- results of clinical trials of our competitors' products;
- regulatory actions with respect to our products or our competitors' products;
- actual or anticipated fluctuations in our financial condition and operating results;
- actual or anticipated changes in our growth rate relative to our competitors;
- actual or anticipated fluctuations in our competitors' operating results or changes in their growth rate;
- competition from existing products or new products that may emerge;
- announcements by us, our collaborators or our competitors of significant acquisitions, strategic collaborations, joint ventures, collaborations or capital commitments;
- issuance of new or updated research or reports by securities analysts;
- fluctuations in the valuation of companies perceived by investors to be comparable to us;
- share price and volume fluctuations attributable to inconsistent trading volume levels of our shares;
- additions or departures of key management or scientific personnel;
- disputes or other developments related to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- announcement or expectation of additional financing efforts;
- sales of our common stock by us, our insiders or our other stockholders;
- market conditions for biopharmaceutical stocks in general; and
- general economic and market conditions.

Furthermore, the stock markets have experienced extreme price and volume fluctuations that have affected and continue to affect the market prices of equity securities of many companies. These fluctuations often have been unrelated or disproportionate to the operating performance of those companies. These broad market and industry fluctuations, as well as general economic, political and market conditions such as recessions, interest rate changes or international currency fluctuations, may negatively impact the market price of shares of our common stock. In addition, such fluctuations could subject us to securities class action litigation, which could result in substantial costs and divert our management's attention from other business concerns, which could seriously harm our business. If the market price of shares of our common stock after this offering does not exceed the initial public offering price, you may not realize any return on your investment in us and may lose some or all of your investment.



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**We have a significant stockholder, which will limit your ability to influence corporate matters and may give rise to conflicts of interest.**

Genextra S.p.A., together with its affiliates, whom we refer to collectively as Genextra, is our largest stockholder. When this offering is completed, Genextra is expected to beneficially own shares representing approximately % of our common stock, without giving effect to any shares that may be purchased by it in the offering. Accordingly, Genextra will exert significant influence over us and any action requiring the approval of the holders of our common stock, including the election of directors and approval of significant corporate transactions. This concentration of voting power, which would increase to the extent Genextra is allocated and purchases shares in this offering, makes it less likely that any other holder of common stock or directors of our business will be able to affect the way we are managed and could delay or prevent an acquisition of us on terms that other stockholders may desire. In addition, if Genextra retains a majority of our common stock after this offering, Genextra would be able to control all matters submitted to our stockholders for approval, as well as our management and affairs. For example, in such instance, Genextra would control the election of directors and approval of any merger, consolidation, sale of all or substantially all of our assets or other business combination or reorganization. In addition, if Genextra continues to hold a majority of our common stock, we would be deemed a controlled company for purposes of NASDAQ listing requirements. Under NASDAQ rules, a controlled company may elect not to comply with certain NASDAQ corporate governance requirements, including (i) the requirement that a majority of our board of directors consist of independent directors, (ii) the requirement that the compensation of our officers be determined or recommended to the board by a majority of independent directors or a compensation committee that is composed entirely of independent directors, and (iii) the requirement that director nominees be selected or recommended to the board by a majority of independent directors or a nominating committee that is composed of entirely independent directors.

Furthermore, the interests of Genextra may not always coincide with your interests or the interests of other stockholders and Genextra may act in a manner that advances its best interests and not necessarily those of other stockholders, including seeking a premium value for its common stock, and might affect the prevailing market price for our common stock. Our board of directors, which currently consists of six directors, including two designated by Genextra, has the power to set the number of directors on our board from time to time. Lorenzo Tallarigo, M.D., the chief executive officer of Genextra, and Paolo Fundaro, the chief financial officer of Genextra, were elected to our board of directors as nominees of Genextra under the provisions of our third amended and restated stockholders agreement that will terminate upon the completion of this offering.

**We have broad discretion in the use of net proceeds from this offering and may not use them effectively.**

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.

Although we currently intend to use the net proceeds from this offering in such a manner, we will have broad discretion in the application of the net proceeds. Our failure to apply these funds effectively could affect our ability to continue to develop and commercialize our product candidates.

## **Being a public company will increase our expenses and administrative burden.**

As a public company, we will incur significant legal, insurance, accounting and other expenses that we did not incur as a private company. In addition, our administrative staff will be required to perform additional tasks. For example, in anticipation of becoming a public company, we will need to adopt additional internal controls and disclosure controls and procedures, retain a transfer agent, adopt an insider trading policy and

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bear all of the internal and external costs of preparing and distributing periodic public reports in compliance with our obligations under the securities laws.

In addition, laws, regulations and standards applicable to public companies relating to corporate governance and public disclosure, including the Sarbanes-Oxley Act and related regulations implemented by the Securities and Exchange Commission and the NASDAQ Stock Market, are creating uncertainty for public companies, increasing legal and financial compliance costs and making some activities more time consuming. These laws, regulations and standards are subject to varying interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. This could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices. We intend to invest resources to comply with evolving laws, regulations and standards, and this investment will result in increased general and administrative expenses and may divert management's time and attention from product development activities. If our efforts to comply with new laws, regulations and standards differ from the activities intended by regulatory or governing bodies due to ambiguities related to practice, regulatory authorities may initiate legal proceedings against us and our business may be harmed. In connection with this offering, we are increasing our directors' and officers' insurance coverage, which will increase our insurance cost. In the future, it will be more expensive for us to obtain director and officer liability insurance, and we may be required to accept reduced coverage or incur substantially higher costs to obtain coverage. These factors could also make it more difficult for us to attract and retain qualified members of our board of directors, particularly to serve on our audit committee and compensation committee, and qualified executive officers.

**We are an emerging growth company and will be able to avail ourselves of reduced disclosure requirements applicable to emerging growth companies, which could make our common stock less attractive to investors.**

We are an emerging growth company, as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, and 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 not being required to comply with the auditor attestation requirements of Section 404(b) of the Sarbanes-Oxley Act, reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements, and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved. We cannot predict if investors will find our common stock less attractive because we may rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile. 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 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.

**Purchasers in this offering will experience immediate and substantial dilution in the book value of their investment.**

The initial public offering price will be substantially higher than the net tangible book value per share of shares of our common stock based on the total value of our tangible assets less our total liabilities immediately following this

We are an emerging growth company and will be able to avail ourselves of reduced disclosure requirements app

offering. Therefore, if you purchase shares of our common stock in this offering, you will experience immediate and substantial dilution of \$     per share in the price you pay for shares of our common stock as compared to its pro forma as adjusted net tangible book value, assuming an initial public offering price of \$     per share, the mid-point of the price range set forth on the cover page of this prospectus. To the extent outstanding options or warrants to purchase shares of common stock that are in the money are exercised, there will be further dilution. For further information on this calculation, see Dilution elsewhere in this prospectus.

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**A significant portion of our total outstanding shares of common stock is restricted from immediate resale but may be sold into the market in the near future. This could cause the market price of our common stock to drop significantly, even if our business is doing well.**

Sales of a substantial number of shares of our common stock in the public market could occur in the future. These sales, or the perception in the market that the holders of a large number of shares of common stock intend to sell shares, could reduce the market price of our common stock. After this offering, we will have                      outstanding shares of common stock based on the number of shares outstanding as of                      , 2012, assuming an initial public offering price of \$                      per share, the mid-point of the price range set forth on the cover page of this prospectus. Of these shares,                      shares, excluding any shares purchased by our affiliates, may be resold in the public market immediately and the remaining                      shares are currently restricted under securities laws or as a result of lock-up agreements but will be able to be resold after this offering as described in the                      Shares Eligible for Future Sale                      section of this prospectus. Moreover, after this offering, holders of an aggregate of 70,157,587 shares of our common stock, including shares underlying options and warrants of such holders, will have rights, subject to certain conditions, to require us to file registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders. We also intend to register all                      shares of common stock that we may issue under our equity compensation plans. Once we register these shares, they can be freely sold in the public market upon issuance and once vested, subject to the 180 day lock-up periods under the lock-up agreements described in the                      Underwriting                      section of this prospectus.

**Future sales and issuances of our common stock or rights to purchase common stock pursuant to our equity incentive plans and our outstanding warrants could result in additional dilution of the percentage ownership of our stockholders and could cause our share price to fall.**

We expect that significant additional capital will be needed in the future to continue our planned operations. To the extent we raise additional capital by issuing equity securities, our stockholders may experience substantial dilution. We may sell common stock, convertible securities or other equity securities in one or more transactions at prices and in a manner we determine from time to time. If we sell common stock, convertible securities or other equity securities in more than one transaction, investors may be materially diluted by subsequent sales. Such sales may also result in material dilution to our existing stockholders, and new investors could gain rights superior to our existing stockholders.

As of June 30, 2012, we had options to purchase 7,565,535 shares outstanding under our 2003 Stock Incentive Plan, as amended, or 2003 Plan, and warrants to purchase 7,122,889 shares of our common stock. On July 31, 2012, we also granted options to purchase 137,500 shares of our common stock under the 2003 Plan to to our non-employee directors as of January 1, 2012 for service during fiscal year 2012. Furthermore, we intend to adopt our 2012 Stock Incentive Plan, or 2012 Plan, under which we may grant equity awards covering up to an additional                      shares of our common stock (including the 3,211,554 shares of common stock to be added from the 2003 Plan), prior to the completion of this offering. In addition, all or some of the 3,211,554 shares of common stock added to the 2012 Plan may be granted under the 2012 Plan to our employees and directors shortly after the completion of this offering. We plan to register the number of shares available for issuance under our 2003 Plan and 2012 Plan. Sales of shares granted under our equity incentive plans or upon exercise of warrants may result in material dilution to our existing stockholders, which could cause our share price to fall.

A significant portion of our total outstanding shares of common stock is restricted from immediate resale but may be

**If securities or industry analysts do not publish research or publish inaccurate or unfavorable research about our business, our share price and trading volume could decline.**

The trading market for our common stock will depend on the research and reports that securities or industry analysts publish about us or our business. We do not have any control over these analysts. There can be no assurance that analysts will cover us or provide favorable coverage. If one or more of the analysts who cover us downgrade our stock or change their opinion of our stock, our share price would likely decline. If one or more of these analysts cease coverage of our company or fail to regularly publish reports on us, we could lose visibility in the financial markets, which could cause our share price or trading volume to decline.

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**NASDAQ may delist our securities from its exchange, which could limit investors' ability to make transactions in our securities and subject us to additional trading restrictions.**

We have applied to list our common stock on the NASDAQ Global Market. In order to make a final determination of compliance with their listing criteria, NASDAQ may look to the first trading day's activity and, particularly, the last bid price on such day. In the event the trading price for our common stock drops below the NASDAQ Global Market's \$4.00 minimum bid requirement, NASDAQ could rescind our initial listing approval. If that were to happen, the liquidity for our common stock would decrease. If we failed to list the stock on the NASDAQ Global Market, the liquidity for our common stock would be significantly impaired, which may substantially decrease the trading price of our common stock.

In addition, we cannot assure you that, in the future, our securities will meet the continued listing requirements to be listed on NASDAQ. If NASDAQ delists our common stock from trading on its exchange, we could face significant material adverse consequences, including:

- a limited availability of market quotations for our securities;
- a determination that our common stock is a penny stock which will require brokers trading in our common stock to adhere to more stringent rules and possibly resulting in a reduced level of trading activity in the secondary trading market for our common stock;
- a limited amount of news and analyst coverage for our company; and
- a decreased ability to issue additional securities or obtain additional financing in the future.

**Some provisions of our charter documents and Delaware law may have anti-takeover effects that could discourage an acquisition of us by others, even if an acquisition would be beneficial to our stockholders, and may prevent attempts by our stockholders to replace or remove our current management.**

Provisions in our restated certificate of incorporation and by-laws that will be effective upon the completion of this offering, as well as provisions of Delaware law, could make it more difficult for a third party to acquire us or increase the cost of acquiring us, even if doing so would benefit our stockholders. These provisions include:

- authorizing the issuance of blank check convertible preferred stock, the terms of which may be established and shares of which may be issued without stockholder approval;
- limiting the removal of directors by the stockholders;
- creating a staggered board of directors;
- prohibiting stockholder action by written consent, thereby requiring all stockholder actions to be taken at a meeting of our stockholders;
- eliminating the ability of stockholders to call a special meeting of stockholders;
- permitting our board of directors to accelerate the vesting of outstanding equity awards upon certain transactions that result in a change of control; and
- establishing advance notice requirements for nominations for election to the board of directors or for proposing matters that can be acted upon at stockholder meetings.

These provisions may also frustrate or prevent any attempts by our stockholders to replace or remove our current management or members of our board of directors. In addition, we are subject to Section 203 of the Delaware General Corporation Law, which generally prohibits a Delaware corporation from engaging in any of a broad range of business

combinations with an interested stockholder for a period of three years following the date on which the stockholder became an interested stockholder, unless such transactions are approved by our board of directors. This provision could have the effect of delaying or preventing a change of control, whether or not it is desired by or beneficial to our stockholders. Further, other provisions of Delaware law may also discourage, delay or prevent someone from acquiring us or merging with us.

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**Claims for indemnification by our directors and officers may reduce our available funds to satisfy successful stockholder claims against us and may reduce the amount of money available to us.**

As permitted by Section 102(b)(7) of the Delaware General Corporation Law, our restated certificate of incorporation to be in effect upon the completion of this offering will limit the liability of our directors to the fullest extent permitted by law. In addition, as permitted by Section 145 of the Delaware General Corporation Law, our restated certificate of incorporation and restated bylaws to be in effect upon the completion of this offering will provide that we shall indemnify, to the fullest extent authorized by the Delaware General Corporation Law, each person who is involved in any litigation or other proceeding because such person is or was a director or officer of our company or is or was serving as an officer or director of another entity at our request, against all expense, loss or liability reasonably incurred or suffered in connection therewith. Our restated certificate of incorporation to be in effect upon the completion of this offering will provide that the right to indemnification includes the right to be paid expenses incurred in defending any proceeding in advance of its final disposition, provided, however, that such advance payment will only be made upon delivery to us of an undertaking, by or on behalf of the director or officer, to repay all amounts so advanced if it is ultimately determined that such director is not entitled to indemnification. If we do not pay a proper claim for indemnification in full within 60 days after we receive a written claim for such indemnification, except in the case of a claim for an advancement of expenses, in which case such period is 20 days, our restated certificate of incorporation and our restated bylaws authorize the claimant to bring an action against us and prescribe what constitutes a defense to such action.

Section 145 of the Delaware General Corporation Law permits a corporation to indemnify any director or officer of the corporation against expenses (including attorney's fees), judgments, fines and amounts paid in settlement actually and reasonably incurred in connection with any action, suit or proceeding brought by reason of the fact that such person is or was a director or officer of the corporation, if such person acted in good faith and in a manner that he reasonably believed to be in, or not opposed to, the best interests of the corporation, and, with respect to any criminal action or proceeding, if he or she had no reason to believe his or her conduct was unlawful. In a derivative action, (*i.e.*, one brought by or on behalf of the corporation), indemnification may be provided only for expenses actually and reasonably incurred by any director or officer in connection with the defense or settlement of such an action or suit if such person acted in good faith and in a manner that he or she reasonably believed to be in, or not opposed to, the best interests of the corporation, except that no indemnification shall be provided if such person shall have been adjudged to be liable to the corporation, unless and only to the extent that the court in which the action or suit was brought shall determine that the defendant is fairly and reasonably entitled to indemnity for such expenses despite such adjudication of liability.

The rights conferred in the restated certificate of incorporation and the restated bylaws are not exclusive, and we are authorized to enter into indemnification agreements with our directors, officers, employees and agents and to obtain insurance to indemnify such persons. We have entered into or plan to enter into indemnification agreements with each of our officers and directors, the form of which is attached as an exhibit to the registration statement of which this prospectus is a part.

The above limitations on liability and our indemnification obligations limit the personal liability of our directors and officers for monetary damages for breach of their fiduciary duty as directors by shifting the burden of such losses and expenses to us. Although we plan to increase the coverage under our directors' and officers' liability insurance, certain liabilities or expenses covered by our indemnification obligations may not be covered by such insurance or the coverage limitation amounts may be exceeded. As a result, we may need to use a significant amount of our funds to satisfy our indemnification obligations, which could severely harm our business and financial condition and limit the

Claims for indemnification by our directors and officers may reduce our available funds to satisfy successful stockholder

funds available to stockholders who may choose to bring a claim against our company.

**We do not anticipate paying cash dividends, and accordingly, stockholders must rely on stock appreciation for any return on their investment.**

We do not anticipate paying cash dividends in the future. As a result, only appreciation of the market price of our common stock, which may never occur, will provide a return to stockholders. Investors seeking cash dividends should not invest in our common stock.

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**Our ability to use our net operating loss carryforwards and certain other tax attributes may be limited.**

As of December 31, 2011 and June 30, 2012, we had federal net operating loss carryforwards, or NOLs, of \$55.0 million and \$63.9 million, respectively, which expire from 2024 through 2032. Our ability to utilize our NOLs may be limited under Section 382 of the Internal Revenue Code. The limitations apply if an ownership change, as defined by

Section 382, occurs. Generally, an ownership change occurs when certain shareholders increase their aggregate ownership by more than 50 percentage points over their lowest ownership percentage in a testing period (typically three years). We have assessed whether one or more ownership changes as defined under Section 382 have occurred since our inception and have determined that there have been at least two such changes. Accordingly, although we believe that these ownership changes have not resulted in material limitations on our ability to use these NOLs, our ability to utilize the aforementioned carryforwards may be limited. Additionally, U.S. tax laws limit the time during which these carryforwards may be utilized against future taxes. As a result, we may not be able to take full advantage of these carryforwards for federal and state tax purposes. Future changes in stock ownership may also trigger an ownership change and, consequently, a Section 382 limitation.

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## **CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS**

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

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

- our ability to obtain additional financing;
- our use of the net proceeds from this offering;
- the accuracy of our estimates regarding expenses, future revenues and capital requirements;
- the success and timing of our preclinical studies and clinical trials;
- our ability to obtain and maintain regulatory approval of OCA and any other product candidates we may develop, and the labeling under any approval we may obtain;
- regulatory developments in the United States and other countries;
- the performance of third-party manufacturers;
- our plans to develop and commercialize our product candidates;
- our ability to obtain and maintain intellectual property protection for our product candidates;
- the successful development of our sales and marketing capabilities;
- the potential markets for our product candidates and our ability to serve those markets;
- the rate and degree of market acceptance of any future products;
- the success of competing drugs that are or become available; and
- the loss of key scientific or management personnel.

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

The forward-looking statements in this prospectus represent our views as of the date of this prospectus. We anticipate that subsequent events and developments will cause our views to change. However, while we may elect to update these forward-looking statements at some point in the future, we have no current intention of doing so except to the extent required by applicable law. You should, therefore, not rely on these forward-looking statements as representing our views as of any date subsequent to the date of this prospectus.



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## **Industry and Market Data**

This prospectus contains estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. We obtained the industry and market data in this prospectus from our own research as well as from industry and general publications, surveys and studies conducted by third parties.

This data involves a number of assumptions and limitations and contains projections and estimates of the future performance of the industries in which we operate that are subject to a high degree of uncertainty. We caution you not to give undue weight to such projections, assumptions and estimates. Further, industry and general publications, studies and surveys generally state that they have been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. While we believe that these publications, studies and surveys are reliable, we have not independently verified the data contained in them. In addition, while we believe that the results and estimates from our internal research are reliable, such results and estimates have not been verified by any independent source.

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## USE OF PROCEEDS

We estimate that our net proceeds from the sale of shares of common stock in this offering will be approximately \$ million after deducting underwriting discounts and commissions and estimated offering expenses payable by us and assuming an initial public offering price of \$ per share, the mid-point of the price range set forth on the cover page of this prospectus. If the over-allotment option is exercised in full, we estimate that our net proceeds will be approximately \$ million. A \$1.00 increase (decrease) in the assumed initial public offering price per share of \$ , the mid-point of the price range set forth on the cover page of this prospectus, would increase (decrease) the net proceeds to us from this offering by \$ million, assuming the number of shares offered by us, as set forth on the cover page of this prospectus, remains the same and after deducting underwriting discounts and estimated offering expenses payable by us.

The principal purposes of this offering are to obtain additional capital to support our operations, to create a public market for our common stock and to facilitate our future access to the public equity markets. We intend to use the net proceeds from this offering as follows:

- approximately \$17.0 million to fund the continued clinical development and other studies and work needed for the anticipated FDA and EMA filings for OCA as a treatment for PBC, as detailed below;
- approximately \$13.0 million to fund the continuation of the long-term safety extension portion of our POISE clinical trial and the Phase 3 clinical outcomes trial after the anticipated FDA and EMA filings;
- approximately \$5.0 million to fund certain pre-commercialization activities of OCA for PBC;
- approximately \$4.0 million to fund further preclinical development work on INT-767 and, if warranted, Phase 1 clinical trials of INT-767;
- approximately \$5.0 million to fund the initiation of a Phase 2 clinical trial for an additional indication for OCA, such as portal hypertension, if warranted; and
- the remainder for general corporate purposes, general and administrative expenses, capital expenditures, working capital and prosecution and maintenance of our intellectual property.

We believe that the remaining clinical development and other studies and work needed for anticipated FDA and EMA filings for the approval of OCA as a treatment for PBC will require approximately \$40.0 million. We believe that our 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, along with the intended net proceeds from this offering, together with interest on cash balances, will be sufficient to fund the continued development of OCA through the following events:

- the completion of our Phase 3 POISE trial;
- initiation of the long-term safety extension portion of the POISE trial and continuation of the ongoing long-term safety extension portion of the Phase 2 monotherapy clinical trial;
- initiation of a Phase 3 clinical outcomes trial to confirm clinical benefit of OCA in PBC;
- two-year animal carcinogenicity studies in both rats and mice;
- 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, and additional Phase 1 clinical trials;
- manufacturing of clinical drug supply and materials necessary for the anticipated FDA and EMA filings;
- the initiation of a Phase 2 clinical trial for an additional indication for OCA, such as portal hypertension, if warranted; and
- the work required for assimilation, preparation and submission of the anticipated FDA and EMA filings.

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The amount and timing of our actual expenditures will depend upon numerous factors, including the ongoing status and results of the POISE trial. Furthermore, we anticipate that we will need to secure additional funding for the further development of OCA for other indications and for the development of our other product candidates.

Our expected use of net proceeds from this offering represents our current intentions based upon our present plans and business condition. As of the date of this prospectus, we cannot predict with certainty all of the particular uses for the net proceeds to be received upon the completion of this offering or the amounts that we will actually spend on the uses set forth above. The amounts and timing of our actual use of net proceeds will vary depending on numerous factors, including our ability to obtain additional financing, the relative success and cost of our research, preclinical and clinical development programs, the amount and timing of additional revenues, if any, received from our collaborations with DSP and Servier and whether we are able to enter into future collaborations. As a result, management will have broad discretion in the application of the net proceeds, and investors will be relying on our judgment regarding the application of the net proceeds of this offering. In addition, we might decide to postpone or not pursue other clinical trials or preclinical activities if the net proceeds from this offering and the other sources of cash are less than expected.

Pending their use, we plan to invest the net proceeds from this offering in short- and intermediate-term, interest-bearing obligations, investment-grade instruments, certificates of deposit or direct or guaranteed obligations of the U.S. government.

## **DIVIDEND POLICY**

We have never paid or declared any cash dividends on our common stock, and we do not anticipate paying any cash dividends on our common stock in the foreseeable future. We intend to retain all available funds and any future earnings to fund the development and expansion of our business. Any future determination to pay dividends will be at the discretion of our board of directors and will depend upon a number of factors, including our results of operations, financial condition, future prospects, contractual restrictions, restrictions imposed by applicable law and other factors our board of directors deems relevant.

TABLE OF CONTENTS**CAPITALIZATION**

The following table sets forth our cash and cash equivalents and capitalization as of June 30, 2012:

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) 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 issuance and sale of shares of our common stock in this offering at an assumed initial public offering price of \$ per share, which is the midpoint of the price range listed on the cover page of this prospectus, after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

The unaudited pro forma as adjusted information below is prepared for illustrative purposes only and our capitalization following the completion of this offering will be adjusted based on the actual initial public offering price and other terms of this offering determined at pricing. You should read this table together with Selected Financial Data, our financial statements and the related notes appearing at the end of this prospectus and the Management's Discussion and Analysis of Financial Condition and Results of Operations section of this prospectus.

	As of June 30, 2012		
	Actual	Pro Forma	Pro Forma as Adjusted <sup>(1)</sup>
	(In thousands, except share amounts) (Unaudited)		
Cash and cash equivalents	\$9,947	\$39,747	\$
Warrant liability	4,856	5,280	
Preferred stock, \$0.001 par value; 27,777,778 shares authorized, issued and outstanding, actual; 52,777,778 shares authorized and no shares issued and outstanding, pro forma; and shares authorized and no shares issued and outstanding, pro forma as adjusted	28		
Stockholders' equity (deficit):			
Common stock, \$0.001 par value; 57,000,000 shares authorized, 19,238,418 shares issued and outstanding, actual; 150,000,000 shares authorized and 62,016,196 shares issued and outstanding, pro forma; shares authorized and shares issued and outstanding, pro forma as adjusted	19	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	
Total capitalization	\$(4,524)	\$25,277	\$

(1)

A \$1.00 increase (decrease) in the assumed initial public offering price of \$      per share would increase (decrease) each of the pro forma as adjusted cash and cash equivalents, additional paid-in capital, total stockholders' equity and total capitalization by \$      million, assuming the shares offered by us as set forth on the cover of this prospectus remain the same and after deducting the underwriting discounts and commissions and estimated offering expenses payable by us.

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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. It does not include:

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;

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.

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If you invest in our common stock, your ownership interest will be diluted to the extent of the difference between the initial public offering price per share of our common stock and the pro forma as adjusted net tangible book value per share of our common stock immediately after this offering. Dilution results from the fact that the initial public offering price per share is substantially in excess of the book value (deficit) per share attributable to the existing stockholders for the presently outstanding stock. As of June 30, 2012, our net tangible book value (deficit) was \$(9.4) million, or \$(0.49) per share of common stock. Net tangible book value (deficit) per share represents the amount of our total tangible assets less total liabilities, divided by 19,238,418, the number of shares of common stock outstanding on June 30, 2012.

Our pro forma net tangible book value (deficit) as of June 30, 2012 was \$20.0 million, or \$0.32 per share of common stock. Pro forma net tangible book value (deficit) per share represents the amount of our total tangible assets less our total liabilities, divided by the number of shares of our common stock outstanding, as of June 30, 2012, 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, (ii) the conversion of the 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) the reclassification of certain warrants with registration rights upon the completion of this offering from stockholders equity to warrant liability.

After giving effect to the sale of      shares of our common stock in this offering, assuming an initial public offering price of \$      per share, the mid-point of the price range set forth on the cover page of this prospectus, after deducting underwriting discounts and commissions and estimated offering expenses payable by us, our pro forma as adjusted net tangible book value as of June 30, 2012 would have been \$      million, or \$      per share. This amount represents an immediate increase in pro forma as adjusted net tangible book value of \$      per share to our existing stockholders and an immediate dilution in pro forma as adjusted net tangible book value of approximately \$      per share to new investors purchasing shares of our common stock in this offering. We determine dilution by subtracting the pro forma as adjusted net tangible book value per share after the offering from the amount of cash that a new investor paid for a share of common stock.

The following table illustrates this dilution on a per share basis:

Assumed initial public offering price per share	\$
Historical net tangible book value (deficit) per share as of June 30, 2012	\$(0.49)
Increase per share due to the conversion of all shares of preferred stock	0.34
Decrease per share due to the reclassification of warrants with registration rights to liability	(0.01)
Increase per share due to the issuance of Series C preferred stock	0.48
Pro forma net tangible book value (deficit) per share as of June 30, 2012	\$0.32
Increase per share attributable to new investors	
Pro forma net tangible book value per share after the offering	
Dilution per share to new investors	\$

If the underwriters exercise their option to purchase additional shares in full, the pro forma as adjusted net tangible book value per share after giving effect to the offering would be \$      per share. This represents an increase in pro forma as adjusted net tangible book value of \$      per share to existing stockholders and dilution in pro forma as

adjusted net tangible book value of \$      per share to new investors.

A \$1.00 increase (decrease) in the assumed initial public offering price of \$      , the mid-point of the price range set forth on the cover page of this prospectus, would increase (decrease) our pro forma as adjusted net tangible book value after this offering by \$      million and the pro forma as adjusted net tangible book value per share after this offering by \$      per share and would increase (decrease) the dilution per share to new investors in this offering by \$      per share, assuming the number of shares offered by us, as set forth on the cover page of this prospectus, remains the same. The information discussed above is illustrative only and may change based on the actual initial public offering price and other terms of the offering determined at pricing.

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The following table summarizes, on a pro forma as adjusted basis as of June 30, 2012, the total number of shares purchased from us, the total consideration paid, or to be paid, and the average price per share paid, or to be paid, by existing stockholders and by new investors in this offering at an assumed initial public offering price of \$     per share, which is the midpoint of the price range listed on the cover page of this prospectus, before deducting underwriting discounts and commissions and estimated offering expenses payable by us. As the table shows, new investors purchasing shares in this offering will pay an average price per share substantially higher than our existing stockholders paid.

	Shares Purchased		Total Consideration		Average Price Per Share
	Number	Percentage	Amount	Percentage	
Existing stockholders		%	\$	%	\$
New investors					
Total		100 %	\$	100 %	\$

The table above is based on (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 table above does not include:

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;

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.

If the underwriters exercise their option to purchase additional shares in full, the following will occur:

the percentage of shares of our common stock held by existing stockholders will decrease to approximately % of the total number of shares of our common stock outstanding after this offering; and the number of shares of our common stock held by new investors will increase to     , or approximately % of the total number of shares of our common stock outstanding after this offering.

To the extent that outstanding options or warrants are exercised, you will experience further dilution. In addition, we may choose to raise additional capital due to market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. To the extent that additional capital is raised through the sale of equity or convertible debt securities, the issuance of these securities may result in further dilution to our stockholders.

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

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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. The foregoing discussion and tables do not reflect any potential purchases by these existing stockholders or their affiliated entities. After giving effect to the purchase of shares in this offering by these existing stockholders, assuming an initial public offering price of \$      per share, the mid-point of the price range set forth on the cover page of this prospectus, our existing stockholders will hold      % (      % if the underwriters exercise their over-allotment in full) of our common stock outstanding after this offering based on (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 new investors purchasing the remaining shares in this offering will hold      % (      % if the underwriters exercise their over-allotment in full) of our common stock outstanding after this offering.

TABLE OF CONTENTS**SELECTED FINANCIAL DATA**

The following table sets forth our selected financial data for the periods and as of the dates indicated. You should read the following selected financial data in conjunction with our audited and unaudited financial statements and the related notes thereto included elsewhere in this prospectus and the Management's Discussion and Analysis of Financial Condition and Results of Operations section of this prospectus.

The statement of operations data for the years ended December 31, 2010 and 2011, and the balance sheet data as of December 31, 2010 and 2011, are derived from our audited financial statements included elsewhere in this prospectus.

The statement of operations data 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, and the balance sheet data as of June 30, 2012, are derived from our unaudited financial statements and the related notes thereto included elsewhere in this prospectus. Our interim unaudited financial statements have been prepared in accordance with generally accepted accounting principles in the United States of America, or GAAP, on the same basis as the annual audited financial statements and, in the opinion of management, reflect all adjustments, consisting only of normal recurring adjustments, necessary to present a fair statement of our financial position as of June 30, 2012 and the results of our operations for the six months ended June 30, 2011 and 2012 and for the period from inception (September 4, 2002) to June 30, 2012.

Our historical results are not necessarily indicative of the results that may be expected in the future and interim results are not necessarily indicative of results to be expected for any other period or the full year.

	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)				(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, 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)

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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	

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	Years Ended December 31,	Six Months Ended June 30,	Period From September 4, 2002 (Inception) Through June 30, 2012
	20102011	2012012	
	(In thousands, except share and per share amounts)		
		(Unaudited)	(Unaudited)
<u>Pro forma information</u> <sup>(1)</sup>			
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.

	December 31, 2010	2011	June 30, 2012
	(In thousands)		
			(Unaudited)
Balance Sheet Data:			
Cash and cash equivalents	\$ 15,424	\$ 17,707	\$ 9,947
Total assets	17,118	19,470	12,145
Accounts payable, accrued expenses, and other liabilities	1,587	1,504	3,578
Warrant liability	6,881	5,836	4,856
Deferred revenue		14,608	13,091
Common and preferred stock	47	47	47
Additional paid-in capital	70,252	72,118	72,879
Accumulated deficit during development stage	(61,803 )	(74,540 )	(82,306 )
Total stockholders' equity (deficit)	8,318	(2,560 )	(9,380 )

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# MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

*You should read the following discussion and analysis of our financial condition and results of operations together with Selected Financial Data and our financial statements and the related notes appearing elsewhere in this prospectus. In addition to historical information, this discussion and analysis contains forward-looking statements that involve risks, uncertainties and assumptions. Our actual results may differ materially from those discussed below. Factors that could cause or contribute to such differences include, but are not limited to, those identified below, and those discussed in the section titled Risk Factors included elsewhere in this prospectus.*

## Overview

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

We have devoted substantially all of our resources to our development efforts relating to our product candidates, including conducting clinical trials of our product candidates, providing general and administrative support for these operations and protecting our intellectual property. We do not have any products approved for sale and have not generated any revenue from product sales. From our inception until June 30, 2012, we have funded our operations primarily through the private placement of preferred stock, common stock, convertible notes and warrants to purchase common stock totaling \$70.6 million and through the receipt of \$16.4 million of up-front payments under our collaborative agreements.

On August 9, 2012, we entered into a securities purchase agreement with an affiliated fund of OrbiMed Advisors LLC and Genextra S.p.A., pursuant to which we agreed to issue up to an aggregate of 25,000,000 shares of our Series C preferred stock at a price of \$2.00 per share for gross proceeds of up to \$50.0 million. The securities purchase agreement provides that the Series C preferred stock may be issued in two tranches consisting of 15,000,000 and 10,000,000 shares. The first tranche of Series C preferred stock was issued on August 9, 2012, and resulted in \$29.8 million of net proceeds to us. The closing of the second tranche of Series C preferred stock will only occur if we do not complete an initial public offering of our common stock on or prior to the one year anniversary of the closing of the first tranche. Each share of Series C preferred stock will initially be convertible into one share of our common stock, subject to adjustment. All of our outstanding shares of Series C preferred stock will convert into 15,000,000 shares of our common stock upon the completion of this offering. The investors have been granted certain demand and piggyback registration rights in respect of their securities under our third amended and restated stockholders agreement.

We have incurred net losses in each year since our inception in 2002. Our net losses were approximately \$15.1 million and \$12.7 million for the years ended December 31, 2010 and 2011, respectively, and \$6.3 million and \$7.8 million for the six months ended June 30, 2011 and 2012, respectively. As of June 30, 2012, we had an accumulated deficit of approximately \$82.3 million. Substantially all our net losses resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations.

We expect to continue to incur significant expenses and increasing operating losses for at least the next several years.

We anticipate that our expenses will increase substantially as we:

complete the development of our lead product candidate, obeticholic acid, or OCA, for the treatment of primary biliary cirrhosis, or PBC;

seek to obtain regulatory approvals for OCA;

outsource the commercial manufacturing of OCA for any indications for which we receive regulatory approval;

contract with third parties for the sales, marketing and distribution of OCA for any indications for which we receive regulatory approval;

maintain, expand and protect our intellectual property portfolio;

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continue our research and development efforts;  
add operational, financial and management information systems and personnel, including personnel to support our product development and commercialization efforts; and

operate as a public company.

We do not expect to generate revenue from product sales unless and until we successfully complete development and obtain marketing approval for one or more of our product candidates, which we expect will take a number of years and is subject to significant uncertainty. Accordingly, we anticipate that we will need to raise additional capital in addition to the net proceeds of this offering prior to the commercialization of OCA or any of our other product candidates. Until such time, if ever, as we can generate substantial revenue from product sales, we expect to finance our operating activities 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. However, we may be unable to raise additional funds or enter into such other arrangements when needed on favorable terms or at all. Our failure to raise capital or enter into such other arrangements as and when needed would have a negative impact on our financial condition and our ability to develop our product candidates.

Prior to April 2011, we operated a wholly-owned subsidiary in Italy where our bile acid receptor research was primarily conducted. We are currently in the process of liquidating this subsidiary. However, we are continuing our early stage TGR5 research through our collaboration with Servier. Although our Italian subsidiary is currently in liquidation and essentially inactive, we do not intend to liquidate this subsidiary for some time because it acts as our legal representative for Phase 3 clinical trials in the European Union to satisfy European Union regulatory requirements.

## **Financial Overview**

### **Revenue**

To date, we have not generated any revenue from the sale of products. All our revenue has been derived from our collaborative agreements for the development and commercialization of certain of our product candidates. In March 2011, we entered into an exclusive licensing agreement with Dainippon Sumitomo Pharma Co. Ltd., or DSP, for the development of OCA in Japan and China. Under the terms of the agreement, we received an up-front payment of \$15.0 million and may be eligible to receive up to approximately \$300 million in additional payments for development, regulatory and commercial sales milestones for OCA in Japan and China. In August 2011, we entered into a collaboration agreement with Les Laboratoires Servier and Institut de Recherches Servier, or collectively Servier, for the discovery, research and development of bile acid-derived agonists, or substances that bind to receptors of cells and trigger responses by those cells, for a dedicated bile acid receptor called TGR5. Under the terms of the agreement, we received an up-front payment from Servier of \$1.4 million. Servier may be required to pay us up to an aggregate amount of approximately €108 million (equivalent to approximately \$135.0 million as of June 30, 2012) upon the achievement of specified development, regulatory and commercial sale milestones, as well as royalties on sales, based on the successful outcome of the collaboration. For accounting purposes, the up-front payments from both transactions are recorded as deferred revenue and amortized over time. Through the six months ended June 30, 2012, we recognized \$3.3 million in license revenue for the relevant amortization of the two up-front payments. We expect to recognize as revenue an additional \$0.9 million for the amortization of these payments through 2012 and do not expect to receive any milestone payments during 2012 related to these agreements. The Servier up-front payment is expected to be fully amortized in the third quarter of 2012. We anticipate that we will recognize revenue of approximately \$1.6 million per year through 2020, the expected end of the development period, for the amortization of the up-front payment from DSP.



TABLE OF CONTENTS***Research and Development Expenses***

Since our inception, we have focused our resources on our research and development activities, including conducting preclinical studies and clinical trials, manufacturing development efforts and activities related to regulatory filings for our product candidates. We recognize research and development expenses as they are incurred. Our research and development expenses consist primarily of:

salaries and related overhead expenses for personnel in research and development functions;  
 fees paid to consultants and clinical research organizations, or CROs, including in connection with our preclinical and clinical trials, and other related clinical trial fees, such as for investigator grants, patient screening, laboratory work, clinical trial database management, clinical trial material management and statistical compilation and analysis;  
 costs related to acquiring and manufacturing clinical trial materials;  
 depreciation of leasehold improvements, laboratory equipment and computers;  
 costs related to compliance with regulatory requirements; and  
 costs related to stock options or other stock-based compensation granted to personnel in research and development functions.

From inception through June 30, 2012, we have incurred approximately \$63.3 million in research and development expenses. We plan to increase our research and development expenses for the foreseeable future as we continue the development of OCA for the treatment of PBC and other indications and to further advance the development of our other product candidates, subject to the availability of additional funding.

The table below summarizes our direct research and development expenses by program for the periods indicated. Our direct research and development expenses consist principally of external costs, such as fees paid to investigators, consultants, central laboratories and CROs, in connection with our clinical trials, and costs related to acquiring and manufacturing clinical trial materials. We have been developing OCA and other agonists of the farnesoid X receptor, or FXR, as well as TGR5 agonists, and typically use our employee and infrastructure resources across multiple research and development programs. We do not allocate salaries, stock-based compensation, employee benefit or other indirect costs related to our research and development function to specific product candidates. Those expenses are included in Indirect research and development expense in the table below.

	Years Ended, December 31, 2010      2011 (In thousands)		Six Months Ended, June 30, 2011      2012 (Unaudited)	
Direct research and development expense by program:				
OCA	\$ 8,001	\$ 8,056	\$ 3,033	\$ 5,922
INT-777	2,234	195	312	13
Total direct research and development expense	10,235	8,251	3,345	5,935
Personnel costs	2,078	2,750	1,180	1,830
Indirect research and development expense	397	425	226	313
Total research and development expense	\$ 12,710	\$ 11,426	\$ 4,751	\$ 8,078

The successful development of our clinical and preclinical product candidates is highly uncertain. At this time, we cannot reasonably estimate the nature, timing or costs of the efforts that will be necessary to complete the remainder of the development of any of our clinical or preclinical product candidates or the period, if any, in which material net cash inflows from these product candidates may commence. This is due to the numerous risks and uncertainties

associated with developing drugs, including the uncertainty of:

the scope, rate of progress and expense of our ongoing, as well as any additional, clinical trials and other research and development activities;

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future clinical trial results; and  
the timing and receipt of any regulatory approvals.

A change in the outcome of any of these variables with respect to the development of a product candidate could mean a significant change in the costs and timing associated with the development of that product candidate. For example, if the U.S. Food and Drug Administration, or FDA, or another regulatory authority were to require us to conduct clinical trials beyond those that we currently anticipate will be required for the completion of clinical development of a product candidate or if we experience significant delays in enrollment in any of our clinical trials, we could be required to expend significant additional financial resources and time on the completion of clinical development.

## **OCA**

The majority of our research and development resources are focused on the Phase 3 POISE trial and our other planned clinical and preclinical studies and other work needed to submit OCA for the treatment of PBC for regulatory approval in the United States and Europe. We have incurred and expect to continue to incur significant expense in connection with these efforts, including:

In January 2012, we initiated enrollment in our POISE trial, a Phase 3 clinical trial in patients with PBC. We currently expect results from the trial to be available by mid-2014. Patients who complete twelve months of treatment will be eligible to continue in an open label safety extension trial for five years.

We are continuing to treat PBC patients from our Phase 2 trial with OCA in a long-term safety extension trial. As of August 31, 2012, there were 27 patients being followed in this trial and we anticipate the trial to continue through 2014.

We are currently dosing both mice and rats to investigate the carcinogenic potential of OCA. We anticipate dosing will be completed in the first quarter of 2014.

We plan to initiate 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, and additional Phase 1 clinical trials in 2013.

We have contracted with third-party manufacturers to produce the quantities of OCA needed for regulatory approval as well as the necessary supplies for our other contemplated trials.

In addition, we are evaluating OCA in other chronic liver and other diseases. In connection with these efforts, we have incurred and expect to incur significant expenses relating to our agreement with the National Institute of Diabetes and

Digestive and Kidney Diseases, or NIDDK, for milestones related to the FLINT trial, a Phase 2b clinical trial in patients with nonalcoholic steatohepatitis, or NASH. These expenses include \$1.0 million that was paid in June 2012 and an additional \$1.25 million that is required to be paid within 60 days of full enrollment of the FLINT trial, which is expected to occur in 2012.

## **INT-767 and INT-777**

We are currently conducting research in collaboration with Servier to discover and develop additional novel TGR5 agonists. We intend to continue to develop our two existing compounds not included in this collaboration, our dual FXR/TGR5 agonist INT-767 through preclinical development and, if warranted, Phase 1 clinical trials and INT-777 through potential collaborations with third parties, over the next several years.

## **General and Administrative Expenses**

General and administrative expenses consist primarily of salaries and related costs for employees in executive, operational, finance and human resources functions. Other significant general and administrative expenses include allocation of facilities costs, professional fees for directors, accounting and legal services and expenses associated

with obtaining and maintaining patents.

We expect that our general and administrative expenses will increase as we operate as a public company and due to the potential commercialization of our product candidates. We believe that these increases will likely include increased costs for director and officer liability insurance, costs related to the hiring of

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additional personnel and increased fees for outside consultants, lawyers and accountants. We also expect to incur increased costs to comply with corporate governance, internal controls and similar requirements applicable to public companies.

### **Interest Income (Expense), Net**

Interest income consists of interest earned on our cash and cash equivalents. We expect our interest income to increase following the completion of this offering as we invest the net proceeds from this offering pending their use in our operations.

Interest expense pertains to equipment currently under a capitalized lease. This capitalized lease matures in 2012 and, as such, we will no longer be subject to the interest expense under this capitalized lease.

### **Mark-to-Market Warrant Revaluation Income (Expense)**

In conjunction with various financing transactions, we issued warrants to purchase shares of our common stock. Certain of the warrants include a provision that provides for a reduction in the warrant exercise price if there are subsequent issuances of additional shares of common stock for consideration per share less than the applicable per share warrant exercise price. The warrants containing this provision are deemed to be derivative instruments and as such, are recorded as a liability and marked-to-market at each reporting period using a Black-Scholes option-pricing model. Certain warrants that do not have these down-round provisions, and are currently classified in equity, contain provisions that require the shares of common stock underlying such warrants to be registered upon an initial public offering. Upon completion of this offering, we will reclassify these warrants as liabilities and record warrant revaluation income (expense) in the statement of operations. The fair value estimates of these warrants are based, in part, on subjective assumptions and could differ materially in the future. Non-cash changes in the fair value of the common stock warrant liability from the prior period is recorded as a component of other income and expense. We will continue to adjust the fair value of the common stock warrant liability at the end of each reporting period for changes in fair values until the earlier of the exercise or expiration of the applicable common stock warrants or until such time that the warrants are no longer determined to be derivative instruments.

## **Critical Accounting Policies and Estimates**

Our management's discussion and analysis of our financial condition and results of operations is based on our consolidated financial statements, which we have prepared in accordance with generally accepted accounting principles in the United States, or GAAP. The preparation of these consolidated financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the financial statements, as well as the reported revenues and expenses during the reporting periods. We evaluate these estimates and judgments on an ongoing basis. We base our estimates on historical experience and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Our actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are more fully described in note 2 to our consolidated financial statements appearing elsewhere in this prospectus, we believe that the following accounting policies are the most critical for fully understanding and evaluating our financial condition and results of operations.

## Revenue Recognition

We recognize revenue when the following criteria are met: persuasive evidence that an arrangement exists, services have been rendered, the price is fixed or determinable and collectability is reasonably assured.

We have entered into collaboration agreements with DSP and Servier. The terms of these agreements include nonrefundable up-front licensing fees, in addition to potential milestone payments and royalties on any future product sales developed by the collaborators under our licenses. We assess these multiple elements in order to determine whether particular components of the arrangement represent separate units of accounting.

We recognize up-front license payments as revenue upon delivery of the license only if the license has stand-alone value. The underlying performance obligations are accounted for separately as the obligations are

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fulfilled. If the license is considered as not having stand-alone value, the arrangement is accounted for as a single unit of accounting and the license payments and payments for performance obligations are recognized as revenue over the estimated period of when the performance obligations are performed.

Whenever we determine that an arrangement should be accounted for as a single unit of accounting, we determine the period over which the performance obligations will be performed and revenue will be recognized. If we cannot reasonably estimate the timing and the level of effort to complete our performance obligations under the arrangement, then we recognize revenue under the arrangement on a straight-line basis over the period that we expect to complete our performance obligations.

Our collaboration agreements also provide for potential milestone payments to us, none of which have been received to date. Revenues from milestone payments, if they are non-refundable and considered substantive, are recognized upon successful accomplishment of the milestones. If milestones are not considered substantive, milestone payments are initially deferred and recognized over the remaining performance obligation.

To date, we have not received any royalty payments and accordingly have not recognized any related revenue. We will recognize royalty revenue upon the sale of the related products, provided we have no remaining performance obligations under the arrangement.

We record deferred revenue when payments are received in advance of the culmination of the earnings process. This revenue is recognized in future periods when the applicable revenue recognition criteria have been met.

## **Valuation of Stock-Based Compensation and Warrant Liability**

### **Stock-Based Compensation**

We record the fair value of stock options issued to employees as of the grant date as compensation expense. We recognize compensation expense over the requisite service period, which is the vesting period. For non-employees, we also record stock options at their fair value as of the grant date. We then periodically re-measure the awards to reflect the current fair value at each reporting period until the non-employee completes the performance obligation or the date on which a performance commitment is reached. Expense is recognized over the related service period.

Stock-based compensation expense includes stock options granted to employees and non-employees and has been reported in our statements of operations as follows:

	Years Ended December 31, 2010      2011 (In thousands)		Six Months Ended June 30, 2011      2012 (Unaudited)	
Research and development	\$ 648	\$ 472	\$ 341	\$ 289
General and administrative	1,045	1,394	411	472
Total	\$ 1,693	\$ 1,866	\$ 752	\$ 761

We calculate the fair value of stock-based compensation awards using the Black-Scholes option-pricing model. The Black-Scholes option-pricing model requires the use of subjective assumptions, including stock price volatility, the expected life of stock options, risk free interest rate and the fair value of the underlying common stock on the date of

grant. Our key assumptions are:

We do not have sufficient history to estimate the volatility of our common stock price. We calculate expected volatility based on reported data for selected reasonably similar publicly traded companies for which the historical information is available. For the purpose of identifying peer companies, we consider characteristics such as industry, length of trading history, similar vesting terms and in-the-money option status. We plan to continue to use the guideline peer group volatility information until the historical volatility of our common stock is relevant to measure expected volatility for future option grants.

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The assumed dividend yield is based on our expectation of not paying dividends for the foreseeable future. We determine the average expected life of stock options based on the simplified method in accordance with the Securities and Exchange Commission Staff Accounting Bulletin Nos. 107 and 110, as our shares are not publicly traded. We expect to use the simplified method until we have sufficient historical exercise data to provide a reasonable basis upon which to estimate expected term.

We determine the risk-free interest rate by reference to implied yields available from U.S. Treasury securities with a remaining term equal to the expected life assumed at the date of grant.

We estimate forfeitures based on our historical analysis of actual stock option forfeitures.

The assumptions used in the Black-Scholes option-pricing model for the years ended December 31, 2010 and 2011 are set forth below:

	Years Ended December 31,			
	2010		2011	
Volatility	112	11%	107	11%
Expected term (in years)	5.6	5.7	5.0	6.0
Risk-free interest rate	1.6	1.7%	1.1	1.4%
Expected dividend yield		%		%
Stock price	\$ 1.50		\$ 1.50	

The following table presents the grant dates, number of underlying shares and related exercise prices of stock options granted to employees and consultants from January 1, 2010 through August 31, 2012, as well as the estimated fair value of the underlying common stock at each grant date.

Grant Date	Number of Shares	Exercise Price and Fair Value Per Share	Aggregate Intrinsic Value (In thousands)
8/16/2010	2,467,500	\$ 1.50	
9/6/2010	167,500	\$ 1.50	
10/13/2011	1,242,100	\$ 1.50	
12/15/2011	35,000	\$ 1.50	
7/31/2012	137,500	\$ 1.61	

The estimated fair value of common stock per share in the table above represents the determination by our board of directors of the fair value of our common stock as of each date of grant, taking into consideration various objective and subjective factors, including the conclusions of valuations of our common stock, as discussed below.

The intrinsic value of all outstanding vested and unvested options as of June 30, 2012, based on an initial public offering price per share of \$ , the mid-point of the price range set forth on the cover page of this prospectus, and the exercise price of the outstanding options are as follows:

	Number of Options	Intrinsic Value
Unvested	1,938,400	\$
Vested	5,627,135	\$



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Due to the absence of an active market for our common stock, the fair value of our common stock for purposes of determining the exercise price for stock option grants was determined by our board of directors, with the assistance and upon the recommendation of management, in good faith, based on a number of objective and subjective factors consistent with the methodologies outlined in the American Institute of Certified Public Accountants Practice Aid, *Valuation of Privately-Held-Company Equity Securities Issued as Compensation*, or the Practice Aid, including:

the prices at which we most recently sold our preferred stock and the rights, preferences and privileges of the preferred stock as compared to those of our common stock, including the liquidation preferences of the preferred stock;

our results of operations, financial position and the status of our research and development efforts, including the status of clinical trials for OCA and our specific regulatory status and interactions with regulatory authorities;

the likelihood of achieving a liquidity event for the holders of our common stock and stock options, such as an initial public offering, or IPO, given prevailing market conditions, or a strategic merger or sale of our company;

the material risks related to our business;

achievement of enterprise milestones, including the results of clinical trials and our entry into or termination of collaboration and license agreements;

the market performance of publicly traded companies in the life sciences and biotechnology sectors, and recently completed mergers and acquisitions of companies comparable to us;

external market conditions affecting the life sciences and biotechnology industry sectors; and

the valuation prepared by an independent third-party consultant performed as of March 31, 2010 and July 31, 2012.

In 2010, we relied, in part, upon a valuation performed by an independent third party as of March 31, 2010, which utilized the probability-weighted expected return method, or PWERM, to value our common stock for purposes of establishing stock option exercise prices and for utilization in the Black-Scholes option-pricing model for calculating stock compensation expense and the value of warrants that are classified as liabilities as discussed below. We performed an update to this valuation in September 2011 and as of June 30, 2012 and relied in part upon an independent third party valuation performed as of July 31, 2012.

The PWERM approach, which was used to determine our enterprise value and related allocation to our common stockholders, models the future enterprise value based on potential future liquidity events and applies probabilities to each scenario. These future liquidity events are then discounted to present value and, after applying the relevant probability for each potential event, result in a probability-weighted equity value of a company. For our valuation, we considered the following future scenarios: a strategic merger or sale of our company, the successful completion of an IPO, continuing operations in various development and commercialization scenarios and failure or dissolution of our company with no value to our common stockholders. In determining the value of the common stock in the scenarios for a strategic merger or sale of our company and an initial public offering, we assumed that the preferred stock then outstanding would be converted into common stock. In allocating value to our common stock in the continuing operations and failure or dissolution scenarios, we first allocated to our then outstanding shares of preferred stock the greater of the liquidation preference of the preferred stock and the amount that would have been payable had all such shares of preferred stock been converted to common stock immediately prior to such event, and then allocated any remaining value to our common stock. The resulting implied per share value of our common stock was \$1.50 per share at both March 31, 2010 and September 30, 2011, \$1.55 at June 30, 2012 and \$1.61 at July 31, 2012. The probability weightings took into consideration the various data quality of Phase 2 and Phase 3 trials completed and to be completed, as well as the overall economic market conditions. In each valuation, we utilized scenarios of overall positive scenario (25% 35% probability), overall mixed scenario (50% 60% probability) and overall negative scenario (15% probability).



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The tables below summarize the probability assessment of the described event in each of these scenarios.

Event	March 2010			September 2011		
	Positive Scenario	Mixed Scenario	Negative Scenario	Positive Scenario	Mixed Scenario	Negative Scenario
Strategic merger or sale of our company	15 %	0 %	0 %	30 %	0 %	0 %
Initial public offering	30 %	15 %	0 %	15 %	15 %	0 %
Continuing operations in various development and commercialization scenarios	55 %	85 %	65 %	55 %	85 %	65 %
Failure or dissolution of our company with no value to common stockholders	0 %	0 %	35 %	0 %	0 %	35 %

Event	June 2012			July 2012		
	Positive Scenario	Mixed Scenario	Negative Scenario	Positive Scenario	Mixed Scenario	Negative Scenario
Strategic merger or sale of our company	15 %	0 %	0 %	15 %	0 %	0 %
Initial public offering	40 %	40 %	0 %	50 %	35 %	0 %
Continuing operations in various development and commercialization scenarios	45 %	60 %	65 %	35 %	65 %	65 %
Failure or dissolution of our company with no value to common stockholders	0 %	0 %	35 %	0 %	0 %	35 %

The probability weightings assigned to the respective exit scenarios were primarily based on consideration of our OCA drug development program, research programs and our specific regulatory status and interactions, industry clinical success rates, our expected near-term and long-term funding requirements, and an assessment of the current financing and biotechnology industry environments at the time the valuations were performed. In all scenarios, an overall discount rate of 25% and an additional discount for lack of marketability of up to 20% was applied. We also considered the rights, preferences and privileges of the preferred stock as compared to those of our common stock, including the liquidation preferences of the preferred stock. Our preferred stockholders have various rights that give them greater control and influence over future liquidity, financing and other decisions relating to our company than the holders of our common stock.

Except as otherwise described below, for the periods from June 30, 2011 to October 13, 2011; October 13, 2011 to December 15, 2011; December 15, 2011 to December 31, 2011; and December 31, 2011 to June 30, 2012, there were numerous changes in our underlying business and, therefore, in the assumptions utilized in the PWERM analysis.

However, taken together, there was no resulting material change in our estimate of the fair value of our common stock.

The absence of any such change is due to the fact that while, on the one hand, we (a) were making progress during these periods in our development program for OCA, including the planning of our Phase 3 program for OCA as a treatment for PBC and the initiation of the POISE trial, and (b) entered into the DSP and Servier collaborations described above, which would have the effect of increasing the estimated fair value of our common stock, on the other hand, (i) we did not receive the clarity that we were seeking from the FDA regarding whether the POISE trial would be sufficient and appropriate for accelerated approval of OCA and we also determined that we may be required to conduct a larger and more expensive confirmatory clinical outcomes trial than we had been anticipating; (ii) European market conditions continued to steadily decline with an increased risk of downward product pricing and

reimbursement pressure across various European countries; and (iii) dynamics in the U.S. market for financing and partnering deteriorated for private development stage biopharmaceutical companies such as ours, all of which had the effect of decreasing the estimated fair value of our common stock. We believe that these factors generally offset each other, resulting in a steady estimate of the fair value of our common stock in the absence of an arm's-length transaction or updated independent valuation indicating otherwise during the period.

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In March 2010, we had just completed a \$25 million Series B preferred stock financing and had recently successfully completed our Phase 2 clinical trial for OCA in PBC. Based upon an analysis of current market conditions, together with the projections of management and the board of directors regarding future development timelines for our product candidates, we determined the probabilities of the different scenarios and events as outlined in the table above.

With regard to the September 2011 valuation date, based primarily at the time on deteriorating market conditions for life science company IPOs and interactions with regulatory authorities about our proposed NDA and MAA program, which resulted in several material changes to our previously contemplated program, including our belief that we may be required to conduct a larger and more expensive confirmatory clinical outcomes trial, management and the board of directors slightly revised these probability assessments to lower the probability of an IPO from 30% to 15% and increased the probability of a strategic merger or sale of our company from 15% to 30%. Since our valuation model had previously incorporated the potential for a licensing deal for OCA in Japan as well as the potential for a licensing deal for our TGR5 program, our entry into the DSP and Servier collaborations in March 2011 and August 2011, respectively, did not have an offsetting effect on the negative developments described above.

With regard to the June 2012 valuation date, based at the time on improving market conditions for life science company IPOs, our holding an organizational meeting and commencement of preparations in May 2012 for an IPO, the initial confidential submission of a draft registration statement on Form S-1 for our IPO in June 2012, our declining cash reserves, the initiation of the Phase 3 POISE trial and the continuation of the FLINT trial, along with our negotiations with several parties regarding a private financing, which increased our confidence in completing an IPO and continuing our clinical development activities, management and the board of directors determined to increase the probability of the IPO in both the positive and mixed scenario from 15% to 40%, with offsetting reductions in the strategic merger or sale of our company in a positive scenario by 15% and reductions in the probabilities of continuing operations from 55% to 45% in the positive scenario and from 85% to 60% in the mixed scenario.

With regard to the July 2012 valuation date, based upon the increased likelihood of completing the potential Series C preferred stock financing that would provide the company with near- and longer-term funding if a successful IPO could not be achieved, management and the board of directors determined (i) to further increase the IPO probability in a positive scenario by 10% to 50%, with an offsetting decrease in the probability of the continuing operations scenario, and (ii) to decrease the IPO probability in a mixed scenario by 5%, with a corresponding increase to the continuing operations scenario, reflecting that an IPO would not be undertaken if it was not attractive.

There are significant judgments and estimates inherent in the determination of these inputs to the valuations. These judgments and estimates include assumptions regarding our future performance, including the regulatory status of our programs; the value of completing an IPO at different time points; the potential value of a strategic merger or sale at different time points; and the timing and probability of continuing to successfully progress our various product candidates toward commercialization (our continued operations scenarios) under differing operational scenarios, as well as determinations of the appropriate valuation methods. If different assumptions had been applied in the valuations, our stock-based compensation expense, warrant liability remeasurement, net loss and net loss per share could have been significantly different. While the assumptions used represent management's best estimates, these estimates involve inherent uncertainties and the application of management's judgment. As a result, if revisions are made to the underlying assumptions and estimates, our stock-based compensation expense and non-cash warrant liability valuations could vary significantly from period to period.

### **Stock Option Grants on August 16, 2010 and September 6, 2010**

Our board of directors granted stock options on August 16, 2010 and September 6, 2010, with each having an exercise price of \$1.50 per share, which our board of directors determined to be equal to the fair value of our common stock on

each date of grant. The exercise price per share determined by our board of directors was supported by an independent third party valuation as of March 31, 2010. The specific facts and circumstances considered by our board of directors for the March 31, 2010 valuation included the following:

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in January 2010, we sold 13,888,889 shares of our Series B preferred stock and a warrant to purchase 5,000,000 shares of our common stock for \$25.0 million in aggregate gross proceeds. We assessed the value of the warrant at approximately \$5.2 million based upon a Black-Scholes option-pricing model, and thus the implied per share value of the Series B preferred stock was \$1.43 per share, and the regulatory status of our programs, the general market conditions for private company financings for development stage companies such as ours and the other items noted above.

The probability weightings, discussed above and listed in the table, assigned to the respective exit scenarios were primarily based on consideration of the factors described above. The resulting value, which represented the estimated fair value of our common stock as of March 31, 2010, was \$1.50 per share.

In addition to the objective and subjective factors listed above, our board of directors also considered input from management and the valuation as of March 31, 2010. After considering the regulatory uncertainty faced by our development program for OCA together with certain countervailing factors, our board of directors determined that there was no change in the fair value of our common stock between March 31, 2010 and August 16, 2010 and September 6, 2010.

### **Stock Option Grants on October 13, 2011 and December 15, 2011**

Our board of directors granted stock options on October 13, 2011 and December 15, 2011, with each having an exercise price of \$1.50 per share, which our board of directors determined to be equal to the fair value of our common stock on each date of grant. We performed an update to the March 31, 2010 valuation as of September 30, 2011. The specific facts and circumstances considered by our board of directors for the September 30, 2011 valuation included the following: the regulatory status of our programs, the general market conditions for private company financings for development stage companies such as ours, the impact of our collaboration agreements with DSP and Servier and the other general items noted above. Among these factors, the board of directors considered the countervailing effects on the fair value of our common stock due to our new collaborative arrangements and the evolving regulatory uncertainty around our development program for OCA.

The probability weightings assigned to the respective exit scenarios, discussed above and detailed in the table, were primarily based on consideration of the factors described above. The resulting value, which represented the estimated fair value of our common stock as of September 30, 2011, was \$1.50 per share.

Our board of directors determined that there was no change in the fair value of our common stock during the period between September 30, 2011 and December 15, 2011 because no significant event or other circumstances had occurred between those dates that would indicate a change had occurred in the fair value of our common stock.

### **Stock Option Grants on July 31, 2012**

Our board of directors granted stock options on July 31, 2012, each having an exercise price of \$1.61 per share, which our board of directors determined to be equal to the fair value of our common stock on the date of grant.

The exercise price per share determined by our board of directors was supported by an independent third party valuation analysis as of July 31, 2012 using the PWERM methodology. The specific facts and circumstances considered by our board of directors for the July 31, 2012 valuation included the following: (i) the clinical development progress of OCA, including the initiation of the POISE trial and the continuation of the FLINT and PESTO trials, as well as risks and costs associated with these trials, (ii) the regulatory status of our programs, including communications received from the FDA concerning our Phase 3 program for OCA as a treatment for PBC and requests from the FDA for additional data regarding the primary endpoint of our POISE trial, (iii) the general

fluctuating market conditions for private company financings for development stage companies such as ours, including our negotiations relating to the potential of a Series C private placement followed by an initial public offering, (iv) the anticipated terms of our Series C preferred stock, including certain control rights and liquidation preferences anticipated to be granted to the holders of our Series C preferred stock, which would result in a higher implied value for our Series C preferred stock as compared to our common stock, (v) the general deteriorating market conditions in European markets for

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health care payor reimbursement of approved products, and (vi) other general factors consistent with the Practice Aid, such as risk factors faced by our company, the investments made in our company and the experience and competence of our management team. The probability weightings assigned to the respective exit scenarios, discussed above and detailed in the table, were primarily based on consideration of these factors.

### **Common Stock Warrant Liability**

Some of our outstanding warrants to purchase shares of our common stock have anti-dilution provisions (commonly referred to as down round provisions) which cause the instruments to be deemed not to be indexed to our common stock and as such are recorded as a liability and remeasured each reporting period using the Black-Scholes option-pricing model. Furthermore, certain warrants that do not have these down-round provisions, and are currently classified in equity, contain provisions that require the shares of common stock underlying such warrants to be registered following an initial public offering. Upon completion of this offering, we will reclassify these warrants as liabilities and record warrant revaluation income (expense) in the statement of operations. These warrants are deemed to be derivative instruments that require liability classification and mark-to-market accounting. As such, at the end of each reporting period, the fair values of the warrants are determined by us using a Black-Scholes option-pricing model. The non-cash changes in the fair value of the warrants are recorded as other income or expense. We expect that the value of the warrants will fluctuate significantly from period to period.

The Black-Scholes option-pricing model requires the use of subjective assumptions, including stock price volatility, the expected life of the warrants, the risk free interest rate and the fair value of the common stock underlying the warrants. The fair value of the underlying common stock is determined as discussed above under Stock-Based Compensation. We will continue to adjust the fair values of the warrants at each period end for any changes in fair value until the earlier of the exercise or expiration of the applicable common stock warrants or until such time that the warrants are no longer determined to be derivative instruments. Our warrant liability is expected to fluctuate based on the assumptions used in the Black-Scholes option-pricing model.

## **JOBS Act**

On April 5, 2012, the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, was enacted. Section 107 of the JOBS Act provides that an emerging growth company can take advantage of the extended transition period provided in Section 7(a)(2)(B) of the Securities Act of 1933, as amended, or the Securities Act, for complying with new or revised accounting standards. In other words, an emerging growth company can delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this extended transition period and, as a result, we will adopt new or revised accounting standards on the relevant dates on which adoption of such standards is required for other public companies.

We are in the process of evaluating the benefits of relying on other exemptions and reduced reporting requirements provided by the JOBS Act. Subject to certain conditions set forth in the JOBS Act, as an emerging growth company, we intend to rely on certain of these exemptions, including without limitation, (i) providing an auditor's attestation report on our system of internal controls over financial reporting pursuant to Section 404(b) of the Sarbanes-Oxley Act and (ii) complying with any requirement that may be adopted by the PCAOB regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements, known as the auditor discussion and analysis. 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 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.

TABLE OF CONTENTS**Results of Operations****Comparison of the Six Months Ended June 30, 2011 and the Six Months Ended June 30, 2012**

The following table summarizes our results of operations for each of the six months ended June 30, 2011 and 2012, together with the changes in those items in dollars and as a percentage:

	Six Months Ended June 30,		Dollar Change	% Change	
	2011	2012			
	(In thousands)				
	(Unaudited)				
Licensing revenue	\$ 405	\$ 1,518	\$ 1,113	*	
Operating expenses:					
Research and development	4,751	8,078	3,327	70.0	%
General and administrative	2,020	2,003	(17 )	(0.8 )	%
Loss from operations	(6,366 )	(8,563 )	(2,197 )	34.5	%
Interest income, net	21	10	(11 )	(52.0 )	%
Foreign currency loss in liquidation		(192 )	(192 )	*	
Warrant revaluation income (expense)	94	979	885	*	
Net loss	\$ (6,251 )	\$ (7,766 )	\$ (1,515 )	24.2	%
Foreign currency translation adjustment	36	185	149	*	

\*

Not meaningful or not calculable.

**Licensing Revenue**

Licensing revenue was \$405,000 and \$1,518,000 for the six months ended June 30, 2011 and 2012, respectively, resulting from the amortization of the up-front payments from the collaboration agreements entered into with DSP on March 29, 2011 and with Servier on August 1, 2011.

**Research and Development Expenses**

Research and development expenses were \$4.8 million and \$8.1 million for the six months ended June 30, 2011 and 2012, respectively, representing an increase of \$3.3 million, or 70.0%. This increase in research and development expense primarily reflects:

increased expenses of \$1.7 million payable by us to the NIDDK relating to milestones achieved and expected to be achieved under the NIDDK agreement;

increased direct development expense for the initiation of our Phase 3 POISE trial of approximately \$1.5 million;

increased direct development expense for the initiation of our two-year animal carcinogenicity studies in two species of approximately \$700,000;

an increase in personnel on our development team to manage the increased activities around our development program for OCA, resulting in increased compensation expense of approximately \$650,000 and associated overhead of approximately \$75,000; and

a partial offset primarily by decreases in costs related to (i) research expenses for our earlier stage pipeline assets of \$300,000, and (ii) reduced direct research and development expense of approximately \$1.0 million resulting from the closure of our research facility in June 2011 and research associated with our TRG5 program, which was previously paid by us and is now funded through our collaboration with Servier.

**General and Administrative Expenses**

General and administrative expenses were \$2.0 million in both the six months ended June 30, 2011 and 2012.

TABLE OF CONTENTS**Interest Income, Net**

Interest income, net was \$21,000 and \$10,000 for the six months ended June 30, 2011 and 2012, respectively.

**Warrant Revaluation Income (Expense)**

Some of our outstanding warrants are deemed to be derivative instruments that require liability classification and mark-to-market accounting. As such, at the end of each reporting period, the fair values of the warrants were determined by us using a Black-Scholes option-pricing model, resulting in the recognition of gains of \$94,000 and \$979,000 for the six months ended June 30, 2011 and 2012, respectively. These gains are primarily due to the reduction in value of the warrants due to declines in their estimated life and changes in volatility of the shares of common stock underlying the warrants. For the six months ended June 30, 2012, these gains were offset to a lesser extent by the increase in fair value of the common stock underlying the warrants.

## Comparison of the Year Ended December 31, 2010 and the Year Ended December 31, 2011

The following table summarizes our results of operations for the years ended December 31, 2010 and 2011, together with the changes in those items in dollars and as a percentage:

	Years Ended December 31,		Dollar Change	% Change
	2010	2011		
	(In thousands)			
Licensing revenue	\$	\$ 1,805	\$ 1,805	*
Operating expenses:				
Research and development	12,710	11,426	(1,284 )	(10.1 )%
General and administrative	3,644	4,209	565	15.5 %
Loss from operations	(16,354 )	(13,830 )	2,524	15.4 %
Interest income, net	105	48	(57 )	(54.3 )%
Warrant revaluation income (expense)	672	1,045	373	55.5 %
Qualified therapeutic development project	489		(489 )	*
Net loss	\$ (15,088 )	\$ (12,737 )	2,351	15.6 %

\*

Not meaningful or not calculable.

**Licensing Revenue**

For the year ended December 31, 2011, we recorded a total of \$1.8 million of licensing revenue, consisting of \$1.2 million and \$600,000 from the amortization of the up-front payments from the collaboration agreements entered into during 2011 with DSP and Servier, respectively. We had no revenue prior to 2011.

**Research and Development Expenses**

Research and development expenses were \$12.7 million and \$11.4 million for the years ended December 31, 2010 and 2011, respectively. The net decline in research and development expenses of \$1.3 million, or 10.1%, was primarily due to:

reduced direct research and development expense relating to INT-777 of approximately \$2.0 million;  
reduced direct research and development expense resulting from the closure of our research facility in June 2011 and research associated with our TGR5 program, which was previously paid by us and is now funded through our collaboration with Servier, of approximately \$1.2 million;  
reduced direct research and development expense with respect to the completion of our Phase 2 trials for OCA of approximately \$600,000;  
reduced direct research and development expense related to payments to the NIDDK for the FLINT trial of \$250,000;

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increased direct expenditures associated with the preparation for the initiation of the POISE trial of approximately \$1.2 million;  
increase in personnel in our development team to manage the increased activities around our development program for OCA, resulting in increased compensation expense of approximately \$400,000;  
increased expenditures for direct research and development expense relating to our Phase 2 clinical trial for portal hypertension of approximately \$400,000;  
increased costs to manufacture our clinical trial supplies of approximately \$500,000; and  
increased costs associated with market research of \$200,000.

### **General and Administrative Expenses**

General and administrative expenses were \$3.6 million and \$4.2 million for the years ended December 31, 2010 and 2011, respectively. The increase in general and administrative expenses of \$565,000, or 15.5%, was mainly due to an increase in stock-based compensation costs for options granted to our employees and legal costs associated with the DSP and Servier collaboration agreements.

### **Interest Income, Net**

Interest income, net was \$105,000 and \$48,000 for the years ended December 31, 2010 and 2011, respectively. The decrease of \$57,000, or 54%, was driven by lower average cash balances.

### **Warrant Revaluation Income (Expense)**

Some of our outstanding warrants are deemed to be derivative instruments that require liability classification and mark-to-market accounting. At the end of each reporting period, the fair values of the warrants were determined using a Black-Scholes option-pricing model, resulting in the recognition of gains of \$700,000 and \$1.0 million for the years ended December 31, 2010 and 2011, respectively. These gains are primarily due to the reduction in value of the warrants as their estimated life declines and changes in volatility of the shares of common stock underlying the warrants.

### **QTDP Grant**

In 2010, we were awarded \$489,000 under the federal Qualifying Therapeutic Discovery Grant Program, or QTDP, in support of our development of OCA and INT-777. The QTDP was included in the healthcare reform legislation, and established a one-time pool of \$1 billion for grants to small biotechnology companies developing novel therapeutics which show potential to result in new therapies that either treat areas of unmet medical need, or prevent, detect or treat chronic or acute diseases and conditions; reduce long-term health care costs in the United States; or significantly advance the goal of curing cancer within a the 30-year period.

## **Liquidity and Capital Resources**

### **Sources of Liquidity**

We have incurred losses and cumulative negative cash flows from operations since our inception in September 2002 and, as of June 30, 2012, we had an accumulated deficit of \$82.3 million. We anticipate that we will continue to incur losses for at least the next several years. We expect that our research and development and general and administrative expenses will continue to increase and, as a result, we will need additional capital to fund our operations, which we may seek to obtain 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.

Since our inception through June 30, 2012, we have funded our operations principally with \$70.6 million (net of issuance costs of \$2.4 million) from the sale of common stock, preferred stock, convertible notes and warrants, and the receipt of \$16.4 million in up-front payments under our licensing and collaboration agreements with DSP and Servier. As of June 30, 2012, we had cash and cash equivalents of approximately \$9.9 million. Cash in excess of immediate requirements is invested in accordance with our investment policy, primarily with a view to liquidity and capital preservation. Currently, our funds are held in cash and money market bank accounts.

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On August 9, 2012, we entered into a securities purchase agreement with an affiliated fund of OrbiMed Advisors LLC and Genextra S.p.A., pursuant to which we agreed to issue up to an aggregate of 25,000,000 shares of our Series C preferred stock at a price of \$2.00 per share for gross proceeds of up to \$50.0 million. The securities purchase agreement provides that the Series C preferred stock may be issued in two tranches consisting of 15,000,000 and 10,000,000 shares. The first tranche of Series C preferred stock was issued on August 9, 2012, and resulted in \$29.8 million of net proceeds to us. The closing of the second tranche of Series C preferred stock will only occur if we do not complete an initial public offering of our common stock on or prior to the one year anniversary of the closing of the first tranche. Each share of Series C preferred stock will initially be convertible into one share of our common stock, subject to adjustment. All of our outstanding shares of Series C preferred stock will convert into 15,000,000 shares of our common stock upon the completion of this offering. The investors have been granted certain demand and piggyback registration rights in respect of their securities under our third amended and restated stockholders agreement.

After giving effect to the \$29.8 million in net proceeds we received in the Series C preferred stock financing, our cash and cash equivalents as of June 30, 2012 would have been \$39.7 million.

The gross proceeds we have received from the issuance and sale of common stock, convertible notes, preferred stock and warrants, as of August 31, 2012, are as follows:

Securities Issued	Year	Number of Shares	Common Stock Underlying Warrant	Gross Proceeds
Common stock and convertible notes	2002 2009	19,238,418		\$22,786,300
Series A preferred stock	2008	13,888,889		25,000,000
Series B preferred stock and warrant	2010	13,888,889	5,000,000	25,000,000
Series C preferred stock	2012	15,000,000		30,000,000
Total		62,016,196	5,000,000	\$102,786,300

**Cash Flows**

The following table sets forth the significant sources and uses of cash for the periods set forth below:

	Years Ended, December 31, 2010 2011 (In thousands)		Six Months Ended, June 30, 2011 2012 (Unaudited)	
Net cash provided by (used in):				
Operating activities	\$(13,658)	\$2,606	\$9,318	\$(7,768 )
Investing activities	58	(66 )	(75 )	97
Financing activities	24,618	(250 )	(107 )	(82 )
Effect of exchange rate changes	(29 )	(6 )	36	(7 )
Net increase (decrease) in cash and cash equivalents	\$10,989	\$2,284	\$9,172	\$(7,760 )

*Operating Activities.* Net cash used in operating activities of \$13.7 million during the year ended December 31, 2010

was primarily a result of our \$15.1 million net loss, offset by the add-back of non-cash expenses of \$1.7 million for stock-based compensation and \$480,000 for depreciation and warrant liability revaluation income of \$672,000. Net cash provided by operating activities of \$2.6 million during the year ended December 31, 2011 was primarily a result of \$16.4 million in up-front payments from our licensing and collaboration agreements with DSP and Servier, \$14.6 million of which was classified as deferred revenue as described in note 3 to our financial statements included elsewhere in this prospectus. The cash payments from the collaboration agreements and the classification of those payments as deferred revenue led to an overall net increase in operating assets of \$13.9 million, to which non-cash items of \$1.9 million for stock-based compensation, \$410,000 for depreciation and \$217,000 for a loss on the sale of assets in connection with the

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liquidation of our Italian subsidiary were added. These positive additions to cash flow were offset against our \$12.7 million net loss and an additional \$1.0 million decrease in assets due to the revaluation of our warrant liabilities.

Net cash provided by operating activities of \$9.3 million during the six months ended June 30, 2011 was primarily a result of the \$15.0 million up-front payment from our licensing and collaboration agreement with DSP, which was classified as deferred revenue as described in note 3 to our financial statements included elsewhere in this prospectus. The cash payment and the classification of this payment as deferred revenue led to an overall net increase in operating assets of \$15.0 million to which non-cash items of \$752,000 for stock-based compensation and \$161,000 for depreciation were added. These positive additions to cash flow were offset against our \$6.3 million net loss and an additional \$94,000 decrease in assets due to the revaluation of our warrant liabilities. Net cash used in operating activities of \$7.8 million during the six months ended June 30, 2012 was primarily a result of our \$7.8 million loss, offset by the add-back of non-cash items of \$761,000 for stock-based compensation, depreciation of \$154,000, warrant liability revaluation income of \$979,000 and net changes in our operating assets and liabilities of \$130,000. The net change in our operating assets and liabilities include an increase in prepaid expenses and other current assets of \$686,000, increases in accounts payable, accrued expense and other current liabilities of \$2.1 million and a decrease in deferred revenue of \$1.5 million. The decrease in deferred revenue is due to the recognition of a portion of the up-front license payment from our license agreement with DSP.

*Investing Activities.* Net cash used in investing activities during the periods presented primarily reflected our use of cash to purchase equipment. Cash provided by short-term investments was partially offset by sales of short-term investments.

*Financing Activities.* Net cash provided by financing activities in the year ended December 31, 2010 consisted primarily of approximately \$24.0 million of net proceeds from the sale of Series B preferred stock and warrants to purchase common stock issued in 2010, offset by capital lease payments. Net cash used in financing activities in the year ended December 31, 2011 consisted primarily of capital lease payments.

## **Future Funding Requirements**

To date, we have not generated any revenue from product sales. We do not know when, or if, we will generate any revenue from product sales. We do not expect to generate significant revenue from product sales unless and until we obtain regulatory approval of and commercialize OCA or any of our other product candidates. At the same time, we expect our expenses to increase in connection with our ongoing development activities, particularly as we continue the research, development and clinical trials of, and seek regulatory approval for, our product candidates. Upon the closing of this offering, we expect to incur additional costs associated with operating as a public company. In addition, subject to obtaining regulatory approval of any of our product candidates, we expect to incur significant commercialization expenses for product sales, marketing, manufacturing and distribution. We anticipate that we will need substantial additional funding in connection with our continuing operations.

Based upon our current operating plan, we believe that the net proceeds from this offering, together with our existing cash, cash equivalents, short-term investments and anticipated funding under our DSP and Servier collaborations, will enable us to fund our operating expenses and capital expenditure requirements through 2015. We intend to devote the net proceeds from this offering to fund our Phase 3 POISE trial and our planned clinical trials and preclinical studies and other work needed to submit applications for OCA for the treatment of PBC for regulatory approval in the United States and Europe; to fund the continuation of the long-term safety extension portion of our POISE clinical trial and the Phase 3 clinical outcomes trial after the anticipated FDA and EMA filings; to fund further preclinical development work on INT-767 and, if warranted, potential Phase 1 clinical trials of INT-767; to fund the initiation of a Phase 2

clinical trial for an additional indication for OCA, such as portal hypertension if warranted; and 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 detailed discussion. We will need to obtain additional financing to fund future clinical trials of OCA in additional indications, including portal hypertension, NASH and bile acid diarrhea, or for progressing INT-767 beyond Phase 1 clinical trials and INT-777. We have based our estimates on assumptions that may prove to be wrong, and we may use our available capital resources

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sooner than we currently expect. Because of the numerous risks and uncertainties associated with the development and commercialization of our product candidates, we are unable to estimate the amounts of increased capital outlays and operating expenditures necessary to complete the development of our product candidates.

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

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

the willingness of the FDA and the European Medicines Agency, or 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;

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;

our need to implement additional internal systems and infrastructure, including financial and reporting systems; and the economic and other terms, timing and success of our existing licensing arrangements and any collaboration, licensing or other arrangements into which we may enter in the future.

Until such time, if ever, as we can generate substantial revenue from product sales, we expect to finance our cash needs 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. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interests of our common stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our common stockholders. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. If we raise additional funds through government or other third-party funding, marketing and distribution arrangements or other collaborations, strategic alliances or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or to grant licenses on terms that may not be favorable to us.

TABLE OF CONTENTS**Contractual Obligations and Commitments**

The following table summarizes our significant contractual obligations and commercial commitments at December 31, 2011 and the effects such obligations are expected to have on our liquidity and cash flows in future periods:

	Total	Less than 1 year	1 3 years	3 5 years	More than 5 years
	(In thousands)				
Operating lease	\$ 838	\$ 294	\$ 544		
Capital lease	82	82			
Purchase obligations	3,568	1,964	1,604		
Total	\$ 4,488	\$ 2,340	\$ 2,148		

In June 2007, we entered into a capital lease agreement for research and development equipment utilized in our research facility. The term of the lease was for five years, required monthly payments of \$22,275, bore interest at a rate of 4.66% per year and matured on May 31, 2012. We lease general and administrative office space in New York, New York and San Diego, California pursuant to operating leases that expire in 2013 and 2014, respectively. We have two contracts that require us to make specified payments necessary to perform our obligations under the Servier collaboration agreement. The amounts payable under these contracts through the initial term of the Servier agreement is included in the table above even though we expect to receive reimbursement from Servier for these costs.

During 2011, we entered into an agreement with WIL Research Laboratories, LLC, or WIL, to perform certain research and laboratory services for animal studies and have agreed to pay WIL a total of \$4.0 million in periodic installment payments. These amounts are included in table above.

We are a party to license agreements with universities and other third parties, as well as patent assignment agreements, under which we have obtained rights to patents, patent applications and know-how. We have employment agreements with certain employees which require the funding of specific levels of payments, if certain events, such as a change in control or termination without cause, occur. We enter into contracts in the normal course of business with CROs for clinical trials and clinical supply manufacturing and with vendors for preclinical research studies and other services and products for operating purposes, which generally provide for termination within 30 days of notice, and therefore are cancelable contracts and not included in the table of contractual obligations and commitments.

Under our contract with the NIDDK, we made a milestone payment of \$1.0 million in June 2012 and will be required to make an additional \$1.25 million payment within 60 days of full enrollment of the FLINT trial, which is expected to occur in 2012. As of December 31, 2011, we were unable to estimate the timing or likelihood of the NIDDK achieving the milestones and, therefore, the amounts are not included in the table above. As of June 30, 2012, we have recorded expenses totaling \$2.0 million and expect to record an additional \$250,000 in 2012 for a total of \$2.25 million in 2012 relating to these milestone obligations.

Under our agreement with DSP, we are required to use our commercially reasonable efforts to develop OCA outside of the territories in which DSP has a license under the agreement. As these amounts are not quantifiable, they are not included in the table above.

Under our agreement with Servier, we are obligated to conduct and are conducting a research program to identify and optimize compounds that meet certain specified criteria sufficient for further development by Servier. We are obligated under the agreement to provide Servier with a specified number of full time equivalent employees for the

research program and Servier has agreed to reimburse us on a quarterly basis for the associated costs up to a set maximum amount per year. Servier has agreed to pay for the development costs we or Servier incur in conducting certain preclinical trials and clinical trials with respect to any compound that meets specified criteria. We have agreed to reimburse Servier for a certain percentage of the development costs incurred by Servier if we enter into a partnership agreement, or commence development or commercialization activities on our own, with respect to a compound in the United States. Servier may credit a portion of any such reimbursable development costs against any milestone or royalty payments due and

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payable by Servier under the agreement until all such reimbursable amounts are repaid. In addition, if we enter into a partnership agreement with respect to a compound developed under the agreement solely in Japan, we and Servier have agreed to enter into good faith negotiations regarding the terms and conditions applicable to the reimbursement of development costs. These amounts are not included in the table above because they are not quantifiable or because they are reimbursable under the agreement.

Our commitments as of December 31, 2011 under our sponsored research agreement with the University of Perugia and Professor Roberto Pellicciari, our two consulting agreements with Professor Pellicciari and our research and development agreement with TES Pharma Srl are reflected in the table above. However, all the commitments as of December 31, 2011 under our consulting agreement with Professor Pellicciari and our agreement with TES Pharma Srl, in each case, for the compounds related to the Servier agreement were covered by the reimbursement provisions under our agreement with Servier.

## **Net Operating Losses**

As of December 31, 2011 and June 30, 2012, we had federal net operating loss carryforwards, or NOLs, of \$55.0 million and \$63.9 million, respectively, which expire from 2024 through 2032. Our ability to utilize our NOLs may be limited under Section 382 of the Internal Revenue Code. The limitations apply if an ownership change, as defined by Section 382, occurs. Generally, an ownership change occurs when certain shareholders increase their aggregate ownership by more than 50 percentage points over their lowest ownership percentage in a testing period (typically three years). We have assessed whether one or more ownership changes as defined under Section 382 have occurred since our inception and have determined that there have been at least two such changes. Accordingly, although we believe that these ownership changes have not resulted in material limitations on our ability to use these NOLs, our ability to utilize the aforementioned carryforwards may be limited. Additionally, U.S. tax laws limit the time during which these carryforwards may be utilized against future taxes. As a result, we may not be able to take full advantage of these carryforwards for federal and state tax purposes. Future changes in stock ownership may also trigger an ownership change and, consequently, a Section 382 limitation.

## **Off-Balance Sheet Arrangements**

We did not have during the periods presented, and we do not currently have, any off-balance sheet arrangements as defined under Securities and Exchange Commission rules.

## **Recent Accounting Pronouncements**

In June 2011, the FASB issued authoritative guidance related to the Presentation of Comprehensive Income. This standard eliminates the current option to report other comprehensive income and its components in the statement of changes in equity. The new GAAP requirements were effective for public entities for fiscal years beginning after December 15, 2011 and interim periods within that year, with early adoption permitted. As we had historically presented a single Statement of Operation and Comprehensive Loss, the adoption of this standard did not impact our financial statements.

In May 2011, the FASB issued amended guidance on fair value measurements. This newly issued accounting standard clarifies the application of certain existing fair value measurement guidance and expands the disclosures for fair value measurements that are estimated using significant unobservable (Level 3) inputs. This accounting standard was effective on a prospective basis for annual and interim reporting periods beginning on or after December 15, 2011.

The adoption of this standard has not had a material impact on our financial position or results of operations.

## **Basic and Diluted Net Loss Attributable to Common Stockholders per Common Share**

Our Series A, B and C preferred stock represent participating securities. However, since we operate at a loss, and losses are not allocated to the preferred stock, the two class method does not affect our calculation of earnings per share. We had a net loss for all periods presented; accordingly, the inclusion of common stock options and warrants would be anti-dilutive.

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Dilutive common stock equivalents would include the dilutive effect of convertible securities, common stock options and warrants for common stock. Potentially dilutive common stock equivalents totaled approximately 48,008,668 shares and 45,578,569 shares for the years ended December 31, 2010 and 2011, respectively. Potentially dilutive common stock equivalents were excluded from the diluted earnings per share denominator for all periods because of their anti-dilutive effect. Therefore, the weighted average shares used to calculate both basic and diluted earnings per share are the same.

## **Quantitative and Qualitative Disclosure About Market Risk**

Our primary exposure to market risk is interest income sensitivity, which is affected by changes in the general level of U.S. interest rates.

Due to the short-term duration of our investment portfolio and the low risk profile of our investments, an immediate 10.0% change in interest rates would not have a material effect on the fair market value of our portfolio. Accordingly, we would not expect our operating results or cash flows to be affected to any significant degree by the effect of a sudden change in market interest rates on our investment portfolio.

We do not believe that our cash, cash equivalents and available-for-sale investments have significant risk of default or illiquidity. While we believe our cash and cash equivalents and certificates of deposits do not contain excessive risk, we cannot provide absolute assurance that in the future our investments will not be subject to adverse changes in market value. In addition, we maintain significant amounts of cash and cash equivalents at one or more financial institutions that are in excess of federally insured limits.

We contract with CROs and investigational sites in Europe, Canada and Australia. We are therefore subject to fluctuations in foreign currency rates in connection with these agreements. We do not hedge our foreign currency exchange rate risk.

Inflation generally affects us by increasing our cost of labor and clinical trial costs. We do not believe that inflation has had a material effect on our results of operations during 2010 or 2011 or through the six months ended June 30, 2012.

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## **BUSINESS**

### **Overview**

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

Our lead product candidate, obeticholic acid, or OCA, is a bile acid analog, a chemical substance that has a structure based on a naturally occurring human bile acid. OCA is a first-in-class product candidate that selectively binds to and induces activity in the farnesoid X receptor, or FXR, which we believe has broad liver-protective properties. We are developing OCA initially for primary biliary cirrhosis, or PBC, as a second line treatment for patients who have an inadequate response to or who are unable to tolerate standard of care therapy and therefore need additional treatment. PBC is a chronic autoimmune liver disease that, if inadequately treated, may eventually lead to cirrhosis, liver failure and death. 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.

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 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.

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According to industry data, there are approximately 300,000 people with PBC in developed countries, of whom we believe approximately 60,000 have been diagnosed and are 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 level of bilirubin, a biomarker of liver function, as compared to placebo. ULN is the uppermost level of a specified parameter that is considered normal in healthy people. 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.

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.

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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 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:

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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.

## **Overview of liver function, bile acids and chronic liver diseases**

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

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

The biological effects of bile acids are mediated through dedicated receptors. The best understood is the farnesoid X receptor, a nuclear receptor that regulates bile acid synthesis and clearance from the liver, thereby preventing excessive bile acid build-up in the liver, which may be toxic. As a result, FXR is a target for the treatment of liver diseases such as PBC that involve impaired bile flow, a condition called cholestasis, in which the liver is exposed to higher than normal levels of bile acids, causing significant damage over time due to the detergent effects of bile acids.

In addition, bile acid activation of FXR induces anti-fibrotic, anti-inflammatory and other mechanisms that are necessary for the normal regeneration of the liver. Based on the discovery of similar FXR-mediated protective mechanisms in other organs exposed to bile acids, we believe that FXR may also be a potential target for the treatment of a number of intestinal, kidney and other diseases.

## **Our Lead Candidate: Obeticholic Acid, or OCA, for PBC**

### **Primary Biliary Cirrhosis**

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

PBC is a liver disease that primarily results from autoimmune destruction of the bile ducts that transport bile acids out of the liver, resulting in cholestasis. As the disease progresses, persistent toxic build-up of bile acids cause progressive liver damage marked by chronic inflammation and fibrosis.

While PBC is rare, it is the most common cholestatic liver disease. An estimated 90% of patients are women, with approximately one in 1,000 women over the age of 40 afflicted by the disease. The mean age of diagnosis is about 40 years and the typical initial presentation is between the ages of 30 and 65 years. In the United States, the disease is the fifth most common cause of liver transplant and accounts for approximately two percent of deaths attributed to cirrhosis. A majority of PBC patients are asymptomatic at the time of initial diagnosis, but most develop symptoms over time. Fatigue and pruritus, or itching, are by far the most common symptoms in PBC patients. Less common symptoms include dry eyes and mouth, as well as jaundice, which can

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be seen in more advanced disease. Based on the guidelines of the American Association for the Study of Liver Disease, or AASLD, and the European Association for the Study of the Liver, or EASL, the clinical diagnosis of PBC is established based on the presence of (i) a positive antimitochondrial antibody, or AMA, a marker of this autoimmune disease seen in up to 95% of PBC patients, and (ii) elevated serum levels of ALP, an enzyme that is released by liver cells in response to the bile acid mediated toxicity and that is a key biomarker of the disease pathology. ALP is routinely measured in blood tests and, in the earlier stages of PBC, it is often the only abnormally elevated liver enzyme, rising to between two to ten times higher than normal values. It is closely monitored in patients as an indicator of treatment response and prognosis. Bilirubin is a marker of liver function and is also monitored in PBC to provide an indication of how well the liver is functioning. Liver biopsy can be used to confirm the diagnosis of PBC, but is not required and is becoming less-frequently performed.

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

## **Currently Available Treatment Options for PBC**

The only approved drug for the treatment of PBC is ursodiol, which is the standard initial course of therapy for all PBC patients. Ursodiol is a naturally occurring bile acid found in small quantities in humans and it is the least detergent of the various types of bile acids that make up the bile pool. In traditional Asian medicine, ursodiol obtained from bears has been used for centuries as a liver tonic for any disease or condition associated with liver malfunction. In humans, the typical daily dose of ursodiol of approximately one gram represents more than one-fifth of the entire bile pool and, after ongoing therapy, it will comprise at least half of the entire bile pool. It is believed that this results in the bile pool being less toxic to the liver due to ursodiol's dilution of other more detergent bile acids.

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

Although drugs such as colchicine, budesonide, methotrexate and others have been tested as treatments in PBC, none has been shown to be both effective and safe in altering the course of the disease.

## **Our PBC Opportunity**

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

The outlook and treatment options for end-stage PBC patients who fail to respond to ursodiol are limited. Although liver transplant can be curative, many patients fail to receive a donor organ in time, and for those who do, there are

very significant clinical risks, such as infection and organ rejection, as well as significant costs. In addition, the disease recurrence rate is as high as 18% at five years and up to 30% at ten years after liver transplant.

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. While ursodiol is the standard of care for the

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treatment of PBC, given the limitations of its efficacy and compliance with the dosing regimen discussed above, we believe that there is a significant unmet need for a novel second line therapy in PBC.

## **Our Solution: OCA for PBC**

### **Overview**

Our lead product candidate, OCA, is a bile acid analog and first-in-class FXR agonist derived from the primary human bile acid chenodeoxycholic acid, or CDCA. CDCA, a natural FXR agonist, has historically been used safely as a chronic therapy for cholesterol gallstone disease. We are initially developing OCA for the second line treatment of PBC for patients with an inadequate therapeutic response to ursodiol or who are unable to tolerate ursodiol. OCA has received orphan drug designation in the United States for the treatment of PBC and a related disease called primary sclerosing cholangitis, or PSC. OCA also has orphan designation in Europe for PBC. We filed an IND with the FDA for OCA for the treatment of PBC in 2006. We believe we are the first company to have advanced an FXR agonist into clinical trials and are currently enrolling our Phase 3 POISE trial to evaluate the safety and efficacy of OCA as a novel treatment in PBC. We own worldwide rights to OCA outside of Japan and China, where we have exclusively licensed the compound to DSP, which also has an option to exclusively license OCA in certain additional Asian countries.

We have completed two randomized, placebo-controlled Phase 2 trials of OCA in PBC patients. The first trial enrolled 165 patients to evaluate the addition of OCA to ursodiol in patients with an inadequate response to ursodiol therapy, and the second trial enrolled 59 patients to evaluate OCA given as monotherapy. Both trials showed that, over a 12-week period, single daily doses of OCA at the lowest dose of 10 mg met the Phase 2 primary and secondary endpoints of those trials, producing statistically significant reductions in levels of ALP and other important liver enzymes. Further, long-term open label extension phases of these trials have demonstrated that the majority of patients taking OCA for at least 12 months, with some on therapy for more than 30 months, maintained a durable treatment response.

### **OCA Benefits in PBC**

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

*Efficacy.* In addition to achieving the primary endpoint in our Phase 2 trials, the data also demonstrated that 80% of OCA-treated patients across our Phase 2 trials experienced a reduction in ALP levels of at least 10%, which we consider to be a clinically meaningful improvement, as compared to 13% of placebo-treated patients. Furthermore, our analysis of the data for those Phase 2 patients who would have met the entry criteria for our POISE trial 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.

*Pharmacological Activity.* Unlike ursodiol, which has no FXR-agonistic activity, OCA is approximately 100-times more potent than CDCA in activating the receptor. In numerous animal models, sustained FXR activation with OCA treatment has resulted in the prevention, and even reversal, of liver damage caused by progressive fibrosis. Our Phase 2 trials have demonstrated that most patients taking OCA also have significant reductions in immunoglobulin M, or IgM, and, in the combination trial with ursodiol, C-reactive protein, or CRP, common indicators of autoimmune activity. We believe that this demonstrates potential disease-modifying therapeutic activity directly addressing the underlying autoimmune pathology.

*Ease of Use.* We anticipate seeking approval of OCA for the treatment of PBC at a dose of a single 10 mg tablet each day, which is approximately 1/100 the amount of ursodiol that a patient is typically prescribed.

### **Phase 3 PBC Program for OCA**

We are currently enrolling our Phase 3 POISE trial, which has been designed to study the safety and efficacy of OCA in PBC patients with an inadequate therapeutic response to ursodiol or who are unable to tolerate ursodiol. In this trial, eligible PBC patients currently taking a stable therapeutic dose of ursodiol will continue their ursodiol treatment and be randomized into one of three trial arms of 60 patients each, adding either: 10 mg of OCA; 5 mg of OCA increasing over the course of the trial to 10 mg of OCA; or a placebo.

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The double-blind phase of the trial is designed to be 12 months in duration, and patients completing this phase will continue in an open label, long-term safety extension phase for another five years, during which all patients will receive OCA treatment with doses as low as 5 mg and as high as 25 mg a day, as clinically indicated.

The primary endpoint of the 12 month double-blind portion of the POISE trial is the achievement of both a reduction in ALP level to below a threshold of 1.67 times upper limit normal, or ULN, with a minimum of 15% reduction in ALP level from baseline, and a normal bilirubin level, compared to placebo after 12 months of therapy. In order to be eligible to enter the POISE trial, patients must have previously met the diagnostic criteria for PBC and have been taking a therapeutic dose of ursodiol for at least 12 months or, if unable to tolerate ursodiol, patients must not have been on therapy for at least three months prior to entering the trial. In addition, patients must have ALP levels of at least 1.67 times ULN and/or bilirubin levels of one to two times ULN. The POISE trial is designed to enroll 180 patients across approximately 60 clinical sites in North America and Europe. We currently expect results from the trial to be available by mid-2014.

The chart below shows an analysis of the extracted intention to treat data for the 10 mg dose groups in our two Phase 2 trials based on patients who would have met the inclusion criteria for entry in the POISE trial. The analysis demonstrated that after 12 weeks of treatment, approximately 40% to 45% of OCA-treated patients in our Phase 2 trials would have met the POISE trial primary endpoint.

If the POISE trial is successful, we intend to submit a NDA to the FDA for approval of OCA for the treatment of PBC in the United States and a MAA to the 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 a reduction in ALP or attaining an ALP below specific thresholds correlates with significant reduction in adverse clinical outcomes, such as liver failure, transplant and death. Similarly, studies have demonstrated that elevated bilirubin levels are predictive of adverse outcomes. 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 academic PBC centers in Europe and North America that are pooling their long-term patient data to further substantiate that the POISE trial primary endpoint is predictive of clinical benefit. We anticipate these results will support what we believe is an emerging consensus among PBC opinion leaders concerning the clinical utility of our selected endpoint. We are calling this collection of centers the PBC Supergroup and it is anticipated that data from at least 4,000 patients will be submitted.

We believe this study will comprise the single largest analysis of outcomes in PBC patients and that the analysis will confirm the results already published, or made available to us, by four different members of the PBC Supergroup (University of Toronto, Mayo Clinic, University of Paris and Erasmus University (Rotterdam)). These groups have independently corroborated that the achievement of an ALP level of less than 1.67 times ULN, together with a normal bilirubin level, correlate with a significant reduction of risk of adverse clinical outcomes such as liver transplant and death.

### **Summary of additional preclinical and clinical studies required for regulatory submissions**

Based on our interactions with the FDA and EMA, we believe that, in addition to the successful completion of the POISE trial, we will need to complete the following clinical studies prior to our planned NDA and MAA filings:

long-term monotherapy safety extension studies, resulting in approximately 650 patient cumulative years of safety data across all clinical trials;  
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; and  
additional clinical pharmacology trials, including, but not limited to, drug interactions, the effects of food and drug-disease interaction studies.

In addition, other preclinical studies that we will need to complete are carcinogenicity studies in two rodent species, which were initiated in early 2012, and reproductive toxicology studies. Finally, before we submit a NDA to the FDA, we believe that we will need to be substantially underway with a Phase 3 clinical outcomes trial to confirm clinical benefit at the time of NDA submission. 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. It is possible that the FDA may require that we conduct and/or complete additional clinical trials and preclinical studies before it will consider our NDA for approval.

### **Summary of Completed OCA PBC Clinical Trials**

#### **Phase 2 Trial: OCA as Combination Therapy in PBC Patients**

We have completed a double-blind, placebo-controlled Phase 2 clinical trial of OCA in 165 patients with PBC. The trial evaluated the effects of adding one of three doses of OCA (10 mg, 25 mg and 50 mg) or placebo to ursodiol therapy in patients with ALP levels of higher than 1.5 times ULN who had not responded adequately to ursodiol therapy alone. Patients continued their prior ursodiol dose throughout the trial. At the end of the 12-week treatment period, all three doses of OCA added to ursodiol therapy produced statistically significant reductions in ALP levels as compared with patients receiving placebo plus ursodiol therapy, the primary endpoint. OCA-treated patients demonstrated a mean reduction of 21% to 25% in ALP levels, as compared to patients receiving placebo plus ursodiol

therapy, who exhibited a mean reduction of less than 3%. At trial entry, the baseline mean ALP value for all the patient groups was approximately 2.4 times ULN. In addition, patients who received OCA experienced similar significant decreases in other clinically relevant liver enzymes such as gamma glutamyl transferase, or GGT, aspartate transaminase, or AST, alanine transaminase, or ALT, and bilirubin. Furthermore, serum markers of inflammation and immune response also improved as seen in reductions of CRP and IgM, which are closely associated with autoimmune dysfunction in PBC.

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With the exception of a higher incidence of pruritus in the two highest OCA dose groups and a higher incidence of severe pruritus in all OCA dose groups, the Phase 2 clinical trial data showed that adverse events were generally similar across all groups, including the placebo group. Pruritus was dose dependent, with the ursodiol plus placebo incidence at 50%, ursodiol plus 10 mg of OCA at 47%, ursodiol plus 25 mg of OCA at 85% and ursodiol plus 50 mg of OCA at 80%. However, the severity of pruritus and the discontinuation rate due to severe pruritus increased with OCA dose and was worse than seen with placebo. There were no other statistically significant side effects observed over the placebo group, except for mild nausea.

### **Open Label Long-Term Safety and Efficacy Trial for OCA as Combination Therapy**

Following the completion of the double-blind portion of the Phase 2 combination trial described above, 78 patients were enrolled in an open label long-term safety and efficacy extension study, or LTSE. Of these patients, 19 subsequently discontinued their participation in the LTSE, ten due to pruritus, one due to elevated bilirubin and eight due to other adverse events or for other reasons. There were five serious adverse events in the LTSE, of which two occurred at each of the 10 mg and 25 mg doses and one occurred at the 50 mg dose. None of the serious adverse events, which were typically related to hospitalizations for pre-existing conditions, was considered likely to be related to OCA therapy, and no serious adverse event was considered to be hepatic in nature.

In the LTSE, patients continued to receive open label OCA, increasing from a dose of 10 mg to as high as 50 mg each day. In patients whose dose was increased, there was a benefit of increasing the dose up to 25 mg from 10 mg (with an incremental 9% fall in ALP), but not in increasing the dose above 25 mg. Over two-thirds of the patients were increased to 20 mg or more. Pruritus was the most common adverse event, reported in 68 of the 78 patients (approximately 87%). Other adverse events included fatigue, insomnia and upper respiratory tract infection, each of which was reported by approximately 13% of the patients in the LTSE.

The chart below demonstrates that patients taking OCA achieved mean reductions in ALP to approximately 1.67 times ULN after having been on therapy for three months and maintained that treatment response throughout a 12-month period and beyond. Furthermore, after 12 months, more than 50% of the patients had met the Phase 3 POISE trial primary endpoint, with a reduction in ALP levels to below 1.67 times ULN, along with at least a 15% reduction in ALP, and a normal bilirubin level. Taken together with the data from our ongoing monotherapy LTSE trial discussed below, we believe that these LTSE phases of our Phase 2 trials demonstrate that a large majority of patients taking OCA for at least 12 months, with some currently on therapy for more than 30 months, maintain a durable therapeutic response.

## **Phase 2 Combination Trial LTSE**

\* SEM is defined as the standard error of the mean, which is a statistical estimate of the amount that an obtained mean may be expected to differ by chance from the true mean.

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### **Phase 2 Trial: OCA as Monotherapy in PBC Patients**

We have completed a 59 patient double-blind, placebo-controlled Phase 2 clinical trial of OCA given as a monotherapy to patients with PBC. The trial evaluated the effects of 10 mg and 50 mg doses of OCA compared to placebo in patients with baseline ALP levels of higher than 1.5 times ULN. Patients either had never taken ursodiol or had not been taking ursodiol for at least 3 months before the start of the trial. At the end of the 12-week treatment period, statistically significant reductions in ALP were seen in the treated patients (38% to 45% mean ALP reductions compared with no change in the placebo-treated patients). Patients in the 10 mg dose group experienced absolute reductions in ALP levels from a mean of approximately 3.9 times ULN to approximately 1.9 times ULN at the end of the study. Even greater reductions in GGT (63% to 75%) were seen in the OCA-treated groups (compared to 3% for placebo-treated groups). There were also significant improvements in ALT levels and bilirubin levels. In addition, IgM also improved. Pruritus was seen more commonly in the patients treated with OCA, with the incidence, severity and discontinuation rate all increasing with dose; otherwise, the other adverse events were not clearly different across the groups.

### **Ongoing Open Label Long-Term Safety and Efficacy Trial for OCA as a Monotherapy**

Following the completion of the double-blind portion of the Phase 2 monotherapy trial described above, some patients were given the option to enroll in an open label long-term safety and efficacy extension study, or monotherapy LTSE. The monotherapy LTSE phase is currently ongoing. Patients continue to receive open label OCA in this phase, and have been increased from a starting dose of 10 mg to as high as 50 mg. Approximately half of the patients are currently taking 20 mg or more of OCA. Consistent with the combination trial LTSE, continued improvements in biochemistry have been seen. Pruritus is the most common adverse event and has been reported over the course of the monotherapy LTSE in 24 of the 28 subjects (or 86%) for whom data are available. Other adverse events include headache, arthralgia, fatigue and nausea, which have been reported in approximately 32%, 25%, 21% and 21% of the patients, respectively.

### **Summary of Completed Phase 1 Trials**

OCA has been evaluated in two Phase 1 clinical trials to study its safety and pharmacokinetic profile in healthy volunteers. The first was a single ascending dose trial in 24 subjects testing single OCA doses in the range of 50 mg to 500 mg. The second was a multiple ascending dose trial in 50 subjects testing repeated OCA doses in the range of 25 mg to 250 mg for 12 consecutive days. Adverse events seen in the Phase 1 trials were generally mild. Only two adverse events, upper abdominal pain and nasopharyngitis, were observed in one subject each in the single ascending dose trial. In the multiple ascending dose trial, doses from 25 mg to 100 mg were generally well-tolerated. At the highest dose of 250 mg, ALT and AST increases were seen, consistent with our animal toxicology data. This dose is 25-times greater than the 10 mg dose in the POISE trial and ten-times greater than the 25 mg dose being tested in our ongoing Phase 2b trial for NASH, called the FLINT trial. Half of the subjects in the 250 mg dosing group reported mild pruritus and one discontinued due to a rash.

## **Additional Potential Clinical Indications for OCA**

Based on the potential protective effects of OCA in the liver, we are conducting clinical trials in additional chronic liver disease indications with potential greater market opportunities, with the view of expanding OCA's therapeutic applications.

## Potential Use of OCA to Treat Portal Hypertension

A study in an animal model of cirrhosis showed that OCA treatment can acutely reverse portal hypertension through a localized vasodilatory mechanism that is independent of its longer term anti-fibrotic effects. Portal hypertension results from increased pressure in the portal vein, which feeds most of the blood supply to the liver. The condition typically occurs as the liver becomes cirrhotic and more rigid, thereby offering more resistance to blood inflow from the portal vein. Many patients with liver cirrhosis go on to develop portal hypertension, which is a common cause of morbidity and mortality at the end stage of all chronic liver diseases. An early manifestation of portal hypertension is the development of esophageal varices, which are distended and weakened veins in the lower part of the esophagus that can burst and cause catastrophic bleeding. There are no approved therapies for the treatment of portal hypertension, although beta blockers are commonly used to treat patients. However, they are effective in only 25% to 33% of patients and

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have significant safety issues in portal hypertension patients. It has been shown clinically that reducing pressure in the portal vein can lower the risk of adverse outcomes such as the incidence of variceal bleeding. We believe that portal pressure reduction is an appropriate therapeutic endpoint to demonstrate clinical proof-of-concept.

### **Phase 2 Trial for Portal Hypertension**

OCA is currently being tested in an open label Phase 2a trial, called the PESTO trial, in patients with portal hypertension to evaluate the ability of OCA to reduce hepatic portal venous pressure in patients with end-stage liver disease. The primary endpoint of the trial is to lower the hepatic venous pressure gradient after seven days of treatment by 15% or more, or to 12 mm Hg or less, a level at which the risk of adverse clinical outcomes has been shown to be significantly reduced. An initial safety cohort of four patients demonstrated that OCA was well-tolerated at the 10 mg dose. We are currently conducting an efficacy trial of the 10 mg dose in seven to nine patients, while also completing a safety cohort at a 25 mg dose before continuing with a planned efficacy cohort at this higher dose. We anticipate receiving results from the 10 mg dose group of our PESTO trial by the end of 2012. We are utilizing the data from this trial to supplement our safety data set for our planned NDA for PBC to include the evaluation of OCA in patients with end-stage liver disease. If the PESTO trial supports the further development of OCA for the treatment of portal hypertension, we may initiate a Phase 2 clinical trial in patients with portal hypertension. However, we will need to secure funding in addition to the proceeds from this offering to continue to advance OCA for this indication.

### **Potential Use of OCA to Treat Nonalcoholic Steatohepatitis (NASH)**

FXR activation has been shown to play a key role in the regulation of the metabolic pathways relevant to NASH, highlighting FXR as a potential drug target for treatment of the disease. Nonalcoholic fatty liver disease, or NAFLD, is believed to be the most common chronic liver disease worldwide and we believe that more than 75 million patients are affected in the United States alone. The disease is associated with the Western diet, which is rich in processed foods with high fat and sugar content. NAFLD can lead to excessive fat accumulation in the liver, insulin resistance and increased risk of developing metabolic syndrome, type 2 diabetes and cardiovascular disease. A subset of approximately 30% of NAFLD patients develop NASH, which is a more serious liver disease. In these patients, for reasons that are still not completely understood, the fat build-up in the liver induces chronic inflammation which leads to progressive fibrosis that can lead to cirrhosis and liver failure.

NASH is currently diagnosed by liver biopsy. Studies have shown that at least 15% of NASH patients will develop liver cirrhosis over a ten to 15 year period. In the United States, the most recent epidemiological studies have concluded that more than 12% of the general population has NASH, while approximately 2.7%, or more than eight million patients, have advanced liver fibrosis or cirrhosis due to the disease. In the past decade, the proportion of liver transplants attributed to NASH increased from 1% to 10%, establishing NASH as the third leading and a rapidly increasing indication for liver transplant in the United States. The epidemiological data from other developed countries in Europe and Japan are similar, and NASH has also become a highly prevalent liver disease in developing countries such as India and China.

There are currently no drugs approved for the treatment of NAFLD or NASH. It has been reported that in 2010, there were approximately \$615 million in off-label sales of various therapeutics for the treatment of NASH, such as insulin sensitizers (e.g., metformin), antihyperlipidemic agents (e.g., gemfibrozil), pentoxifylline and ursodiol. Lifestyle changes and exercise to reduce body weight and treatment of concomitant diabetes and dyslipidemia are accepted as the standard of care but have not conclusively been shown to prevent disease progression.

### **Ongoing Phase 2 Trial for NASH**

OCA is currently being tested in a Phase 2b NASH trial, called the FLINT trial, that is testing a 25 mg single daily dose of OCA versus placebo in 280 patients with NASH. We are sponsoring the FLINT trial in collaboration with the U.S. National Institute of Diabetes and Digestive and Kidney Diseases, or NIDDK, which oversees a clinical research network of eight leading NASH centers in the United States. The NIDDK filed an IND with the FDA for OCA for the treatment of NASH in 2010. The primary endpoint in the 72-week double-blind FLINT trial is based on liver biopsy and is defined as an improvement of two or more points in the NAFLD activity score (a system of scoring the histopathological features in the liver) with no

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worsening of liver fibrosis. The NIDDK is providing the majority of funding for the trial, which we anticipate will be fully enrolled in 2012, with final results expected in late 2014. If this trial supports the further development of OCA as a treatment for NASH, we anticipate that we will need to secure additional funding to advance OCA for this indication.

In June 2012, the NIDDK's data and safety monitoring board, or DSMB, for the FLINT trial completed an interim analysis and recommended that the trial should continue based on data from 101 patients who had completed at least 24 weeks and up to 15 months of the trial. The interim analysis reviewed the change from baseline in ALT levels as the efficacy criterion variable and all available safety data. Based on the recommendation of the DSMB, the NIDDK decided to continue the FLINT trial.

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

We have also completed a Phase 2 clinical trial of OCA in 64 type 2 diabetic patients with NAFLD. This double-blind, placebo-controlled trial tested 25 mg and 50 mg doses of OCA over a six-week period and assessed the effects of OCA on insulin sensitivity. The trial demonstrated that OCA therapy significantly improved insulin sensitivity both in the liver and peripheral tissues, thereby meeting the primary endpoint in the trial. Significant improvements in weight loss and reductions in liver enzymes such as GGT and ALT were also noted. The trial also showed that OCA was well-tolerated by the trial patients, with side effects no different than those reported on placebo (apart from mild constipation in the 50 mg group).

### **Potential Use of OCA to Treat Bile Acid Diarrhea**

In July 2012, investigators at the Imperial College of London initiated enrollment of an open label Phase 2a trial, called the OBADIAH trial, to investigate whether OCA can stimulate the hormone known as fibroblast growth factor 19, or FGF19, in patients with bile acid diarrhea. Bile acid diarrhea is an under-recognized but common subtype of inflammatory bowe