IRONWOOD PHARMACEUTICALS INC
Form S-1/A
January 20, 2010

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As filed with the Securities and Exchange Commission on January 20, 2010

Registration No. 333-163275

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

PRE-EFFECTIVE
AMENDMENT NO. 2 TO
FORM S-1

REGISTRATION STATEMENT UNDER THE SECURITIES ACT OF 1933

IRONWOOD PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**2834**	**04-3404176**
(State or other jurisdiction of incorporation or organization)	*(Primary Standard Industrial Classification Code Number)*	*(I.R.S. Employer Identification Number)*

320 Bent Street
Cambridge, Massachusetts 02141
(617) 621-7722
(Address, including zip code, and telephone number, including area code, of registrant's principal executive offices)

Peter M. Hecht
Chief Executive Officer
320 Bent Street
Cambridge, Massachusetts 02141
(617) 621-7722
(Name, address, including zip code, and telephone number, including area code, of agent for service)

Copies to:

Paul M. Kinsella	**Richard D. Truesdell, Jr.**
Ropes & Gray LLP	**Davis Polk & Wardwell LLP**
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Telephone (617) 951-7000	**Telephone (212) 450-4000**
Fax (617) 951-7050	**Fax (212) 701-5800**

Approximate date of commencement of proposed sale to public: As soon as practicable after this Registration Statement becomes effective.

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, as amended (the "Securities Act"), check the following box. o

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

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

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

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

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

CALCULATION OF REGISTRATION FEE

Title of Each Class of Securities to be Registered	Amount to be Registered[(1)]	Proposed Maximum Offering Price Per Share	Proposed Maximum Aggregate Offering Price[(2)]	Amount of Registration Fee[(3)]
Class A Common Stock, $0.001 par value per share	19,166,667	$16.00	$306,666,672	$21,865.33

(1) Includes 2,500,000 shares of Class A common stock issuable upon exercise of an option to purchase additional shares granted to the underwriters.

(2) Estimated solely for the purpose of calculating the registration fee pursuant to Rule 457(a) under the Securities Act, based on an estimate of the proposed maximum aggregate offering price.

(3) $9,625.50 was previously paid on November 20, 2009. The difference of $12,239.83 is being submitted herewith.

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 OR UNTIL THE REGISTRATION STATEMENT SHALL BECOME EFFECTIVE ON SUCH DATE AS THE SECURITIES AND EXCHANGE COMMISSION, ACTING PURSUANT TO SAID SECTION 8(A), MAY DETERMINE.

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PROSPECTUS (Subject to Completion)

The information in this 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 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.

Issued January 20, 2010

16,666,667 Shares

CLASS A COMMON STOCK

This is the initial public offering of Class A common stock by Ironwood Pharmaceuticals, Inc. We are offering 16,666,667 shares of Class A common stock. The estimated initial public offering price is between $14.00 and $16.00 per share.

Currently, no public market exists for our Class A common stock. We have applied to list our shares of Class A common stock on The NASDAQ Global Market under the symbol "IRWD."

Following this offering, we will have two classes of authorized common stock, Class A common stock and Class B common stock. The rights of the holders of Class A common stock and Class B common stock are identical, except with respect to voting. In certain circumstances pertaining to change in control matters, holders of our Class A common stock are entitled to one vote per share and holders of our Class B common stock are entitled to ten votes per share.

Investing in our Class A common stock involves risks. See "Risk Factors" beginning on page 8.

Price $ Per Share

	Price to Public	Underwriting Discounts and Commissions[1]	Proceeds to Us, Before Expenses
Per Share	**$**	**$**	**$**
Total	**$**	**$**	**$**

(1) The underwriters will not receive any underwriting discount or commission on the sale of shares of our Class A common stock to certain of our existing stockholders and certain specified affiliated entities. We have directed the underwriters to reserve up to approximately 7,000,000 shares of our Class A common stock for such sales.

We have granted the underwriters an option for a period of 30 days to purchase up to 2,500,000 additional shares of Class A common stock on the same terms and conditions set forth above.

Neither the Securities and Exchange Commission nor any state securities commission nor any other regulatory body has approved or disapproved of these securities or passed on the accuracy or adequacy of this prospectus. Any representation to the contrary is a criminal offense.

The underwriters expect to deliver the shares of Class A common stock to purchasers on or about , 2010.

J.P.Morgan **Morgan Stanley** **Credit Suisse**

BofA Merrill Lynch

Wedbush PacGrow Life Sciences

, 2010

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You should rely only on the information contained in this prospectus. We have not, and the underwriters have not, authorized anyone to provide you with additional information or information different from that contained in this prospectus. We are not, and the underwriters are not, making an offer to sell these securities in any jurisdiction where an offer or sale is not permitted. You should assume that the information appearing in this prospectus is accurate as of the date on the front cover of this prospectus only, regardless of the time of delivery of this prospectus or of any sale of our Class A common stock. Our business, prospects, financial condition and results of operations may have changed since that date.

Until , 2010, all dealers that effect transactions in these securities, whether or not participating in this offering, may be required to deliver a prospectus. This is in addition to the dealers' obligation to deliver a prospectus when acting as underwriters and with respect to their unsold allotments or subscriptions.

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PROSPECTUS SUMMARY

This summary highlights selected information contained elsewhere in this prospectus. This summary does not contain all of the information you should consider before investing in our Class A common stock. You should read this entire prospectus carefully, especially the risks of investing in our Class A common stock discussed under "Risk Factors" beginning on page 8 and the consolidated financial statements and notes to those consolidated financial statements, before making an investment decision.

Overview

We are an entrepreneurial pharmaceutical company that discovers, develops and intends to commercialize innovative medicines targeting important therapeutic needs. Our goal is to build the next great pharmaceutical company, an outstanding business that will thrive and endure well beyond our lifetimes and generate substantial returns for our shareholders. Our experienced team of researchers is focused on a portfolio of internally discovered drug candidates that includes one Phase 3 drug candidate (linaclotide), one Phase 1 pain drug candidate, and multiple preclinical programs.

We believe that linaclotide could present patients and healthcare practitioners with a unique therapy for a major medical need not yet met by existing therapies. Linaclotide is a first-in-class compound currently in confirmatory Phase 3 clinical trials evaluating its safety and efficacy for the treatment of patients with irritable bowel syndrome with constipation (IBS-C) or chronic constipation (CC). IBS-C and CC are gastrointestinal disorders that affect millions of sufferers worldwide, according to our estimates. Linaclotide recently achieved favorable efficacy and safety results in two Phase 3 CC trials, meeting all 32 primary and secondary endpoints, including the improvement of abdominal symptoms such as bloating and discomfort as well as constipation symptoms, across both doses evaluated in these independent trials involving 1,287 subjects. We expect to have data from our Phase 3 IBS-C trials in the second half of 2010. If those trials are successful, we intend to file a New Drug Application with the U.S. Food and Drug Administration, or the FDA, in the first half of 2011, seeking approval to market linaclotide to IBS-C and CC patients age 18 and older in the U.S. If the FDA approves linaclotide for those indications, we may seek to expand linaclotide's market opportunity by exploring its utility in other gastrointestinal indications and in the pediatric population.

Linaclotide was designed by Ironwood scientists to target the defining attributes of IBS-C: abdominal pain, discomfort, bloating and constipation. Linaclotide acts locally in the gut with no detectable systemic exposure in humans at therapeutic doses. In the six Phase 2 and Phase 3 clinical trials we have completed to date in over 2,000 IBS-C and CC patients, linaclotide has demonstrated rapid and sustained improvement of the multiple symptoms of IBS-C and CC, with favorable tolerability and convenient once-daily oral dosing.

In a Phase 2b study in patients with IBS-C, linaclotide rapidly reduced abdominal pain, abdominal discomfort and bloating, and improved constipation symptoms, throughout the 12-week treatment period of the trial, with improvements noted for all symptoms assessed within the first week of initiation of therapy. In particular, abdominal pain was reduced 37% to 47%, and pain reduction was observed within the first week following initiation of therapy and was sustained throughout the treatment period, even among patients with severe or very severe abdominal pain.

In a Phase 2b study in patients with CC, linaclotide rapidly reduced abdominal discomfort and bloating, and improved constipation symptoms, throughout the 4-week treatment periods of the trials.

In five of the six Phase 2 and Phase 3 trials, diarrhea was the most common adverse event (seen in 5% to 20% of subjects) and the most common cause for discontinuation (1% to 7% of the patients discontinued participation in the trials). Diarrhea has generally been mild to moderate.

We have pursued a partnering strategy for commercializing linaclotide that has enabled us to retain significant control over linaclotide's development and commercialization, share the costs with high-quality

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collaborators whose capabilities complement ours, and, should linaclotide meet our sales expectations, retain approximately half of linaclotide's future long-term value in the major pharmaceutical markets. In September 2007, we entered into a partnership with Forest Laboratories, Inc., or Forest, to co-develop and co-market linaclotide in the U.S. In April 2009, we entered into a license agreement with Almirall, S.A., or Almirall, to develop and commercialize linaclotide in Europe for the treatment of IBS-C and other gastrointestinal conditions. In November 2009, we entered into a license agreement with Astellas Pharma Inc., or Astellas, to develop and commercialize linaclotide for the treatment of IBS-C and other gastrointestinal conditions in several Asian countries. To date, licensing fees, milestone payments, related equity investments and development costs received from our linaclotide partners total greater than $250 million. We have retained all rights to linaclotide outside of the territories discussed above.

In addition to five years of exclusivity under the Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Act, that would be granted if the FDA approves linaclotide, linaclotide is covered by a U.S. composition of matter patent that expires in 2025, subject to possible patent term extension. Linaclotide is also covered by a European Union composition of matter patent that expires in 2024, subject to possible patent term extension. A patent application is pending in Japan, and if issued, would expire in 2024.

If linaclotide continues to advance to regulatory submission in the U.S., the European Union and Asia, we expect to receive an additional $190 million in pre-commercial payments from our partners. We believe that these milestone payments, together with our existing cash and the anticipated proceeds of this offering, should enable us to launch and commercialize linaclotide in the U.S. with our partner Forest and to fund our currently contemplated research and development efforts for at least the next five years, based on our current business plan.

Our Strategy

Our goal is to build the next great pharmaceutical company by discovering, developing and commercializing innovative and differentiated medicines that target important unmet needs. Key elements of our strategy include:

- attract and incentivize a team with a singular passion for creating and commercializing medicines that can make a significant difference in patients' lives;
- successfully commercialize linaclotide in collaboration with Forest in the U.S.;
- support our international partners to commercialize linaclotide outside of the U.S.;
- if approved for IBS-C and CC, develop linaclotide for the treatment of other gastrointestinal disorders and for the pediatric population;
- invest in our pipeline of novel product candidates and evaluate candidates outside of the company for in-licensing or acquisition opportunities;
- participate in a meaningful way in the economics of the drugs that we bring to the market; and
- execute our strategy with our shareholders' long-term interests in mind by seeking to maximize long-term per share cash flows.

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Risks Affecting Us

Our ability to implement our business strategy is subject to numerous risks and uncertainties. As an early stage pharmaceutical company, we face many risks inherent in our business and our industry generally. We currently have no commercial products and we have not received regulatory approval for, nor have we generated commercial revenue from, any of our product candidates. The regulatory approval process is expensive, time-consuming and uncertain, and our product candidates may not be approved for sale by regulatory authorities. We are largely dependent on the success of our lead product candidate, linaclotide, which may never be successfully commercialized. Even if linaclotide receives regulatory approval, it may still face future development and regulatory difficulties and may never achieve profitability. Our other product candidates are at an early stage of development and are unproven. If we do not successfully commercialize our product candidates, we will be unable to achieve our business objectives. Our patents may not adequately protect our present and future candidates or prevent third parties from competing against us. We have a limited operating history and have incurred substantial losses since inception. We incurred a net loss attributable to Ironwood Pharmaceuticals, Inc. of approximately $47.3 million for the nine months ended September 30, 2009 and had an accumulated deficit of approximately $290.6 million as of September 30, 2009. We anticipate that we will continue to incur additional losses for the foreseeable future. You should carefully consider all of the information set forth in this prospectus and, in particular, the information under the heading "Risk Factors," prior to making an investment in our Class A common stock.

Corporate Information

We were incorporated in Delaware in 1998. Prior to April 7, 2008, we were named Microbia, Inc., which is now the name of our majority-owned subsidiary (formerly Microbia Precision Engineering, Inc.). Our address is 320 Bent Street, Cambridge, Massachusetts 02141. Our telephone number is 617-621-7722. Our website address is www.ironwoodpharma.com. Information contained in, and that can be accessed through, our website is not incorporated into and does not form a part of this prospectus.

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THE OFFERING

Class A common stock we are offering	16,666,667 shares
Over-allotment option	2,500,000 shares
Common stock to be outstanding after this offering	
Class A common stock	16,666,667 shares
Class B common stock	78,246,222 shares
Total common stock	94,912,889 shares
Voting rights	Until at least December 31, 2018, each share of Class A common stock and each share of Class B common stock has one vote per share, except on the following matters (in which each share of Class A common stock has one vote per share and each share of Class B common stock has ten votes per share): adoption of a merger or consolidation agreement involving Ironwood; a sale of all or substantially all of Ironwood's assets; a dissolution or liquidation of Ironwood; or every matter, if and when any individual, entity or "group" (as such term is used in Regulation 13D of the Securities Exchange Act of 1934, as amended, or the Exchange Act) has, or has publicly disclosed (through a press release or a filing with the Securities and Exchange Commission, or the SEC) an intent to have, beneficial ownership of 30% or more of the number of outstanding shares of Class A common stock and Class B common stock, combined. See "Description of Capital Stock" for a description of the material terms of our Class A common stock and our Class B common stock.
Use of proceeds after expenses	We estimate that the net proceeds from this offering will be approximately $237.5 million, or approximately $272.4 million if the underwriters exercise their over-allotment option in full. We expect to use the net proceeds from this offering to fund the development and commercialization of linaclotide, to fund research and development of other products and for other general corporate purposes. See "Use of Proceeds."
Risk factors	You should read the "Risk Factors" section of this prospectus beginning on page 8 for a discussion of factors to consider carefully before deciding whether to purchase shares of our Class A common stock.

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Directed share program	We have directed the underwriters to reserve up to approximately 7,000,000 of the shares of our Class A common stock to be issued in this offering for sale to certain of our existing stockholders and certain specified affiliated entities. The underwriters will not receive any underwriting discount or commission on the sale of such shares. See "Underwriting."
Proposed NASDAQ Global Market symbol	IRWD

The number of shares of our common stock to be outstanding after this offering is based on 78,246,222 shares of Class B common stock outstanding as of December 31, 2009, after giving effect to the conversion of 69,904,843 shares of convertible preferred stock outstanding as of December 31, 2009 into 70,391,620 shares of our Class B common stock at the completion of this offering.

The number of shares of our common stock outstanding immediately after this offering excludes:

- 13,691,579 shares of Class B common stock issuable upon the exercise of options outstanding as of December 31, 2009, with exercise prices ranging from $0.10 to $7.36 per share and a weighted average exercise price of $2.45 per share; and
- 2,255,516 additional shares of Class B common stock reserved for future grants under our 2002 Stock Incentive Plan and 2005 Stock Incentive Plan as of December 31, 2009.

Unless otherwise indicated, all information in this prospectus:

- assumes an initial public offering price of $15.00 per share of Class A common stock, the mid-point of the range set forth on the cover page of this prospectus;
- gives effect to the automatic conversion of all outstanding shares of our convertible preferred stock into shares of our Class B common stock upon the completion of this offering;
- gives effect to our eleventh amended and restated certificate of incorporation that we will file with Delaware immediately prior to the closing of this offering;
- assumes no conversion of our Class B common stock into our Class A common stock prior to the completion of this offering; and
- assumes no exercise by the underwriters of their option to purchase up to 2,500,000 shares of our Class A common stock in this offering to cover over-allotments.

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SUMMARY CONSOLIDATED FINANCIAL DATA

The following tables present a summary of our historical consolidated financial information and pro forma net loss per common share. You should read the following summary financial data in conjunction with "Selected Consolidated Financial Data," "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.

	December 31,			Nine Months Ended September 30,	
	2006	2007	2008	2008	2009
				(unaudited)	
	(in thousands, except share and per share data)				
Consolidated Statement of Operations Data:					
Revenue:					
Collaborative arrangements	$	$ 4,608	$ 18,383	$ 13,933	$ 25,917
Services	3,140	5,856	3,833	3,309	1,581
Total revenue	3,140	10,464	22,216	17,242	27,498
Operating expenses:					
Research and development	35,543	57,246	59,809	43,309	58,824
General and administrative	7,192	10,833	18,328	13,054	17,309
Total operating expenses	42,735	68,079	78,137	56,363	76,133
Loss from operations	(39,595)	(57,615)	(55,921)	(39,121)	(48,635)
Other income (expense):					
Interest expense	(217)	(263)	(334)	(253)	(370)
Interest and investment income	2,533	4,118	2,124	1,901	214
Remeasurement of forward purchase contracts		600	(900)	(5,900)	(100)
Other income (expense), net	2,316	4,455	890	(4,252)	(256)
Loss before income tax benefit	(37,279)	(53,160)	(55,031)	(43,373)	(48,891)
Income tax benefit					(153)
Net loss	(37,279)	(53,160)	(55,031)	(43,373)	(48,738)
Net loss attributable to noncontrolling interest	99	408	1,157	726	1,483
Net loss attributable to Ironwood Pharmaceuticals, Inc.	$ (37,180)	$ (52,752)	$ (53,874)	$ (42,647)	$ (47,255)
Net loss per share attributable to Ironwood Pharmaceuticals, Inc. basic and diluted	$ (5.79)	$ (7.91)	$ (7.82)	$ (6.22)	$ (6.70)
Weighted average number of common shares used in net loss per share attributable to Ironwood Pharmaceuticals, Inc. basic and diluted	6,417,499	6,666,601	6,889,817	6,859,285	7,054,291

Pro forma net loss per share attributable to Ironwood Pharmaceuticals, Inc. basic and diluted (unaudited)[1]	$ (0.72)	$ (0.62)
Pro forma weighted average number of common shares used in net loss per share attributable to Ironwood Pharmaceuticals, Inc. basic and diluted (unaudited)[1]	74,495,452	75,574,117

(1) Pro forma basic and diluted net loss per share have been calculated assuming: (a) the automatic conversion of all outstanding shares of convertible preferred stock as of December 31, 2008 into 67,605,635 shares of our Class B common stock and as of September 30, 2009 into 69,709,801 shares of our Class B common stock upon the closing

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of this offering; (b) the issuance of 681,819 shares of our convertible preferred stock sold at a price of $22.00 per share for cash proceeds of $15.0 million, which were received on November 13, 2009, including a $0.7 million gain on the final remeasurement of the forward purchase contract at the time of settlement, and the conversion of such shares into 681,819 shares of our Class B common stock upon the closing of this offering and (c) compensation expense of approximately $56,000 and $107,000 related to 30,000 and 45,000 time-accelerated stock options at December 31, 2008 and September 30, 2009, respectively, that will fully vest upon the closing of this offering. Pro forma basic and diluted net loss per share does not give effect to the sale of 16,666,667 shares of Class A common stock that we are offering pursuant to this prospectus.

	As of September 30, 2009 (unaudited)		
	Actual	Pro Forma[(a)]	Pro Forma as Adjusted[(b)]
		(in thousands)	
Consolidated Balance Sheet Data:			
Cash, cash equivalents and available-for-sale securities	$ 98,928	$ 113,928	$ 351,428
Working capital (excluding deferred revenue)	99,412	108,612	346,112
Total assets	149,647	158,847	396,347
Deferred revenue, including current portion	104,487	104,487	104,487
Long-term debt, including current portion	3,406	3,406	3,406
Capital lease obligations, including current portion	220	220	220
Total liabilities	135,640	135,640	135,640
Convertible preferred stock	289,849		
Noncontrolling interest	3,856	3,856	3,856
Total stockholders' equity (deficit)	(275,842)	23,207	260,707

(a)

The pro forma consolidated balance sheet data gives effect to: (i) the automatic conversion of all outstanding shares of our convertible preferred stock into 69,709,801 shares of our Class B common stock upon the closing of this offering; (ii) the issuance of 681,819 shares of our convertible preferred stock sold at a price of $22.00 per share for cash proceeds of $15.0 million, which were received on November 13, 2009, including a $0.7 million gain on the final remeasurement of the forward purchase contract at the time of settlement, and the conversion of such shares into 681,819 shares of our Class B common stock upon the closing of this offering and (iii) compensation expense of approximately $107,000 related to 45,000 time-accelerated stock options at September 30, 2009 that will fully vest upon the closing of this offering.

(b)

The pro forma as adjusted consolidated balance sheet data also gives effect to the sale of 16,666,667 shares of our Class A common stock in this offering at an assumed initial public offering price of $15.00 per share, which is the midpoint of the price range set forth on the cover page of this prospectus, after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us.

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RISK FACTORS

Investing in our Class A 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, before deciding to invest in our Class A common stock. The occurrence of any of the following risks could harm our business, financial condition, results of operations or prospects. In that case, the trading price of our Class A common stock could decline, and you may lose all or part of your investment.

Risks Related to Our Business and Industry

We are largely dependent on the success of linaclotide, which may never receive regulatory approval or be successfully commercialized.

We currently have one product candidate, linaclotide, in Phase 3 clinical development. Our other drug candidates are in earlier stages of development. Our business depends entirely on the successful development and commercialization of our product candidates. We currently generate no revenue from sales, and we may never be able to develop marketable drugs. The research, testing, manufacturing, labeling, approval, sale, marketing and distribution of pharmaceutical products is subject to extensive regulation by the FDA and foreign regulatory authorities, and regulations differ from jurisdiction to jurisdiction. We are not permitted to market any of our product candidates in the U.S. until we receive approval of a new drug application, or an NDA, from the FDA, or in any foreign jurisdictions until we receive the requisite approvals from such jurisdictions. We have neither submitted an NDA nor received marketing approval for linaclotide in any jurisdiction. Obtaining approval of an NDA is a lengthy, expensive and uncertain process. The FDA also has substantial discretion in the drug approval process, including the ability to delay, limit or deny approval of a product candidate for many reasons. For example:

- the FDA may not deem linaclotide or another product candidate safe and effective;
- the FDA may not find the data from preclinical studies and clinical trials sufficient to support approval;
- the FDA may not approve of manufacturing processes and facilities; or
- the FDA may change its approval policies or adopt new regulations.

Linaclotide is a first-in-class compound that is currently in Phase 3 clinical development for the treatment of irritable bowel syndrome with constipation, or IBS-C, and chronic constipation, or CC, and will require the successful completion of at least two Phase 3 clinical trials for each indication before submission of an NDA to the FDA for potential approval in such indication. In November 2009, we announced that we achieved favorable results in our CC trials. Even though linaclotide met the endpoints of the CC trial, it may not be approved for the CC indication or for any other indication for which we are seeking approval from the FDA. The FDA may disagree with our trial design or our interpretation of data from clinical trials, or may change the requirements for approval even after it has reviewed and commented on the design for our clinical trials. The FDA might also approve linaclotide for fewer or more limited indications than we request, or may grant approval contingent on the performance of costly post-approval clinical trials. In addition, the FDA may not approve the labeling claims that we believe are necessary or desirable for the successful commercialization of linaclotide. Any failure to obtain regulatory approval of linaclotide would significantly limit our ability to generate revenues, and any failure to obtain such approval for all of the indications and labeling claims we deem desirable could reduce our potential revenue.

Our clinical trials may fail to demonstrate acceptable levels of safety and efficacy of linaclotide, which could prevent or significantly delay regulatory approval.

Our product candidates are prone to the risks of failure inherent in drug development most pharmaceutical product candidates fail. Before obtaining regulatory approvals for the commercial sale of

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linaclotide or any other product candidate for a specific indication, we must demonstrate with substantial evidence gathered in well-controlled clinical trials and to the satisfaction of the FDA, with respect to approval in the U.S., and to the satisfaction of similar regulatory authorities in other jurisdictions, with respect to approval in those jurisdictions, that the product candidate is safe and effective for use for the target indication.

The results from the preclinical and clinical trials that we have completed for linaclotide may not be replicated in future trials, or we may be unable to demonstrate sufficient safety and efficacy to obtain the requisite regulatory approvals for linaclotide. A number of companies in the biotechnology and pharmaceutical industries have suffered significant setbacks in advanced clinical trials, even after promising results in earlier trials. If linaclotide is not shown to be safe and effective, our clinical development programs could be delayed or terminated. Our failure to adequately demonstrate the efficacy and safety of linaclotide or any other product candidates that we may develop, in-license or acquire would prevent receipt of regulatory approval and, ultimately, the commercialization of that product candidate.

The positive top-line results from our two Phase 3 clinical trials assessing the safety and efficacy of linaclotide in patients with CC may not be indicative of our two Phase 3 clinical trials assessing the safety and efficacy of linaclotide in patients with IBS-C.

In November 2009, we announced that the primary endpoint was achieved in each of our two Phase 3 clinical trials assessing the safety and efficacy of linaclotide in patients with CC. Additional data from each of these Phase 3 clinical trials may become available and may have a bearing on the safety and efficacy of linaclotide. In addition, the primary efficacy endpoint in each of these two clinical trials is only one of the three primary efficacy endpoints in each of our two Phase 3 clinical trials assessing the safety and efficacy of linaclotide in patients with IBS-C. Positive results in the CC trial or from earlier clinical trials are not necessarily indicative of future success in the IBS-C trials, even with respect to similar endpoints. Therefore, unless we meet all three primary efficacy endpoints in our two IBS-C clinical trials, we may be unable to demonstrate sufficient safety and efficacy of linaclotide in patients with IBS-C. Finally, our partners Almirall and Astellas intend to seek approval from regulatory authorities in each of their respective territories solely for the IBS-C indication. Accordingly, if we are unable to establish safety and efficacy of linaclotide in our U.S. IBS-C trials, our partners may be unable to utilize our data in the U.S. in their regulatory filings, and may be hindered from obtaining approval for linaclotide in their respective territories.

Linaclotide may cause undesirable side effects or have other properties that could delay or prevent its regulatory approval or limit its commercial potential.

Undesirable side effects caused by linaclotide could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in the denial of regulatory approval by the FDA or other regulatory authorities and potential products liability claims. We are currently completing our evaluation of the data from our CC studies and conducting two Phase 3 IBS-C trials as well as a long-term safety study in patients dosed with linaclotide over a 78-week period. Serious adverse events deemed to be caused by linaclotide could have a material adverse effect upon the linaclotide program and our business as a whole. The most common adverse event to date in the clinical studies evaluating the safety and efficacy of linaclotide has been diarrhea. For the most part, the diarrhea has been considered mild or moderate by the patients, but in a small percentage of patients, it has been severe enough for patients to discontinue participation in a study. There have been no serious adverse events in patients treated with linaclotide that were deemed by a study investigator to be definitively related or probably related to linaclotide treatment. There have been serious adverse events in patients treated with linaclotide that were deemed by a study investigator to be possibly related to linaclotide treatment, involving single cases of aplastic anemia, atrial fibrillation, bronchitis, cholecystectomy, gastroenteritis, vertigo, and illeus. These serious adverse events may or may not have been related to linaclotide and our understanding of the relationship between

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linaclotide and these events may change as we gather more information. Finally, there have been no deaths in our trials that were considered to be related to linaclotide treatment.

If linaclotide receives marketing approval, and we or others later identify undesirable side effects caused by the product, a number of potentially significant negative consequences could result, including:

- regulatory authorities may withdraw approvals of linaclotide;
- regulatory authorities may require additional warnings on the label;
- we may be required to create a medication guide outlining the risks of such side effects for distribution to patients;
- we could be sued and held liable for harm caused to patients; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of linaclotide and could substantially increase commercialization costs.

Delays in the completion of clinical testing could result in increased costs and delay or limit our ability to generate revenues.

Delays in the completion of clinical testing could significantly affect our product development costs. We do not know whether planned clinical trials will be completed on schedule, if at all. The commencement and completion of clinical trials can be delayed for a number of reasons, including delays related to:

- obtaining regulatory approval to commence a clinical trial;
- reaching agreement on acceptable terms with prospective clinical research organizations, or CROs, and trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- manufacturing sufficient quantities of a product candidate for use in clinical trials;
- obtaining institutional review board approval to conduct a clinical trial at a prospective site;
- recruiting and enrolling patients to participate in clinical trials for a variety of reasons, including competition from other clinical trial programs for the treatment of similar conditions; and
- signing-up patients who have initiated a clinical trial but may be prone to withdraw due to side effects from the therapy, lack of efficacy or personal issues, or who are lost to further follow-up.

Clinical trials may also be delayed as a result of ambiguous or negative interim results. In addition, a clinical trial may be suspended or terminated by us, an institutional review board overseeing the clinical trial at a clinical trial site (with respect to that site), the FDA, or other regulatory authorities due to a number of factors, including:

failure to conduct the clinical trial in accordance with regulatory requirements or the study protocols;

inspection of the clinical trial operations or trial sites by the FDA or other regulatory authorities resulting in the imposition of a clinical hold;

unforeseen safety issues; and

lack of adequate funding to continue the clinical trial.

Additionally, changes in regulatory requirements and guidance may occur, and we may need to amend clinical trial protocols to reflect these changes. Amendments may require us to resubmit our clinical trial

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protocols to institutional review boards for reexamination, which may impact the costs, timing or successful completion of a clinical trial. If we experience delays in completion of, or if we terminate any of our clinical trials, the commercial prospects for our product candidates may be harmed, and our ability to generate product revenues will be delayed. In addition, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our product candidates.

Because we work with Forest Laboratories, Inc. to develop, promote and manufacture linaclotide in North America, we are dependent upon a third party in our efforts to obtain regulatory approval for, and to commercialize, linaclotide within our expected timeframes.

We co-develop and plan to co-promote linaclotide in the U.S. with Forest Laboratories, Inc., or Forest. Forest plays a significant role in the conduct of the clinical trials for linaclotide and the subsequent collection and analysis of data. In addition, Forest is responsible for completing the manufacturing process of linaclotide upon production of the active pharmaceutical ingredient, or API, which consists of finishing and packaging linaclotide into capsules. Employees of Forest are not our employees, and we have limited ability to control the amount or timing of resources that they devote to linaclotide. If Forest fails to devote sufficient time and resources to linaclotide, or if its performance is substandard, it will delay the potential approval of our regulatory applications as well as the commercialization and manufacturing of linaclotide. A material breach by Forest of our collaboration agreement could also delay regulatory approval and commercialization of linaclotide. In addition, the execution of clinical trials, and the subsequent compilation and analysis of the data produced, requires coordination among various parties. These functions may not be carried out effectively and efficiently if these parties fail to communicate and coordinate with one another. Moreover, although we have non-compete restrictions in place with Forest, Forest may have relationships with other commercial entities, some of which may compete with us. If Forest assists our competitors, it could harm our competitive position.

We may face competition in the IBS-C and CC marketplace for linaclotide, and new products may emerge that provide different or better alternatives for treatment of gastrointestinal conditions.

If approved and commercialized, linaclotide will compete with one existing prescription therapy for the treatment of IBS-C and CC, Amitiza. In addition, over the counter products are also used to treat certain symptoms of IBS-C and CC. The availability of prescription competitors and over the counter products for gastrointestinal conditions could limit the demand, and the price we are able to charge, for linaclotide unless we are able to differentiate linaclotide on the basis of its clinical benefits in our clinical trials. New developments, including the development of other drug technologies and methods of preventing the incidence of disease, occur in the pharmaceutical and medical technology industries at a rapid pace. These developments may render linaclotide obsolete or noncompetitive.

We believe certain companies are developing other products which could compete with linaclotide should they be approved by the FDA. Currently, there is only one compound in late stage development, and it is being developed by Theravance, Inc. This compound has completed Phase 2 trials for CC. To our knowledge, other potential competitors are in earlier stages of development. If our potential competitors are successful in completing drug development for their drug candidates and obtain approval from the FDA, they could limit the demand for linaclotide.

Many of our competitors have substantially greater financial, technical and human resources than us. Mergers and acquisitions in the pharmaceutical industry may result in even more resources being concentrated in our competitors. Competition may increase further as a result of advances made in the commercial applicability of technologies and greater availability of capital for investment in these fields.

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We have limited sales and marketing experience and resources, and we may not be able to effectively market and sell linaclotide.

With linaclotide, we are developing a product candidate for large markets traditionally served by general practitioners and internists, as well as gastrointestinal specialists. Traditional pharmaceutical companies employ groups of sales representatives to call on these large generalist physician populations. In order to adequately address these physician groups, we must optimize our co-development and co-promotion relationship in the U.S., Canada and Mexico with Forest, our license and commercialization relationship in Europe with Almirall, and our license and commercialization relationship in certain Asian countries with Astellas. Likewise, we must either establish sales and marketing collaborations or co-promotion arrangements or expend significant resources to develop our own sales and marketing presence outside of North America, Europe, and those Asian countries. We currently possess limited resources and may not be successful in establishing additional collaborations or co-promotion arrangements on acceptable terms, if at all. We also face competition in our search for collaborators, co-promoters and sales force personnel. By entering into strategic collaborations or similar arrangements, we rely on third parties for financial resources and for development, commercialization, sales and marketing and regulatory expertise. Our collaborators may fail to develop or effectively commercialize linaclotide because they cannot obtain the necessary regulatory approvals, lack adequate financial or other resources or decide to focus on other initiatives.

Even if linaclotide receives regulatory approval, it may still face future development and regulatory difficulties.

Even if U.S. regulatory approval is obtained, the FDA may still impose significant restrictions on a product's indicated uses or marketing or impose ongoing requirements for potentially costly post-approval studies. Linaclotide and our other product candidates would also be subject to ongoing FDA requirements governing the labeling, packaging, storage, advertising, promotion, recordkeeping and submission of safety and other post-market information. In addition, manufacturers of drug products and their facilities are subject to continual review and periodic inspections by the FDA and other regulatory authorities for compliance with current good manufacturing practices, or GMP, regulations. If we or 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, a regulatory agency may impose restrictions on that product or the manufacturer, including requiring withdrawal of the product from the market or suspension of manufacturing. If we, our product candidates or the manufacturing facilities for our product candidates fail to comply with applicable regulatory requirements, a regulatory agency may:

issue warning letters or untitled letters;

impose civil or criminal penalties;

suspend regulatory approval;

suspend any ongoing clinical trials;

refuse to approve pending applications or supplements to applications filed by us;

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

seize or detain products or require us to initiate a product recall.

Even if linaclotide receives regulatory approval in the U.S., we or our collaborators may never receive approval to commercialize linaclotide outside of the U.S.

In May 2009, we entered into an out-license agreement with Almirall for European rights to develop and commercialize linaclotide. In November 2009, we entered into an out-license agreement with Astellas for rights to develop and commercialize linaclotide in certain Asian countries. In the future, we may seek

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to commercialize linaclotide in foreign countries outside of Europe and those Asian countries with other parties or by ourselves. In order to market any products outside of the U.S., we must establish and comply with numerous and varying regulatory requirements of other jurisdictions regarding safety and efficacy. Approval procedures vary among jurisdictions and can involve product testing and administrative review periods different from, and greater than, those in the U.S. The time required to obtain approval in other jurisdictions might differ from that required to obtain FDA approval. The regulatory approval process in other jurisdictions may include all of the risks detailed above regarding FDA approval in the U.S. as well as other risks. Regulatory approval in one jurisdiction does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one jurisdiction may have a negative effect on the regulatory processes in others. Failure to obtain regulatory approvals in other jurisdictions or any delay or setback in obtaining such approvals could have the same adverse effects detailed above regarding FDA approval in the U.S. As described above, such effects include the risks that linaclotide may not be approved for all indications requested, which could limit the uses of our linaclotide and have an adverse effect on its commercial potential or require costly post-marketing studies.

If the manufacturers upon whom we rely fail to produce linaclotide in the volumes that we require on a timely basis, or fail to comply with stringent regulations applicable to pharmaceutical drug manufacturers, we may face delays in the development and commercialization of our product candidates.

We do not currently possess internal manufacturing capacity. We currently utilize the services of contract manufacturers to manufacture our clinical supplies. With respect to the manufacturing of linaclotide, we are currently pursuing long-term commercial supply agreements with multiple manufacturers. These manufacturers will be responsible for the linaclotide API. These third party manufacturers acquire the raw materials for the API from a limited number of sources. Any curtailment in the availability of these raw materials could result in production or other delays with consequent adverse effects on us. In addition, because regulatory authorities must generally approve raw material sources for pharmaceutical products, changes in raw material suppliers may result in production delays or higher raw material costs.

We may be required to agree to minimum volume requirements, exclusivity arrangements or other restrictions with the contract manufacturers. We may not be able to enter into long-term agreements on commercially reasonable terms, or at all. If we change or add manufacturers, the FDA and comparable foreign regulators must approve these manufacturers' facilities and processes prior to use, which would require new testing and compliance inspections, and the new manufacturers would have to be educated in or independently develop the processes necessary for the production of our product candidates. Peptide manufacturing is a highly specialized manufacturing business. While we believe we will have long term arrangements with a sufficient number of API manufacturers, if we lose a manufacturer, it would take us a substantial amount of time to identify and develop a relationship with an alternative manufacturer.

Upon production of our API, each of our collaboration partners, Forest, Almirall and Astellas, is responsible for completing the manufacturing process of linaclotide which consists of finishing and packaging linaclotide into capsules, and we will be dependent upon those parties' success in producing drug product for commercial sale. No party has experience producing the API or finished drug product for linaclotide at commercial scale, and such efforts may fail. Traditionally, peptide manufacturing is costly, time consuming, resulting in low yields and poor stability. We cannot give any assurances that we will not encounter these issues when scaling up manufacturing for linaclotide.

The manufacture of pharmaceutical products requires significant expertise and capital investment, including the development of advanced manufacturing techniques and process controls. Manufacturers of pharmaceutical products often encounter difficulties in production, particularly in scaling up production. These problems include difficulties with production costs and yields, quality control, including stability of the product and quality assurance testing, shortages of qualified personnel, as well as compliance with federal, state and foreign regulations. We are currently evaluating the stability of different batch sizes of

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linaclotide at various points in time. If we are unable to demonstrate stability in accordance with commercial requirements, or if our manufacturers were to encounter difficulties or otherwise fail to comply with their obligations to us, our ability to obtain FDA approval and market linaclotide would be jeopardized. In addition, any delay or interruption in the supply of clinical trial supplies could delay the completion of our clinical trials, increase the costs associated with conducting our clinical trials and, depending upon the period of delay, require us to commence new trials at significant additional expense or to terminate a trial.

Each of the linaclotide manufacturers would need to comply with GMP requirements enforced by the FDA through its facilities inspection program. These requirements include, among other things, quality control, quality assurance and the maintenance of records and documentation. Manufacturers of linaclotide may be unable to comply with these GMP requirements and with other FDA and foreign regulatory requirements. We have little control over our manufacturers' or collaboration partners' compliance with these regulations and standards. A failure to comply with these requirements may result in fines and civil penalties, suspension of production, suspension or delay in product approval, product seizure or recall, or withdrawal of product approval. If the safety of linaclotide is compromised due to a manufacturers' or collaboration partners' failure to adhere to applicable laws or for other reasons, we may not be able to obtain regulatory approval for or successfully commercialize linaclotide, and we may be held liable for any injuries sustained as a result. Any of these factors could cause a delay of clinical trials, regulatory submissions, approvals or commercialization of linaclotide or our other product candidates, entail higher costs or result in our being unable to effectively commercialize linaclotide or our other product candidates. Furthermore, if our manufacturers or collaboration partners fail to deliver the required commercial quantities on a timely basis and at commercially reasonable prices, we may be unable to meet demand for any approved products and would lose potential revenues.

Guidelines and recommendations published by various organizations can reduce the use of our products.

Government agencies promulgate regulations and guidelines directly applicable to us and to our products. In addition, professional societies, practice management groups, private health and science foundations and organizations involved in various diseases from time to time may also publish guidelines or recommendations to the health care and patient communities. Recommendations of government agencies or these other groups or organizations may relate to such matters as usage, dosage, route of administration and use of concomitant therapies. Recommendations or guidelines suggesting the reduced use of our products or the use of competitive or alternative products that are followed by patients and health care providers could result in decreased use of our products.

We are subject to uncertainty relating to reimbursement policies which, if not favorable for linaclotide, could hinder or prevent linaclotide's commercial success.

Our ability to commercialize linaclotide successfully will depend in part on the coverage and reimbursement levels set by governmental authorities, private health insurers and other third-party payors. As a threshold for coverage and reimbursement, third-party payors generally require that drug products have been approved for marketing by the FDA. Third-party payors also are increasingly challenging the effectiveness of and prices charged for medical products and services. We may not obtain adequate third-party coverage or reimbursement for linaclotide or we may be required to sell linaclotide at a discount.

We expect that private insurers will consider the efficacy, cost effectiveness and safety of linaclotide in determining whether to approve reimbursement for linaclotide and at what level. Obtaining these approvals can be a time consuming and expensive process. Our business would be materially adversely affected if we do not receive approval for reimbursement of linaclotide from private insurers on a timely or satisfactory basis. Our business could also be adversely affected if private insurers, including managed care organizations, the Medicare program or other reimbursing bodies or payors limit the indications for which linaclotide will be reimbursed to a smaller set than we believe it is effective in treating.

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In some foreign countries, particularly Canada and the countries of Europe, the pricing of prescription pharmaceuticals is subject to strict governmental control. In these countries, pricing negotiations with governmental authorities can take six to 12 months or longer after the receipt of regulatory approval and product launch. To obtain favorable reimbursement for the indications sought or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our products, including linaclotide, to other available therapies. If reimbursement for our products is unavailable in any country in which reimbursement is sought, limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be materially harmed.

We expect to experience pricing pressures in connection with the sale of linaclotide and our future products due to the potential healthcare reforms discussed below, as well as the trend toward programs aimed at reducing health care costs, the increasing influence of health maintenance organizations and additional legislative proposals.

We face potential product liability exposure, and, if successful claims are brought against us, we may incur substantial liabilities.

The use of our product candidates in clinical trials and the sale of any products for which we obtain marketing approval expose us to the risk of product liability claims. If we cannot successfully defend ourselves against product liability claims, we could incur substantial liabilities. In addition, regardless of merit or eventual outcome, product liability claims may result in:

decreased demand for any approved product;

impairment of our business reputation;

withdrawal of clinical trial participants;

initiation of investigations by regulators;

costs of related litigation;

distraction of management's attention from our primary business;

substantial monetary awards to patients or other claimants;

loss of revenues; and

the inability to commercialize our product candidates.

We have obtained product liability insurance coverage for our clinical trials. Our insurance coverage is limited to $5 million per occurrence, and $10 million in the aggregate, and covers bodily injury and property damage arising from our clinical trials, subject to industry-standard terms, conditions and exclusions. Our insurance coverage 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. If and when we obtain marketing approval for any of our product candidates, we intend to expand our insurance coverage to include the sale of commercial products; however, we may be unable to obtain this product liability insurance on commercially reasonable terms. On occasion, 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 could cause our stock price to decline and, if judgments exceed our insurance coverage, could decrease our cash and adversely affect our business.

Our failure to successfully discover, acquire, develop and market additional product candidates or approved products would impair our ability to grow.

As part of our growth strategy, we intend to develop and market additional products and product candidates. We are pursuing various therapeutic opportunities through our pipeline. We may spend several

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years completing our development of any particular current or future internal product candidate, and failure can occur at any stage. The product candidates to which we allocate our resources may not end up being successful. In addition, because our internal research capabilities are limited, we may be dependent upon pharmaceutical and biotechnology companies, academic scientists and other researchers to sell or license products or technology to us. The success of this strategy depends partly upon our ability to identify, select, discover and acquire promising pharmaceutical product candidates and products.

The process of proposing, negotiating and implementing a license or acquisition of a product candidate or approved product is lengthy and complex. Other companies, including some with substantially greater financial, marketing and sales resources, may compete with us for the license or acquisition of product candidates and approved products. We have limited resources to identify and execute the acquisition or in-licensing of third-party products, businesses and technologies and integrate them into our current infrastructure. Moreover, we may devote resources to potential acquisitions or in-licensing opportunities that are never completed, or we may fail to realize the anticipated benefits of such efforts. We may not be able to acquire the rights to additional product candidates on terms that we find acceptable, or at all.

In addition, future acquisitions may entail numerous operational and financial risks, including:

- exposure to unknown liabilities;
- disruption of our business and diversion of our management's time and attention to develop acquired products or technologies;
- incurrence of substantial debt, dilutive issuances of securities or depletion of cash to pay for acquisitions;
- higher than expected acquisition and integration costs;
- difficulty in combining the operations and personnel of any acquired businesses with our operations and personnel;
- increased amortization expenses;
- impairment of relationships with key suppliers or customers of any acquired businesses due to changes in management and ownership; and
- inability to motivate key employees of any acquired businesses.

Further, any product candidate that we acquire may require additional development efforts prior to commercial sale, including extensive clinical testing and approval by the FDA and applicable foreign regulatory authorities. All product candidates are prone to risks of failure typical of pharmaceutical product development, including the possibility that a product candidate will not be shown to be sufficiently safe and effective for approval by regulatory authorities.

Healthcare reform measures could hinder or prevent our product candidates' commercial success.

The U.S. government and other governments have shown significant interest in pursuing healthcare reform. Any government-adopted reform measures could adversely impact the pricing of healthcare products and services in the U.S. or internationally and the amount of reimbursement available from governmental agencies or other third party payors. The continuing efforts of the U.S. and foreign governments, insurance companies, managed care organizations and other payors of health care services to contain or reduce health care costs may adversely affect our ability to set prices for our products which we believe are fair, and our ability to generate revenues and achieve and maintain profitability.

New laws, regulations and judicial decisions, or new interpretations of existing laws, regulations and decisions, that relate to healthcare availability, methods of delivery or payment for products and services, or sales, marketing or pricing, may limit our potential revenue, and we may need to revise our research and

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development programs. The pricing and reimbursement environment may change in the future and become more challenging due to several reasons, including policies advanced by the current executive administration in the U.S., new healthcare legislation or fiscal challenges faced by government health administration authorities. Specifically, in both the U.S. and some foreign jurisdictions, there have been a number of legislative and regulatory proposals to change the health care system in ways that could affect our ability to sell our products profitably. In the U.S., changes in federal health care policy are being considered by Congress this year. Some of these proposed reforms could result in reduced reimbursement rates for linaclotide and our other potential products, which would adversely affect our business strategy, operations and financial results.

In addition, the Medicare Prescription Drug Improvement and Modernization Act of 2003 reforms the way Medicare will cover and reimburse for pharmaceutical products. This legislation could decrease the coverage and price that we may receive for our products. Other third-party payors are increasingly challenging the prices charged for medical products and services. It will be time consuming and expensive for us to go through the process of seeking reimbursement from Medicare and private payors. Our products may not be considered cost-effective, and coverage and reimbursement may not be available or sufficient to allow us to sell our products on a profitable basis. Further federal and state proposals and health care reforms are likely which could limit the prices that can be charged for the product candidates that we develop and may further limit our commercial opportunity. Our results of operations could be materially adversely affected by the proposed healthcare reforms, by the Medicare prescription drug coverage legislation, by the possible effect of such current or future legislation on amounts that private insurers will pay and by other health care reforms that may be enacted or adopted in the future.

In September 2007, the Food and Drug Administration Amendments Act of 2007 was enacted, giving the FDA enhanced post-marketing authority, including the authority to require post-marketing studies and clinical trials, labeling changes based on new safety information, and compliance with risk evaluations and mitigation strategies approved by the FDA. The FDA's exercise of this authority could result in delays or increased costs during product development, clinical trials and regulatory review, increased costs to assure compliance with post-approval regulatory requirements, and potential restrictions on the sale and/or distribution of approved products.

If our strategic alliances are unsuccessful, our operating results will be negatively impacted.

Our three primary strategic alliances are with Forest, Almirall and Astellas. The success of these arrangements is largely dependent on the resources, efforts and skills of these partners. Disputes and difficulties in such relationships are common, often due to conflicting priorities or conflicts of interest. Merger and acquisition activity may exacerbate these conflicts. The benefits of these alliances are reduced or eliminated when strategic partners:

- terminate the agreements covering the strategic alliance;
- fail to devote financial or other resources to the alliances and thereby hinder or delay development, manufacturing or commercialization activities; or
- fail to maintain the financial resources necessary to continue financing their portion of the development, manufacturing or commercialization costs, or become insolvent or declare bankruptcy.

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

We will need to expand our managerial, operational, financial and other resources in order to manage our operations and clinical trials, continue our development activities and commercialize our product

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candidates. Our personnel, systems and facilities currently in place may not be adequate to support this future growth. Our need to effectively execute our growth strategy requires that we:

- manage our clinical trials effectively, including our Phase 3 clinical trials for linaclotide;
- manage our internal development efforts effectively while complying with our contractual obligations to licensors, licensees, contractors, collaborators and other third parties;
- improve our operational, financial and management controls, reporting systems and procedures; and
- attract and motivate sufficient numbers of talented employees.

We may not be able to manage our business effectively if we lose any of our current management team or if we are unable to attract and motivate key personnel.

We may not be able to attract or motivate qualified management and scientific and clinical personnel in the future due to the intense competition for qualified personnel among biotechnology, pharmaceutical and other businesses, particularly in the greater-Boston area. Our industry has experienced a high rate of turnover of management personnel in recent years. If we are not able to attract and motivate necessary personnel to accomplish our business objectives, we may experience constraints that will significantly impede the achievement of our objectives.

We are highly dependent on the development, regulatory, commercial and financial expertise of our management, particularly Peter M. Hecht, Ph.D., our Chief Executive Officer; Mark G. Currie, Ph.D., our Senior Vice President of Research and Development and our Chief Scientific Officer; Michael J. Higgins, our Senior Vice President, Chief Operating Officer and Chief Financial Officer; and Thomas McCourt, our Senior Vice President, Marketing and Sales and Chief Commercial Officer. Although no member of our management team has informed us to date that he or she intends to resign or retire, if we lose any members of our management team in the future, we may not be able to find suitable replacements, and our business may be harmed as a result. In addition to the competition for personnel, the Boston area in particular is characterized by a high cost of living. As such, we could have difficulty attracting experienced personnel to our company and may be required to expend significant financial resources in our employee recruitment efforts.

We also have scientific and clinical advisors who assist us in formulating our product 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, or may have arrangements with other companies to assist in the development of products that may compete with ours.

We will need to obtain FDA approval of any proposed product names, and any failure or delay associated with such approval may adversely impact our business.

Any name we intend to use for our product candidates will require approval from the FDA regardless of whether we have secured a formal trademark registration from the U.S. Patent and Trademark Office. The FDA typically conducts a review of proposed product names, including an evaluation of potential for confusion with other product names. The FDA may also object to a product name if it believes the name inappropriately implies medical claims. If the FDA objects to any of our proposed product names, we may be required to adopt an alternative name for our product candidates. If we adopt an alternative name, we would lose the benefit of our existing trademark applications for such product candidate, such as linaclotide, and may be required to expend significant additional resources in an effort to identify a suitable product name that would qualify under applicable trademark laws, not infringe the existing rights of third parties and be acceptable to the FDA. We may be unable to build a successful brand identity for a new trademark in a timely manner or at all, which would limit our ability to commercialize our product candidates.

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If we fail to comply with healthcare regulations, we could face substantial penalties and our business, operations and financial condition could be adversely affected.

As a manufacturer of pharmaceuticals, even though we do not and will not control referrals of healthcare services or bill directly to Medicare, Medicaid or other third-party payors, certain federal and state healthcare laws and regulations pertaining to fraud and abuse and patients' rights are and will be applicable to our business. We could be subject to healthcare fraud and abuse and patient privacy regulation by both the federal government and the states in which we conduct our business. The regulations include:

- the federal healthcare program anti-kickback law, which prohibits, among other things, persons from soliciting, receiving or providing remuneration, directly or indirectly, to induce either the referral of an individual, for an item or service or the purchasing or ordering of a good or service, for which payment may be made under federal healthcare programs such as the Medicare and Medicaid programs;

- federal false claims laws which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other third-party payors that are false or fraudulent, and which may apply to entities like us which provide coding and billing advice to customers;

- the federal Health Insurance Portability and Accountability Act of 1996, which prohibits executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters and which also imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information;

- the Federal Food, Drug, and Cosmetic Act, which among other things, strictly regulates drug product marketing, prohibits manufacturers from marketing drug products for off-label use and regulates the distribution of drug samples; and

- state law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which may apply to items or services reimbursed by any third-party payor, including commercial insurers, and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and often are not preempted by federal laws, thus complicating compliance efforts.

If our operations are found to be in violation of any of the laws described above or any governmental regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines and the curtailment or restructuring of our operations. Any penalties, damages, fines, curtailment or restructuring of our operations could adversely affect our ability to operate our business and our financial results. Although compliance programs can mitigate the risk of investigation and prosecution for violations of these laws, the risks cannot be entirely eliminated. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business. Moreover, achieving and sustaining compliance with applicable federal and state privacy, security and fraud laws may prove costly.

Our business involves the use of hazardous materials, and we must comply with environmental laws and regulations, which can be expensive and restrict how we do business.

Our activities involve the controlled storage, use and disposal of hazardous materials. We are subject to federal, state, city and local laws and regulations governing the use, manufacture, storage, handling and disposal of these hazardous materials. Although we believe that the safety procedures we use for handling and disposing of these materials comply with the standards prescribed by these laws and regulations, we cannot eliminate the risk of accidental contamination or injury from these materials. In the event of an

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accident, local, city, state or federal authorities may curtail the use of these materials and interrupt our business operations. We do not currently maintain hazardous materials insurance coverage.

Our business and operations would suffer in the event of system failures.

Despite the implementation of security measures, our internal computer systems and those of our contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. Such an event could cause interruption of our operations. For example, the loss of clinical trial data from completed or ongoing clinical trials for linaclotide could result in delays in our regulatory approval efforts and significantly increase our costs. To the extent that any disruption or security breach were to result in a loss of or damage to our data, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the development of our product candidates could be delayed.

If the proprietary strain-development platform of our biomanufacturing segment does not succeed, we may lose our investment in Microbia, Inc.

Our biomanufacturing segment consists of our majority ownership interest in Microbia, Inc. (formerly known as Microbia Precision Engineering), or Microbia. Microbia focuses on building a specialty biochemicals business based on a proprietary strain-development platform. The success of this segment is dependent on Microbia successfully developing, scaling up manufacturing and establishing commercial partnerships for biochemicals produced using its industrial biotechnology platform. If Microbia is not successful in developing products from its strain-development platform or partnering its platform, we may lose some or all of the value of our equity investment in Microbia.

Risks Related to Intellectual Property

Limitations on our patent rights relating to our product candidates may limit our ability to prevent third parties from competing against us.

Our success will depend on our ability to obtain and maintain patent protection for our product candidates, preserve our trade secrets, prevent third parties from infringing upon our proprietary rights and operate without infringing upon the proprietary rights of others.

The strength of patents in the pharmaceutical industry involves complex legal and scientific questions and can be uncertain. Patent applications in the U.S. and most other countries are confidential for a period of time until they are published, and publication of discoveries in scientific or patent literature typically lags actual discoveries by several months or more. As a result, we cannot be certain that we were the first to conceive inventions covered by our patents and pending patent applications or that we were the first to file patent applications for such inventions. In addition, we cannot be certain that our patent applications will be granted, that any issued patents will adequately protect our intellectual property or that such patents will not be challenged, narrowed, invalidated or circumvented.

We also rely upon unpatented trade secrets, unpatented know-how and continuing technological innovation to develop and maintain our competitive position, which we seek to protect, in part, by confidentiality agreements with our employees and our collaborators and consultants. We also have agreements with our employees and selected consultants that obligate them to assign their inventions to us. It is possible that technology relevant to our business will be independently developed by a person that is not a party to such an agreement. Furthermore, if the employees and consultants that are parties to these agreements breach or violate the terms of these agreements, we may not have adequate remedies, and we could lose our trade secrets through such breaches or violations. Further, our trade secrets could otherwise become known or be independently discovered by our competitors.

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In addition, the laws of certain foreign countries do not protect proprietary rights to the same extent or in the same manner as the U.S., and therefore, we may encounter problems in protecting and defending our intellectual property in certain foreign jurisdictions.

If we are sued for infringing intellectual property rights of third parties, it will be costly and time consuming, and an unfavorable outcome in that litigation would have a material adverse effect on our business.

Our commercial success depends upon our ability and the ability of our collaborators to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing the proprietary rights of third parties. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we and our collaborators are developing products. As the biotechnology and pharmaceutical industry expands and more patents are issued, the risk increases that our potential products may give rise to claims of infringement of the patent rights of others. There may be issued patents of third parties of which we are currently unaware, that may be infringed by our product candidates. Because patent applications can take many years to issue, there may be currently pending applications which may later result in issued patents that our product candidates may infringe.

We may be exposed to, or threatened with, future litigation by third parties alleging that our product candidates infringe their intellectual property rights. If one of our product candidates is found to infringe the intellectual property rights of a third party, we or our collaborators could be enjoined by a court and required to pay damages and could be unable to commercialize the applicable product candidate unless we obtain a license to the patent. A license may not be available to us on acceptable terms, if at all. In addition, during litigation, the patent holder could obtain a preliminary injunction or other equitable relief which could prohibit us from making, using or selling our products, pending a trial on the merits, which may not occur for several years.

There is a substantial amount of litigation involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries generally. If a third party claims that we or our collaborators infringe its intellectual property rights, we may face a number of issues, including, but not limited to:

- infringement and other intellectual property claims which, regardless of merit, may be expensive and time-consuming to litigate and may divert our management's attention from our core business;
- substantial damages for infringement, which we may have to pay if a court decides that the product at issue infringes on or violates the third party's rights, and, if the court finds that the infringement was willful, we could be ordered to pay treble damages and the patent owner's attorneys' fees;
- a court prohibiting us from selling our product unless the third party licenses its rights to us, which it is not required to do;
- if a license is available from a third party, we may have to pay substantial royalties, fees or grant cross-licenses to our intellectual property rights; and
- redesigning our products so they do not infringe, which may not be possible or may require substantial monetary expenditures and time.

We may become involved in lawsuits to protect or enforce our patents, which could be expensive, time consuming and unsuccessful.

Competitors may infringe our patents. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming. In addition, in an infringement proceeding, a court may decide that a patent of ours is not valid or is unenforceable, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation or defense proceedings could put one or more of our patents at risk of being invalidated or interpreted narrowly and could put our patent application at risk of not issuing.

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Interference proceedings brought by the U.S. Patent and Trademark Office may be necessary to determine the priority of inventions with respect to our patents and patent applications or those of our collaborators. An unfavorable outcome could require us to cease using the technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if a prevailing party does not offer us a license on terms that are acceptable to us. Litigation or interference proceedings may fail and, even if successful, may result in substantial costs and distraction of our management and other employees. We may not be able to prevent, alone or with our collaborators, misappropriation of our proprietary rights, particularly in countries where the laws may not protect those rights as fully as in the U.S.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. In addition, there could be public announcements of the results of hearings, motions or other interim proceeding or developments. If securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our Class A common stock.

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.

The U.S. Patent and Trademark Office and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other provisions during the patent process. There are situations in which noncompliance can result in abandonment or lapse of a patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, competitors might be able to enter the market earlier than would otherwise have been the case.

We have not yet registered trademarks for linaclotide in our potential markets, and failure to secure those registrations could adversely affect our business.

We have not yet registered trademarks for linaclotide in any jurisdiction. Although we have filed trademark applications for linaclotide in the U.S., our trademark applications in the U.S. and any other jurisdictions where we may file may not be allowed for registration, and 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 U.S. Patent and Trademark Office and in comparable agencies in many foreign 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.

We may be subject to claims that our employees have wrongfully used or disclosed alleged trade secrets of their former employers.

We employ individuals who were previously employed at other biotechnology or pharmaceutical companies, including our competitors or potential competitors, and as such, we may be subject to claims that these employees, or we, have 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 such claims, litigation could result in substantial costs and be a distraction to management.

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Risks Related to Our Finances and Capital Requirements

We have incurred significant operating losses since our inception and anticipate that we will incur continued losses for the foreseeable future.

We have a limited operating history. In recent years, we have focused primarily on developing linaclotide, with the goal of supporting regulatory approval for this product candidate. We have financed our operations primarily through private placements of preferred stock and our collaboration and license arrangements, and we have incurred losses in each year since our inception in 1998. We incurred net losses attributable to Ironwood Pharmaceuticals, Inc. of approximately $37.2 million, $52.8 million and $53.9 million in the years ended December 31, 2006, 2007 and 2008, respectively, and approximately $47.3 million in the nine months ended September 30, 2009. As of September 30, 2009, we had an accumulated deficit of approximately $290.6 million. Our prior losses, combined with expected future losses, have had and will continue to have an adverse effect on our stockholders' equity and working capital. We expect our expenses to increase in connection with our efforts to commercialize linaclotide and our research and development of our other product candidates. As a result, we expect to continue to incur significant and increasing operating losses for the foreseeable future. Because of the numerous risks and uncertainties associated with developing pharmaceutical products, we are unable to predict the extent of any future losses or when, or if, we will become profitable.

We have not generated any product revenue from our product candidates and may never be profitable.

Our ability to become profitable depends upon our ability to generate revenue from sales. To date, we have not generated any product revenue, and we do not know when, or if, we will generate any such revenue. Our ability to generate product revenue depends on a number of factors, including, but not limited to, our ability to:

- successfully complete our ongoing and planned clinical trials for linaclotide;
- obtain regulatory approvals for linaclotide;
- if regulatory approvals are received, manufacture commercial quantities of linaclotide at acceptable cost levels;
- optimize our relationship to co-develop and co-promote linaclotide in the U.S. with Forest, to commercialize linaclotide in Europe with Almirall and to commercialize linaclotide in certain Asian countries with Astellas; and
- identify and enter into one or more strategic collaborations to market and sell linaclotide outside of North America, Europe and those Asian countries.

Even if linaclotide is approved for commercial sale, we anticipate incurring significant costs associated with commercialization. We may not achieve profitability after generating product sales. If we are unable to generate product revenues, we will not become profitable.

We may need additional funding and may be unable to raise capital when needed, which would force us to delay, reduce or eliminate our product development programs or commercialization efforts.

Developing product candidates, conducting clinical trials, establishing manufacturing relationships and marketing drugs are expensive and uncertain. We believe that our cash on hand as of the date of this prospectus, additional cash milestone payments we may receive from our collaborators, and the proceeds of this offering, will enable us to launch and commercialize linaclotide in the U.S. with our partner, Forest, and to fund our currently contemplated research and development efforts for at least the next five years based on our existing business plan. However, unforeseen circumstances may arise, or our strategic

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imperatives could change, requiring us to seek to raise additional funds. The amount and timing of our future funding requirements will depend on many factors, including, but not limited to:

- the rate of progress and cost of our clinical trials and other product development programs for linaclotide and our other product candidates;
- the costs and timing of in-licensing additional product candidates or acquiring other complementary companies;
- the timing of any regulatory approvals of our product candidates;
- the costs of establishing sales, marketing and distribution capabilities; and
- the status, terms and timing of any collaborative, licensing, co-promotion or other arrangements.

Additional funding may not be available on acceptable terms or at all. If adequate funds are not available, we may be required to delay, reduce the scope of or eliminate one or more of our development programs or our commercialization efforts.

Our quarterly operating results may fluctuate significantly.

We expect our operating results to be subject to quarterly fluctuations. Our net loss and other operating results will be affected by numerous factors, including:

- variations in the level of expenses related to our development programs;
- addition or termination of clinical trials;
- any intellectual property infringement lawsuit in which we may become involved;
- regulatory developments affecting our product candidates;
- our execution of any collaborative, licensing or similar arrangements, and the timing of payments we may make or receive under these arrangements;
- the achievement and timing of milestone payments under our existing collaboration and license agreements; and
- if linaclotide receives regulatory approval, the level of underlying demand for that product and wholesalers' buying patterns.

If our quarterly operating results fall below the expectations of investors or securities analysts, the price of our Class A common stock could decline substantially. Furthermore, any quarterly fluctuations in our operating results may, in turn, cause the price of our stock to fluctuate substantially.

Raising additional funds by issuing securities may cause dilution to existing stockholders and raising funds through borrowing or licensing arrangements may restrict our operations or require us to relinquish proprietary rights.

If we need to raise additional funds by issuing equity securities as a result of unforeseen circumstances or new strategic imperatives, our existing stockholders' ownership will be diluted. If we seek to raise capital through debt financing, such transactions typically require covenants that restrict operating activities. Any borrowings under debt financing will need to be repaid, which creates additional financial risk, particularly if our business or prevailing financial market conditions are not conducive to paying-off or refinancing our outstanding debt obligations at maturity.

If we raise additional funds through collaboration, licensing or other similar arrangements, it may be necessary to relinquish potentially valuable rights to our product candidates or technologies, or to grant licenses on terms that are not favorable to us. If adequate funds are not available when and if needed, our

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ability to achieve profitability or to respond to competitive pressures would be significantly limited, and we may be required to delay, significantly curtail or eliminate one or more of our programs.

We have operated as a private company and have no experience attempting to comply with public company obligations. Attempting to comply with these requirements will increase our costs and require additional management resources, and we still may fail to comply.

We will face increased legal, accounting, administrative and other costs and expenses as a public company. Compliance with the Sarbanes-Oxley Act of 2002, as well as other rules of the SEC, for example, will result in significant initial cost to us as well as ongoing increases in our legal, audit and financial compliance costs. As a public company, we will become subject to Section 404 of the Sarbanes-Oxley Act relating to internal controls over financial reporting. Although we have not identified any material weaknesses in our internal controls over financial reporting to date, we cannot assure that our internal controls over financial reporting will prove to be effective.

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

Effective internal controls over financial reporting are necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, are designed to prevent fraud. Any failure to implement required new or improved controls, or difficulties encountered in their implementation, including at our subsidiary, Microbia, could cause us to fail to meet our reporting obligations. Inferior internal controls could also cause investors to lose confidence in our reported financial information, which could have a negative effect on the trading price of our Class A common stock.

Our ability to use net operating loss and tax credit carryforwards and certain built-in losses to reduce future tax payments is limited by provisions of the Internal Revenue Code, and may be subject to further limitation as a result of the transactions contemplated by this offering.

Section 382 and 383 of the Internal Revenue Code of 1986, as amended, or the Code, contain rules that limit the ability of a company that undergoes an ownership change, which is generally any change in ownership of more than 50% of its stock over a three-year period, to utilize its net operating loss and tax credit carryforwards and certain built-in losses recognized in years after the ownership change. These rules generally operate by focusing on ownership changes involving stockholders owning directly or indirectly 5% or more of the stock of a company and any change in ownership arising from a new issuance of stock by the company. Generally, if an ownership change occurs, the yearly taxable income limitation on the use of net operating loss and tax credit carryforwards and certain built-in losses is equal to the product of the applicable long term tax exempt rate and the value of the company's stock immediately before the ownership change. We may be unable to offset our taxable income with losses, or our tax liability with credits, before such losses and credits expire and therefore would incur larger federal income tax liability.

In addition, it is possible that the transactions described in this offering, either on a standalone basis or when combined with future transactions (including issuances of new shares of our Class A common stock or Class B common stock and sales of shares of our Class A common stock), will cause us to undergo one or more additional ownership changes. In that event, we generally would not be able to use our pre-change loss or credit carryovers or certain built-in losses prior to such ownership change to offset future taxable income in excess of the annual limitations imposed by Sections 382 and 383 and those attributes already subject to limitations (as a result of our prior ownership changes) may be subject to more stringent limitations. As of December 31, 2008, we had an immaterial amount of net operating loss carryforwards and tax credit carryforwards at risk of loss due to a prior ownership change, as well as approximately $78.2 million of net operating loss carryforwards and approximately $10.1 million of tax credit carryforwards at risk of limitation in the event of a future ownership change.

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Risks Relating to Securities Markets and Investment in Our Stock

The concentration of our capital stock ownership with our founders, directors, executives, employees and current holders of our preferred stock (and their affiliates) will limit your ability to influence certain corporate matters.

Each share of Class A common stock and each share of Class B common stock has one vote per share on all matters except certain ones pertaining to change in control matters. After our offering, our Class B common stock will have ten votes per share and our Class A common stock, which is the stock we are selling in this offering, will have one vote per share in the following matters:

- adoption of a merger or consolidation agreement involving Ironwood;
- a sale of all or substantially all of Ironwood's assets;
- a dissolution or liquidation of Ironwood; and,
- every matter, if and when any individual, entity or "group" (as such term is used in Regulation 13D of the Exchange Act) has, or has publicly disclosed (through a press release or a filing with the SEC) an intent to have, beneficial ownership of 30% or more of the number of outstanding shares of Class A common stock and Class B common stock, combined.

Because of our dual class common stock structure, the holders of our Class B common stock, who consist of our founders, directors, executives, employees and current holders of our preferred stock (and their affiliates), will continue to be able to control the corporate matters listed above if any such matter is submitted to our stockholders for approval even if they come to own less than 50% of the outstanding shares of our common stock. Immediately after this offering, the holders of our Class A common stock will own 17.6% and the holders of our Class B common stock will own 82.4% of the outstanding shares of Class A common stock and Class B common stock, combined. However, because of our dual class common stock structure these holders of our Class A common stock will have 2.1% and holders of our Class B common stock will have 97.9% of the total votes immediately after this offering in each of the matters identified in the list above. This concentrated control with our Class B common stock holders will limit your ability to influence those corporate matters and, as a result, we may take actions that our stockholders do not view as beneficial. The market price of our Class A common stock could be adversely affected by the structure. We have directed the underwriters to reserve up to approximately 7,000,000 of the shares of our Class A common stock to be issued in this offering for sale to certain of our existing stockholders and certain specified affiliated entities, as designated by us, at the public offering price. Participation in this offering by existing holders of our convertible preferred stock will further concentrate voting rights and may negatively impact liquidity for shares of our Class A common stock.

Anti-takeover provisions under our charter documents and Delaware law could delay or prevent a change of control which could negatively impact the market price of our Class A common stock.

Provisions in our certificate of incorporation and bylaws, as amended and restated upon the completion of this offering, may have the effect of delaying or preventing a change of control. These provisions include the following:

- Our certificate of incorporation provides for a dual class common stock structure. As a result of this structure, our founders, directors, executives, employees and current holders of our preferred stock (and each of their affiliates), each of whom will hold shares of our Class B common stock following this offering, will have significant influence over certain matters requiring stockholder approval, including significant corporate transactions, such as a merger. This concentrated control could discourage others from initiating a change of control transaction that other stockholders may view as beneficial.

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Our board of directors is divided into three classes serving staggered three-year terms, such that not all members of the board will be elected at one time. This staggered board structure prevents stockholders from replacing the entire board at a single stockholders' meeting.

Our board of directors has the right to elect directors to fill a vacancy created by the expansion of the board of directors or the resignation, death or removal of a director, which prevents stockholders from being able to fill vacancies on our board of directors.

Our board of directors may issue, without stockholder approval, shares of preferred stock. The ability to authorize preferred stock makes it possible for our board of directors to issue preferred stock with voting or other rights or preferences that could impede the success of any attempt to acquire us.

Stockholders must provide advance notice to nominate individuals for election to the board of directors or to propose matters that can be acted upon at a stockholders' meeting. Furthermore, stockholders may only remove a member of our board of directors for cause. These provisions may discourage or deter a potential acquiror from conducting a solicitation of proxies to elect such acquiror's own slate of directors or otherwise attempting to obtain control of our company.

Our stockholders may not act by written consent. As a result, a holder, or holders, controlling a majority of our capital stock would not be able to take certain actions outside of a stockholders' meeting.

Special meetings of stockholders may be called only by the chairman of our board of directors, our chief executive officer, our president or a majority of our board of directors. As a result, a holder, or holders, controlling a majority of our capital stock would not be able to call a special meeting.

A majority of the outstanding shares of Class B common stock are required to amend our certificate of incorporation and a super-majority (80%) of the outstanding shares of Class B common stock are required to amend our by-laws, which make it more difficult to change the provisions described above.

In addition, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which may prohibit certain business combinations with stockholders owning 15% or more of our outstanding voting stock. These and other provisions in our certificate of incorporation and our bylaws and in the Delaware General Corporation Law could make it more difficult for stockholders or potential acquirers to obtain control of our board of directors or initiate actions that are opposed by the then-current board of directors.

If holders of shares of our Class B common stock convert their shares of Class B common stock into shares of Class A common stock and exercise their registration rights, a significant number of shares of our Class A common stock could be sold into the market, which could reduce the trading price of our Class A common stock and impede our ability to raise future capital.

After this offering, holders of approximately 70,170,477 shares of Class B common stock (after giving effect to the conversion of 69,683,700 shares of convertible preferred stock outstanding as of December 31, 2009 into shares of our Class B common stock) will have rights under our eighth amended and restated investors' rights agreement, subject to some 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. These rights will continue following this offering and will terminate five years following the completion of this offering, or for any particular holder with registration rights who at such time holds less than 1% of our outstanding Class B common stock, at such time following this offering when all securities held by that stockholder subject to registration rights may be sold pursuant to Rule 144 under the Securities Act of 1933, as amended, or the Securities Act, within a single 90 day period. We also intend to register all shares of Class A common stock that we may issue under our equity compensation plans. Once

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we register these shares, they can be freely sold in the public market upon issuance, subject to the lock-up agreements described in the "Underwriting" section of this prospectus.

There may not be a viable public market for our Class A common stock.

Prior to this offering, there has been no public market for our Class A common stock, and a regular trading market may not develop and continue after this offering. Furthermore, the market price of our Class A common stock may decline below the initial public offering price. The initial public offering price will be determined through negotiations between us and the representatives of the underwriters and may not be indicative of the market price of our Class A common stock following this offering. Among the factors considered in such negotiations are prevailing market conditions, certain of our financial information, market valuations of other companies that we and the representatives of the underwriters believe are comparable to us, estimates of our business potential and the present state of our business. See "Underwriting" for additional information.

As a new investor, you will experience immediate and substantial dilution in the net tangible book value of your shares.

The initial public offering price of our Class A common stock in this offering is considerably more than the net tangible book value per share of our Class A common stock. Investors purchasing shares of Class A common stock in this offering will pay a price that substantially exceeds the value of our tangible assets after subtracting liabilities. As a result, investors will, as of September 30, 2009:

- incur immediate dilution of $12.25 per share of Class A common stock, based on an assumed initial public offering price of $15.00 per share of Class A common stock, the mid-point of the price range set forth on the cover page of this prospectus; and

- contribute 43.0% of the total amount invested to date to fund our company based on an assumed initial offering price to the public of $15.00 per share of Class A common stock, the mid-point of the price range set forth on the cover page of this prospectus, but will own only 17.6% of the outstanding shares of Class A common stock and Class B common stock, combined, after the offering.

To the extent outstanding stock options are exercised, there will be further dilution to new investors.

As of December 31, 2009, we had options to purchase 13,691,579 shares of Class B common stock outstanding, with exercise prices ranging from $0.10 to $7.36 per share and a weighted average exercise price of $2.45 per share. Upon the vesting of each of these options, the holder may exercise his or her options, which would result in further dilution to investors.

We expect that the price of our Class A common stock will fluctuate substantially.

The market price of our Class A common stock may be highly volatile due to many factors, including:

- the results from our clinical trials, including our current and planned Phase 3 clinical trials for linaclotide;

- FDA or international regulatory actions, including actions on regulatory applications for any of our product candidates;

- the commercial performance of any of our product candidates that receive marketing approval;

- announcements of the introduction of new products by us or our competitors;

market conditions in the pharmaceutical and biotechnology sectors;

announcements concerning product development results or intellectual property rights of others;

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litigation or public concern about the safety of our potential products;

actual and anticipated fluctuations in our quarterly operating results;

deviations in our operating results from the estimates of securities analysts;

additions or departures of key personnel;

any third-party coverage and reimbursement policies for linaclotide;

developments concerning current or future strategic collaborations; and

discussion of us or our stock price in the financial or scientific press or in online investor communities.

The realization of any of the risks described in these "Risk Factors" could have a dramatic and material adverse impact on the market price of our Class A common stock. In addition, class action litigation has often been instituted against companies whose securities have experienced periods of volatility. Any such litigation brought against us could result in substantial costs and a diversion of management attention, which could hurt our business, operating results and financial condition.

Our management team may invest or spend the proceeds of this offering in ways with which you may not agree or in ways which may not yield a significant return, if any.

Our management will have broad discretion over the use of proceeds from this offering. The net proceeds from this offering will be used to fund the continued development and commercialization of linaclotide, the research and development of our other product candidates and other general corporate purposes. Our management will have considerable discretion in the application of the net proceeds, and you will not have the opportunity, as part of your investment decision, to assess whether the proceeds are being used appropriately. The net proceeds may be used for corporate purposes that do not increase our operating results or market value. Until the net proceeds are used, they may be placed in investments that do not produce significant income or investments that lose value.

Future sales of our Class A common stock may depress our stock price.

While we do not currently anticipate making additional offers of Class A common stock, such sales, or the perception in the market that the holders of a large number of shares intend to sell shares, could reduce the market price of our Class A common stock. Immediately after this offering, we will have outstanding 16,666,667 shares of Class A common stock and 78,246,222 shares of Class B common stock, based on the number of outstanding shares of Class A common stock and Class B common stock as of December 31, 2009 and after giving effect to the conversion of 69,904,843 shares of convertible preferred stock outstanding as of December 31, 2009 into 70,391,620 shares of our Class B common stock at the completion of this offering. The shares of Class A common stock that we are selling in connection with this offering may be resold in the public market immediately.

We have never paid dividends on our capital stock, and because we do not anticipate paying any cash dividends in the foreseeable future, capital appreciation, if any, of our common stock will be your sole source of gain on an investment in our Class A common stock.

We have paid no cash dividends on any of our classes of capital stock to date, and we currently intend to retain our future earnings, if any, to fund the development and growth of our business. We do not anticipate paying any cash dividends on our common stock in the foreseeable future. As a result, capital appreciation, if any, of our common stock will be your sole source of gain for the foreseeable future.

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SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus, including the sections titled "Prospectus Summary," "Risk Factors," "Management's Discussion and Analysis of Financial Condition and Results of Operations" and "Business," contains forward-looking statements. Forward-looking statements convey our current expectations or forecasts of future events. All statements contained in this prospectus other than statements of historical fact are forward-looking statements. Forward-looking statements include statements regarding our future financial position, business strategy, budgets, projected costs, plans and objectives of management for future operations. The words "may," "continue," "estimate," "intend," "plan," "will," "believe," "project," "expect," "seek," "anticipate" and similar expressions may identify forward-looking statements, but the absence of these words does not necessarily mean that a statement is not forward-looking. These forward-looking statements include, among other things, statements about:

- our expectations related to the use of proceeds from this offering;
- the progress of, timing of and amount of expenses associated with our research, development and commercialization activities;
- the timing, conduct and success of our clinical studies for our product candidates;
- our ability to obtain U.S. and foreign regulatory approval for our product candidates and the ability of our product candidates to meet existing or future regulatory standards;
- our expectations regarding federal, state and foreign regulatory requirements;
- the therapeutic benefits and effectiveness of our product candidates;
- the accuracy of our estimates of the size and characteristics of the markets that may be addressed by our product candidates;
- our ability to manufacture sufficient amounts of our product candidates for clinical studies and products for commercialization activities;
- our plans with respect to collaborations and licenses related to the development, manufacture or sale of our product candidates;
- our expectations as to future financial performance, expense levels and liquidity sources;
- the timing of commercializing our product candidates;
- our plan to develop a high-quality commercial organization;
- our ability to compete with other companies that are or may be developing or selling products that are competitive with our product candidates;

anticipated trends and challenges in our potential markets;

our ability to attract and motivate key personnel; and

other factors discussed elsewhere in this prospectus.

Any or all of our forward-looking statements in this prospectus may turn out to be inaccurate. We have based these forward-looking statements largely on our current expectations and projections about future events and financial trends that we believe may affect our financial condition, results of operations, business strategy and financial needs. They may be affected by inaccurate assumptions we might make or by known or unknown risks and uncertainties, including the risks, uncertainties and assumptions described in "Risk Factors." In light of these risks, uncertainties and assumptions, the forward-looking events and circumstances discussed in this prospectus may not occur as contemplated, and actual results could differ materially from those anticipated or implied by the forward-looking statements.

You should not unduly rely on these forward-looking statements, which speak only as of the date of this prospectus. Unless required by law, we undertake no obligation to publicly update or revise any forward-looking statements to reflect new information or future events or otherwise. You should, however, review the factors and risks we describe in the reports we will file from time to time with the SEC after the date of this prospectus. See "Where You Can Find Additional Information."

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USE OF PROCEEDS

We estimate that the net proceeds of the sale of the Class A common stock that we are offering will be approximately $237.5 million, or $272.4 million if the underwriters exercise their over-allotment option in full, assuming an initial public offering price of $15.00 per share, which is the midpoint of the range listed on the cover page of this prospectus, and after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us.

The principal purposes of this offering are to obtain additional working capital to fund anticipated operating expenses, establish a public market for our Class A common stock and facilitate future access to the public markets.

We estimate that we will use the proceeds of this offering, in combination with existing cash resources of approximately $123.1 million as of December 31, 2009, as follows:

- approximately $225.0 million to fund the development and commercialization of linaclotide;
- approximately $39.0 million to fund the research and development of IW-6118, an inhibitor of Fatty Acid Amide Hydrolase, or FAAH, being evaluated for the treatment of pain and inflammation, in Phase 1 and Phase 2 studies, and to continue discovery and preclinical research of early-stage compounds in gastrointestinal pain, inflammation and cardiovascular indications during the twelve month period following the date of this offering; and
- the remainder for general corporate purposes, such as general and administrative expenses, capital expenditures, working capital, prosecution and maintenance of our intellectual property, the potential investment in technologies or products that complement our business, and further investments in our pipeline.

Although we currently anticipate that we will use the net proceeds of this offering as described above, there may be circumstances where a reallocation of funds may be necessary. The amounts and timing of our actual expenditures will depend upon numerous factors, including the progress of our development and commercialization efforts of linaclotide, the progress of our clinical studies, our existing and future strategic collaborations and partnerships and our operating costs and expenditures. Accordingly, our management will have significant flexibility in the expenditure of the net proceeds of this offering.

The costs and timing of drug development and commercialization and of regulatory approval, particularly conducting clinical studies, are highly uncertain, are subject to substantial risks and can often change. Accordingly, we may change the allocation of use of these proceeds as a result of contingencies such as the progress and results of our clinical studies and other development activities, the continuation of our existing collaborations and the establishment of new arrangements, our manufacturing requirements and regulatory or competitive developments.

Pending use of the proceeds from this offering as described above or otherwise, we intend to invest the net proceeds in short-term interest-bearing, investment-grade securities.

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DIVIDEND POLICY

Subject to preferences that may apply to any shares of preferred stock outstanding at the time, the holders of Class A common stock and Class B common stock will be entitled to share equally in any dividends that our board of directors may determine to issue from time to time. In the event a dividend is paid in the form of shares of common stock or rights to acquire shares of common stock, the holders of Class A common stock will receive Class A common stock, or rights to acquire Class A common stock, as the case may be, and the holders of Class B common stock will receive Class B common stock, or rights to acquire Class B common stock, as the case may be.

We have never declared or paid any cash dividends on our capital stock and we do not currently anticipate declaring or paying cash dividends on our capital stock in the foreseeable future. We currently intend to retain all of our future earnings, if any, to finance operations. Any future determination relating to our dividend policy will be made at the discretion of our board of directors and will depend on a number of factors, including future earnings, capital requirements, financial conditions, future prospects, contractual restrictions and covenants and other factors that our board of directors may deem relevant.

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CAPITALIZATION

The following table sets forth our capitalization as of September 30, 2009:

- on an actual basis;
- on a pro forma basis after giving effect to: (a) the automatic conversion of all outstanding shares of our convertible preferred stock into an aggregate of 69,709,801 shares of our Class B common stock, which will occur upon the completion of this offering; (b) the issuance of 681,819 shares of our convertible preferred stock sold at a price of $22.00 per share for cash proceeds of $15.0 million, which were received on November 13, 2009, including a $0.7 million gain on the final remeasurement of the forward purchase contract at the time of settlement, and the conversion of such shares into 681,819 shares of our Class B common stock, which will occur upon the closing of this offering and (c) compensation expense of approximately $107,000 related to 45,000 time-accelerated stock options at September 30, 2009 that will fully vest upon the closing of this offering; and
- on a pro forma as adjusted basis to give effect to the receipt by us of net proceeds of $237.5 million from the sale of shares of our Class A common stock that we are offering, assuming an initial public offering price of $15.00 per share, which is the midpoint of the range listed on the cover page of this prospectus, and after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us.

You should read the following table in conjunction with our financial statements and related notes, "Selected Financial Data" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" appearing elsewhere in this prospectus.

	As of September 30, 2009		
	Actual	Pro Forma	Pro Forma As Adjusted[1]
		(unaudited)	
	(in thousands, except share and per share data)		
Cash, cash equivalents and available-for-sale securities	$ 98,928	$ 113,928	$ 351,428
Long-term debt, including current portion	3,406	3,406	3,406
Class A common stock, $0.001 par value: 98,530,700 shares authorized, no shares issued and outstanding, actual and pro forma; 500,000,000 shares authorized, 16,666,667 shares issued and outstanding, pro forma as adjusted			17
Class B common stock, $0.001 par value: 98,530,700 shares authorized, 7,713,407 shares issued and outstanding, actual; 98,530,700 shares authorized, 78,105,027 shares issued and outstanding, pro forma; 100,000,000 shares authorized, 78,105,027 shares issued and outstanding, pro forma as adjusted	8	78	78
Convertible preferred stock, $0.001 par value: 74,942,226 shares authorized, 69,223,024 shares issued and outstanding, actual; 74,942,226 shares authorized, no shares issued or outstanding, pro forma; no shares authorized, issued or outstanding, pro forma as adjusted	289,849		
Preferred stock, $0.001 par value: no shares authorized, no shares issued or outstanding, actual and pro forma; 75,000,000 shares authorized, no shares issued and outstanding, pro forma as adjusted			
Additional paid-in capital	10,921	309,307	546,790
Accumulated deficit	(290,629)	(290,036)	(290,036)
Accumulated other comprehensive income	2	2	2
Total Ironwood Pharmaceuticals, Inc. stockholders' equity (deficit)	(279,698)	19,351	256,851
Noncontrolling interest	3,856	3,856	3,856
Total stockholders' equity (deficit)	$ (275,842)	$ 23,207	$ 260,707

Total capitalization	$ 17,413	$ 26,613	$ 264,113

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(1) Each $1.00 increase (decrease) in the assumed initial public offering price of $15.00 per share would increase (decrease) the amount of pro forma as adjusted cash, cash equivalents and available-for-sale securities; additional paid-in capital; total stockholders' equity (deficit) and total capitalization by approximately $15.5 million, assuming the number of shares offered by us, as set forth on the cover of this prospectus, remains the same and after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us.

The table above does not include:

- 14,094,470 shares of Class B common stock issuable upon the exercise of options outstanding as of September 30, 2009, with exercise prices ranging from $0.10 to $5.48 per share and a weighted average exercise price of $2.45 per share; and

- 1,293,820 additional shares of Class B common stock reserved for future grants under our 2002 Stock Incentive Plan and 2005 Stock Incentive Plan as of September 30, 2009.

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DILUTION

The historical net tangible book value of our common stock as of September 30, 2009 was approximately $(275.8) million, or $(35.76) per share, based on no shares of Class A common stock and 7,713,407 shares of Class B common stock outstanding as of such date. Historical net tangible book value per share represents the amount of our total tangible assets less total liabilities and convertible preferred stock, divided by the number of shares of common stock issued and outstanding.

Our pro forma net tangible book value as of September 30, 2009 was approximately $23.2 million, or $0.30 per share, based on the aggregate of Class A and Class B common stock. Pro forma net tangible book value per share represents the amount of our total tangible assets, less our total liabilities, divided by the pro forma number of shares of Class A and Class B common stock outstanding as of September 30, 2009, after giving effect to (a) the automatic conversion of all outstanding shares of our convertible preferred stock into an aggregate of 69,709,801 shares of our Class B common stock, which will occur upon the completion of this offering, and the recognition of compensation expense of approximately $107,000 related to 45,000 time-accelerated stock options outstanding at September 30, 2009 that will fully vest upon the completion of this offering, and (b) the issuance of 681,819 shares of our convertible preferred stock sold at a price of $22.00 per share for cash proceeds of $15.0 million, which were received on November 13, 2009, including a $0.7 million gain on the final remeasurement of the forward purchase contract at the time of settlement, and the conversion of such shares into 681,819 shares of our Class B common stock, which will occur upon the completion of this offering.

After giving effect to the sale of 16,666,667 shares of Class A common stock that we are offering, assuming an initial public offering price of $15.00 per share, which is the midpoint of the range listed on the cover page of this prospectus, and after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us, our pro forma as adjusted net tangible book value as of September 30, 2009 would have been approximately $260.7 million, or approximately $2.75 per share based on the aggregate of Class A and Class B common stock. This amount represents an immediate increase in pro forma net tangible book value of $2.45 per share to our existing stockholders and an immediate dilution in pro forma net tangible book value of approximately $12.25 per share to new investors purchasing shares of Class A common stock in this offering, assuming an initial public offering price of $15.00 per share, which is the midpoint of the range listed on the cover page of this prospectus. We determine dilution by subtracting the pro forma as adjusted net tangible book value per share from the amount of cash that a new investor paid for a share of Class A common stock. The following table illustrates this dilution:

Assumed initial offering price per share of Class A common stock		$ 15.00
Historical net tangible book value per share as of September 30, 2009	$ (35.76)	
Increase attributable to the conversion of the outstanding shares of convertible preferred stock as of September 30, 2009 and the recognition of compensation expense	$ 35.94	
Increase attributable to the issuance and conversion of 681,819 shares of convertible preferred stock	$ 0.12	
Pro forma net tangible book value per share as of September 30, 2009	$ 0.30	
Increase in pro forma net tangible book value attributable to this offering	$ 2.45	
Pro forma as adjusted net tangible book value per share after this offering		$ 2.75
Dilution per share to new investors		$ 12.25

A $1.00 increase (decrease) in the assumed initial public offering price of $15.00 per share of Class A common stock, which is the midpoint of the range listed on the cover page of this prospectus, would increase (decrease) our pro forma as adjusted net tangible book value per share by $0.16 and the dilution per share to new investors by $0.84, in each case assuming the number of shares offered, as set forth on the

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cover page of this prospectus, remains the same and after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us.

If the underwriters exercise their over-allotment option in full in this offering, the pro forma as adjusted net tangible book value would be $3.04 per share, the increase in pro forma net tangible book value per share to existing stockholders would be $2.74 and the dilution per share to new investors would be $11.96 in each case assuming an initial public offering price of $15.00 per share, which is the midpoint of the range listed on the cover page of this prospectus.

The following table summarizes, as of September 30, 2009, the differences between the number of shares of Class A common stock purchased from us, the total consideration paid to us in cash and the average price per share that existing stockholders and new investors paid. The calculation below is based on an assumed initial public offering price of $15.00 per share, which is the midpoint of the range listed on the cover page of this prospectus, before deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us.

	Shares Purchased		Total Consideration		Average Price
	Number	Percent	Amount	Percent	per Share
Existing Stockholders	78,105,027	82.4%	$ 315,030,404	57.0%	$ 4.03
New Investors	16,666,667	17.6%	$ 237,500,005	43.0%	$ 14.25
Total	94,771,694	100.0%	$ 552,530,409	100.0%	$ 5.83

A $1.00 increase (decrease) in the assumed initial public offering price of $15.00 per share of Class A common stock, which is the midpoint of the range listed on the cover page of this prospectus, would increase (decrease) total consideration paid by new investors by $16.7 million and increase (decrease) the percent of total consideration paid to us by new investors by 1.7%, assuming the number of shares offered, as set forth on the cover of this prospectus, remains the same and without deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us.

The foregoing tables and calculations are based on the number of shares of our common stock outstanding as of September 30, 2009, after giving effect to: (a) the automatic conversion of all outstanding shares of our convertible preferred stock into our Class B common stock, which will occur upon the completion of this offering, (b) the issuance of 681,819 shares of our convertible preferred stock sold at a price of $22.00 per share for cash proceeds of $15.0 million, which were received on November 13, 2009, including a $0.7 million gain on the final remeasurement of the forward purchase contract at the time of settlement, and the conversion of such shares into 681,819 shares of our Class B common stock, which will occur upon the closing of this offering and (c) compensation expense of approximately $107,000 related to 45,000 time-accelerated stock options at September 30, 2009 that will fully vest upon the closing of this offering, and excludes:

- 14,094,470 shares of Class B common stock issuable upon the exercise of options outstanding as of September 30, 2009, with exercise prices ranging from $0.10 to $5.48 per share and a weighted average exercise price of $2.45 per share; and

- 1,293,820 additional shares of Class B common stock reserved for future grants under our 2002 Stock Incentive Plan and 2005 Stock Incentive Plan as of September 30, 2009.

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SELECTED CONSOLIDATED FINANCIAL DATA

You should read the following selected financial data together with our consolidated 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. We have derived the consolidated statements of operations data for the years ended December 31, 2006, 2007 and 2008 and the consolidated balance sheet data as of December 31, 2007 and 2008 from our audited financial statements included elsewhere in this prospectus. We have derived the consolidated statement of operations data for the years ended December 31, 2004 and 2005 and consolidated balance sheet data as of December 31, 2004, 2005 and 2006 from our audited financial statements not included in this prospectus. We have derived the consolidated statements of operations data for the nine months ended September 30, 2008 and 2009 and the consolidated balance sheet data as of September 30, 2009 from our unaudited consolidated financial statements included elsewhere in this prospectus. Our unaudited consolidated financial statements for the nine months ended September 30, 2008 and 2009 have been prepared on the same basis as the annual consolidated financial statements and include all adjustments, which include only normal recurring adjustments, necessary for fair presentation of this data in all material respects. Pro forma financial information reflects: (a) the automatic conversion of all outstanding shares of our convertible preferred stock into shares of our Class B common stock upon the completion of this offering, (b) the issuance of 681,819 shares of our convertible preferred stock sold at a price of $22.00 per share for cash proceeds of $15.0 million, which were received on November 13, 2009, including a $0.7 million gain on the final remeasurement of the forward purchase contract at the time of settlement, and the conversion of such shares into 681,819 shares of our Class B common stock upon the closing of this offering and (c) compensation expense of approximately $56,000 and $107,000 related to 30,000 and 45,000 time-accelerated stock options at December 31, 2008 and September 30, 2009, respectively, that will fully vest upon the closing of this offering. Our historical results for any prior period are not necessarily indicative of results to be expected in any future period, and our results for any interim period are not necessarily indicative of results for a full fiscal year.

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	December 31,					Nine months ended September 30,	
	2004	2005	2006	2007	2008	2008	2009
						(unaudited)	
	(In thousands, except share and per share data)						
Consolidated Statement of Operations Data:							
Revenue:							
Collaborative arrangements	$	$	$	$ 4,608	$ 18,383	$ 13,933	$ 25,917
Services	3,569	1,574	3,140	5,856	3,833	3,309	1,581
Total revenue	3,569	1,574	3,140	10,464	22,216	17,242	27,498
Operating expenses:							
Research and development(1)	18,600	23,011	35,543	57,246	59,809	43,309	58,824
General and administrative(1)	3,693	4,627	7,192	10,833	18,328	13,054	17,309
Total operating expenses	22,293	27,638	42,735	68,079	78,137	56,363	76,133
Loss from operations	(18,724)	(26,064)	(39,595)	(57,615)	(55,921)	(39,121)	(48,635)
Other income (expense):							
Interest expense	(375)	(207)	(217)	(263)	(334)	(253)	(370)
Interest and investment income	320	353	2,533	4,118	2,124	1,901	214
Remeasurement of forward purchase contracts				600	(900)	(5,900)	(100)
Other income (expense), net	(55)	146	2,316	4,455	890	(4,252)	(256)
Loss before income tax benefit	(18,779)	(25,918)	(37,279)	(53,160)	(55,031)	(43,373)	(48,891)
Income tax benefit							(153)
Net loss	(18,779)	(25,918)	(37,279)	(53,160)	(55,031)	(43,373)	(48,738)
Net loss attributable to noncontrolling interest			99	408	1,157	726	1,483
Net loss attributable to Ironwood Pharmaceuticals, Inc.	$ (18,779)	$ (25,918)	$ (37,180)	$ (52,752)	$ (53,874)	$ (42,647)	$ (47,255)
Net loss per share attributable to Ironwood Pharmaceuticals, Inc. basic and diluted	$ (3.48)	$ (4.35)	$ (5.79)	$ (7.91)	$ (7.82)	$ (6.22)	$ (6.70)
Weighted average number of common shares used in net loss per share attributable to Ironwood Pharmaceuticals, Inc. basic and diluted	5,389,863	5,963,326	6,417,499	6,666,601	6,889,817	6,859,285	7,054,291
Pro forma net loss per share attributable to Ironwood Pharmaceuticals, Inc. basic and diluted (unaudited)(2)					$ (0.72)		$ (0.62)
Pro forma weighted average number of common shares used in net loss per share attributable to Ironwood Pharmaceuticals, Inc. basic and diluted (unaudited)(2)					74,495,452		75,574,117

(1) Includes share-based compensation expense as indicated in the following table:

Research and development	$ 208	$ 253	$ 316	$ 795	$ 1,708	$ 1,203	$ 1,332
General and administrative	56	64	633	359	1,086	640	1,919

(2)

Pro forma basic and diluted net loss per share have been calculated assuming: (a) the automatic conversion of all outstanding shares of convertible preferred stock as of December 31, 2008 into 67,605,635 shares of our Class B common stock and as of September 30, 2009 into 69,709,801 shares of our Class B common stock upon the closing of this offering, (b) the issuance of 681,819 shares of our convertible preferred stock sold at a price of $22.00 per share for cash proceeds of $15.0 million, which were received on November 13, 2009, including a $0.7 million gain on the final remeasurement of the forward purchase contract at the time of settlement, and the conversion of such shares into 681,819 shares of our Class B common stock upon the closing of this offering and (c) compensation expense of approximately $56,000 and $107,000 related to 30,000 and 45,000 time-accelerated stock options at December 31, 2008 and September 30, 2009, respectively, that will fully vest upon the closing of this offering. Pro forma basic and diluted net loss per share does not give effect to the sale of 16,666,667 shares of Class A common stock that we are offering pursuant to this prospectus.

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	As of December 31,					As of September 30,
	2004	2005	2006	2007	2008	2009
			(unaudited)			
			(In thousands)			
Consolidated Balance Sheet Data:						
Cash, cash equivalents and available-for-sale securities	$ 26,459	$ 5,134	$ 49,501	$ 91,936	$ 89,767	$ 98,928
Working capital (deficit) (excluding deferred revenue)	22,985	(1,635)	43,793	105,043	86,780	99,412
Total assets	32,079	10,490	57,520	135,908	140,723	149,647
Deferred revenue, including current portion	123	543	930	74,392	66,054	104,487
Long-term debt, including current portion	1,847	4,182	2,243	2,963	1,815	3,406
Capital lease obligations, including current portion					306	220
Total liabilities	4,859	8,570	9,900	90,480	97,734	135,640
Convertible preferred stock	98,924	98,924	173,851	223,802	273,400	289,849
Noncontrolling interest			6,903	6,495	5,339	3,856
Total stockholders' deficit	(71,704)	(97,004)	(126,231)	(178,374)	(230,411)	(275,842)

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

The following discussion of our financial condition and results of operations should be read in conjunction with our financial statements and the notes to those financial statements appearing elsewhere in this prospectus. This discussion contains forward-looking statements that involve significant risks and uncertainties. As a result of many factors, such as those set forth under "Risk Factors" and elsewhere in this prospectus, our actual results may differ materially from those anticipated in these forward-looking statements.

Overview

We are an entrepreneurial pharmaceutical company that discovers, develops and intends to commercialize innovative medicines targeting important therapeutic needs. To achieve this, we are building a sustainable culture centered on creating and marketing important new drugs. Our experienced team of researchers is focused on a portfolio of internally discovered drug candidates that includes one Phase 3 drug candidate (linaclotide), one Phase 1 pain drug candidate, and multiple preclinical programs. We have pursued a partnering strategy for the commercialization of linaclotide that has enabled us to retain significant control over linaclotide's development and commercialization, share the costs of drug development and commercialization with collaborators whose capabilities complement ours, and retain approximately half of the future long-term value of linaclotide in the major pharmaceutical markets, should linaclotide meet our sales expectations.

We were incorporated in Delaware as Microbia, Inc. (which is now the name of our majority-owned subsidiary) on January 5, 1998. On April 7, 2008, we changed our name to Ironwood Pharmaceuticals, Inc.

We operate in two reportable business segments human therapeutics and biomanufacturing. Our human therapeutics segment comprises the vast majority of our business, and it consists of the development and commercialization of our product candidates, including linaclotide. Our biomanufacturing segment, which comprises a much smaller part of our business, consists of our majority ownership interest in Microbia, which focuses on building a specialty biochemicals business based on a proprietary strain-development platform. Our human therapeutics segment represented 96%, 97% and 97% and our biomanufacturing segment represented 4%, 3% and 3% of our total assets at December 31, 2007 and 2008 and September 30, 2009, respectively. Our human therapeutics segment represented 87%, 95%, 86%, 88% and 81% and our biomanufacturing segment represented 13%, 5%, 14%, 12% and 19% of our loss from operations for the years ended December 31, 2006, 2007 and 2008 and the nine months ended September 30, 2008 and 2009, respectively. In November 2009, Microbia amended its existing facility lease to include an early termination option and subsequently implemented a strategic restructuring plan that includes an immediate reduction of Microbia's workforce (see Note 21 to our consolidated financial statements). We expect that after the restructuring actions are completed, Microbia's operating expenses will decrease and as a result, its percentage of our consolidated loss from operations will decrease.

To date we have dedicated substantially all of our activities to the research and development of our product candidates. We have not generated any revenue to date from product sales and have incurred significant operating losses since our inception in 1998. We incurred net losses attributable to Ironwood Pharmaceuticals, Inc. of approximately $37.2 million, $52.8 million and $53.9 million in the years ended December 31, 2006, 2007 and 2008, respectively, and approximately $47.3 million in the nine months ended September 30, 2009. As of September 30, 2009, we had an accumulated deficit of approximately $290.6 million, and we expect to incur losses for the foreseeable future.

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Financial Overview

Revenue. Revenue to date from our human therapeutics segment is generated primarily through collaborative research, development and/or commercialization agreements. The terms of these agreements typically include payment to us of one or more of the following: nonrefundable, up-front license fees; milestone payments; and royalties on product sales. Revenue from our human therapeutics segment is shown in our consolidated statements of operations as collaborative arrangements revenue. Revenue from our biomanufacturing segment is generated by our subsidiary, Microbia, which has entered into research and development service agreements with various third parties. These agreements generally provide for fees for research and development services rendered, and may include additional payments at the conclusion of the research period upon achieving specified events. These service agreements also contemplate royalty payments to us on future sales of Microbia's customers' products. Revenue from our biomanufacturing segment is shown as services revenue. We expect our revenue to fluctuate for the foreseeable future as our collaborative arrangements revenue is principally based on the achievement of clinical and commercial milestones. Additionally, we expect our services revenue to decline as existing Microbia customer contracts are completed and no new services contracts are anticipated.

Research and development expense. Research and development expense consists of expenses incurred in connection with the discovery and development of our product candidates. These expenses consist primarily of compensation, benefits and other employee related expenses, facility costs and third-party contract costs relating to research, formulation, manufacturing, preclinical study and clinical trial activities. Also included in research and development expenses are the costs of revenue related to the Microbia services contracts. We charge all research and development expenses to operations as incurred. Under our Forest collaboration agreement we are reimbursed for certain research and development expenses and we net these reimbursements against our research and development expenses as incurred.

Our lead product candidate is linaclotide and it represents the largest portion of our research and development expense for our product candidates. Linaclotide is a first-in-class compound currently in confirmatory Phase 3 trials evaluating its safety and efficacy for the treatment of patients with IBS-C or CC. Our other clinical stage program is IW-6118, an inhibitor of FAAH being evaluated for the treatment of pain and inflammation. IW-6118 is a novel small molecule inhibitor of FAAH, that decreased inflammation and pain and elevated fatty acid amides in preclinical models. We have an active investigational new drug application, or IND, for IW-6118 and are currently investigating the safety, tolerability, and pharmacokinetic properties of this molecule in Phase 1 studies.

The following table sets forth our research and development expenses related to linaclotide and IW-6118 for the years ended December 31, 2006, 2007 and 2008 and the nine months ended September 30, 2008 and 2009. We began tracking program expenses for linaclotide in 2004, and program expenses from inception to September 30, 2009 were approximately $81.5 million. We began tracking program expenses for IW-6118 in 2008, and program expenses from inception to September 30, 2009 were approximately $6.9 million. These expenses relate primarily to external costs associated with manufacturing, preclinical studies and clinical trial costs. The expenses for linaclotide include both reimbursements to us by Forest as well as our portion of costs incurred by Forest for linaclotide and invoiced to us under the cost-sharing provisions of our collaboration agreement. Costs related to facilities, depreciation, share-based compensation and research and development support services are not directly charged to programs.

	December 31,			Nine Months Ended September 30,	
	2006	2007	2008	2008	2009
			(unaudited)		
			(in thousands)		
Linaclotide	$ 10,974	$ 23,450	$ 13,588	$ 9,473	$ 25,850
IW-6118			2,577	1,312	4,328

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The lengthy process of securing FDA approvals for new drugs requires the expenditure of substantial resources. Any failure by us to obtain, or any delay in obtaining, regulatory approvals would materially adversely affect our product development efforts and our business overall. Accordingly, we cannot currently estimate with any degree of certainty the amount of time or money that we will be required to expend in the future on linaclotide or IW-6118 prior to their regulatory approval, if such approval is ever granted. As a result of these uncertainties surrounding the timing and outcome of any approvals, we are currently unable to estimate precisely when, if ever, linaclotide, IW-6118 or any of our other product candidates will generate revenues and cash flows.

We have multiple product candidates in earlier stages of development, and are pursuing various therapeutic opportunities. We invest carefully in our pipeline, and the commitment of funding for each subsequent stage of our development programs is dependent upon the receipt of clear, positive data. In addition, we are actively engaged in identifying externally-discovered drug candidates at various stages of clinical development and accessing them through in-licensing or acquisition. In evaluating potential assets, we apply the same criteria as those used for investments in internally-discovered assets. To date, we have not in-licensed any drug candidates, but we do expect to do so from time to time.

The majority of our external costs are spent on linaclotide, as costs associated with later stage clinical trials are, in most cases, more significant than those incurred in earlier stages of our pipeline. We expect external costs related to the linaclotide program to begin decreasing if its current Phase 3 clinical trials yield positive data and no other clinical trials are necessary to obtain regulatory approval in the U.S. If IW-6118 is successful in early stage clinical trials, we would expect the program's external costs to increase as it progresses through later stage clinical trials. The remainder of our research and development expense is not tracked by project as it consists primarily of our internal costs, and it benefits multiple projects that are in earlier stages of development and which typically share resources.

The successful development of our product candidates is highly uncertain and subject to a number of risks including, but not limited to:

- The duration of clinical trials may vary substantially according to the type, complexity and novelty of the product candidate.
- The FDA and comparable agencies in foreign countries impose substantial requirements on the introduction of therapeutic pharmaceutical products, typically requiring lengthy and detailed laboratory and clinical testing procedures, sampling activities and other costly and time-consuming procedures.
- Data obtained from nonclinical and clinical activities at any step in the testing process may be adverse and lead to discontinuation or redirection of development activity. Data obtained from these activities also are susceptible to varying interpretations, which could delay, limit or prevent regulatory approval.
- The duration and cost of discovery, nonclinical studies and clinical trials may vary significantly over the life of a product candidate and are difficult to predict.
- The costs, timing and outcome of regulatory review of a product candidate.
- The emergence of competing technologies and products and other adverse market developments.

As a result of the uncertainties discussed above, we are unable to determine the duration and costs to complete current or future clinical stages of our product candidates or when, or to what extent, we will generate revenues from the commercialization and sale of any of our product candidates. Development timelines, probability of success and development costs vary widely. We anticipate that we will make determinations as to which additional programs to pursue and how much funding to direct to each program on an ongoing basis in response to the scientific and clinical data of each product candidate, as well as ongoing assessments of such product candidate's commercial potential.

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We expect our research and development costs to continue to be substantial for the foreseeable future and to increase with respect to our product candidates other than linaclotide as we advance those product candidates through preclinical studies and clinical trials.

General and administrative expense. General and administrative expense consists primarily of compensation, benefits and other employee related expenses for personnel in our administrative, finance, legal, information technology, business development, commercial and human resource functions. Other costs include the legal costs of pursuing patent protection of our intellectual property, facility costs and professional fees for accounting and legal services. After this offering, we anticipate increases in general and administrative expense relating to operating as a public company. These increases will likely include legal fees, accounting fees and directors' and officers' insurance premiums, as well as fees for investor relations services. We also anticipate substantial expenses related to developing the organization necessary to commercialize linaclotide.

Critical Accounting Policies and Estimates

Our discussion and analysis of our financial condition and results of operations is based upon our consolidated financial statements prepared in accordance with generally accepted accounting principles in the United States, or GAAP. The preparation of these financial statements requires us to make certain estimates and assumptions that affect the reported amounts of assets and liabilities and the reported amounts of revenues and expenses during the reported periods. These items are monitored and analyzed by us for changes in facts and circumstances, and material changes in these estimates could occur in the future. These critical estimates and assumptions are based on our historical experience, our observance of trends in the industry, and various other factors that are believed to be reasonable under the circumstances and form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Changes in estimates are reflected in reported results for the period in which they become known. Actual results may differ from our estimates.

We believe that our application of the following accounting policies, each of which require significant judgments and estimates on the part of management, are the most critical to aid in fully understanding and evaluating our reported financial results. Our significant accounting policies are more fully described in Note 2, "Summary of Significant Accounting Policies," to our consolidated financial statements appearing elsewhere in this prospectus.

Revenue Recognition

Our revenue is generated primarily through collaborative research and development and license agreements. The terms of these agreements typically include payment to us of one or more of the following: nonrefundable, up-front license fees; milestone payments; and royalties on product sales. In addition, we generate services revenue through agreements that generally provide for fees for research and development services rendered, and may include additional payments at the conclusion of the research period upon achieving specified events. These service agreements also contemplate royalty payments to us on future sales of our customers' product.

We recognize revenue when there is persuasive evidence that an arrangement exists, services have been rendered or delivery has occurred, the price is fixed or determinable, and collection is reasonably assured. We evaluate revenue from agreements that have multiple elements and account for those components as separate elements when the following criteria are met:

- the delivered items have value to the customer on a stand-alone basis;
- there is objective and reliable evidence of fair value of the undelivered items; and
- if there is a general right of return relative to the delivered items, delivery or performance of the undelivered items is considered probable and within our control.

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The determination that multiple elements in an arrangement meet the criteria for separate units of accounting requires us to exercise our judgment.

The determination of whether we should recognize revenue on a gross or net basis involves judgment based on the relevant facts and circumstances, which relate primarily to whether we act as a principal or agent in the process of generating revenues from our collaboration and licensing arrangements.

For certain of our arrangements, particularly our license agreement with Almirall, it is required that taxes be withheld on payments to us. We have adopted a policy to recognize revenue net of these tax withholdings.

Up-Front License Fees

We recognize revenues from nonrefundable, up-front license fees related to collaboration and license agreements, including the $70.0 million up-front license fee under the Forest collaboration agreement entered into in September 2007 and the $40.0 million up-front license fee, of which $38.0 million was received net of foreign withholding taxes, under the Almirall license agreement entered into in April 2009, on a straight-line basis over the contracted or estimated period of performance due to our continued involvement in research and development. The period of performance over which the revenues are recognized is typically the period over which the research and/or development is expected to occur. As a result, we often are required to make estimates regarding drug development and commercialization timelines for compounds being developed pursuant to a collaboration or license agreement. Because the drug development process is lengthy and our collaboration and license agreements typically cover activities over several years, this approach has resulted in the deferral of significant amounts of revenue into future periods. In addition, because of the many risks and uncertainties associated with the development of drug candidates, our estimates regarding the period of performance may change in the future. Any change in our estimates could result in substantial changes to the period over which the revenues from an up-front license fee are recognized. To date, we have had no material changes to our estimated periods of continuing involvement under existing collaboration and license agreements.

Milestones

At the inception of each agreement that includes contingent milestone payments, we evaluate whether the contingencies underlying each milestone are substantive and at risk to both parties, specifically reviewing factors such as the scientific and other risks that must be overcome to achieve the milestone, as well as the level of effort and investment required. If we do not consider a milestone to be substantive and at risk to both parties, the revenues from the related milestone payment cannot be recognized when the milestone is achieved, but must be recognized on a straight-line basis over the remaining performance period. All of the milestones that have been achieved under our Forest collaboration agreement to date have been considered substantive. As of September 30, 2009, we had not achieved any milestones under our Almirall license agreement.

In those circumstances where a substantive milestone is achieved, collection of the related receivable is reasonably assured and we have remaining obligations to perform under the collaboration arrangement, we recognize as revenue on the date the milestone is achieved an amount equal to the applicable percentage of the performance period that has elapsed as of the date the milestone is achieved, with the balance being deferred and recognized over the remaining period of performance.

Payments received or reasonably assured after performance obligations are fully met are recognized as earned. Because the recognition of a substantive milestone under a collaboration agreement typically requires the completion of a number of activities conducted over a significant period of time, the expenses related to achieving the milestone often are incurred prior to the period in which the milestone payment is recognized. When we do achieve milestones that we consider substantive under any of our collaborations,

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we may experience significant fluctuations in our collaborative revenues from quarter to quarter and year to year depending on the timing of achieving such substantive milestones.

Services Revenue

Services revenue is recognized when there is persuasive evidence that an arrangement exists, services have been rendered or delivery has occurred, the price is fixed or determinable, and collection is reasonably assured. Revenue from research and development services rendered is recognized as services are performed. These arrangements may include additional payments upon achieving specified events. We recognize these additional payments as revenue when achieved and the payments are due and collectible. Royalty revenue related to research and development services is recognized in the period the sales occur.

Research and Development Expense

All research and development expenses are expensed as incurred. Research and development expenses comprise costs incurred in performing research and development activities, including compensation, benefits and other employee costs; share-based compensation expense; laboratory supplies and other direct expenses; facilities expenses; overhead expenses; contractual services, including clinical trial and related clinical manufacturing expenses; and other external expenses. In addition, research and development expense includes reimbursements from Forest for services performed pursuant to our collaboration agreement. Clinical trial expenses include expenses associated with contract research organizations, or CROs. The invoicing from CROs for services rendered can lag several months. We accrue the cost of services rendered in connection with CRO activities based on our estimate of site management, monitoring costs, project management costs, and investigator fees. We maintain regular communication with our CRO vendors to gauge the reasonableness of our estimates. Differences between actual clinical trial expenses and estimated clinical trial expenses recorded have not been material and are adjusted for in the period in which they become known. Under our Forest collaboration agreement we are reimbursed for certain research and development expenses and we net these reimbursements against our research and development expenses as incurred. Nonrefundable advance payments for research and development activities are capitalized and expensed over the related service period or as goods are received.

Share-based Compensation Expense

Prior to January 1, 2006, we accounted for employee share-based awards, including stock options, to employees using the intrinsic value method. Under the intrinsic value method, compensation expense was measured on the date of award as the difference, if any, between the deemed fair value of our common stock and the option exercise price, multiplied by the number of options granted. The option exercise prices and fair value of our common stock are determined by our management and board of directors based on a review of various objective and subjective factors. No compensation expense was recorded for stock options issued to employees prior to January 1, 2006 for awards with fixed amounts and with fixed exercise prices at least equal to the fair value of our common stock at the date of grant.

Effective January 1, 2006, we recognize compensation expense for all share-based awards granted, modified, repurchased or cancelled on or after January 1, 2006, based on the grant date fair value. These costs are recognized on a straight-line basis over the requisite service period for all time-based vested awards. We continue to account for share-based awards granted prior to January 1, 2006 under the intrinsic value method.

We record the expense of services rendered by non-employees based on the estimated fair value of the stock option using the Black-Scholes option-pricing model as of the respective vesting date. Further, we expense the fair value of non-employee stock options over the vesting term of the underlying stock options.

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For employee share-based awards subsequent to January 1, 2006, we estimate the fair value of the share-based awards, including stock options, using the Black-Scholes option-pricing model. Determining the fair value of share-based awards requires the use of highly subjective assumptions, including the expected term of the award and expected stock price volatility. The assumptions used in calculating the fair value of share-based awards granted in 2006, 2007, 2008 and the nine months ended September 30, 2009 are set forth below:

	Years Ended December 31,			Nine Months Ended
	2006	2007	2008	September 30, 2009
Volatility	69.0%	65.0%	64.0%	62.4%
Dividend yield	%	%	%	%
Expected life of options (in years)	7.0	7.0	6.5	6.5
Risk-free interest rate	4.8%	4.6%	3.1%	2.7%

The assumptions used in determining the fair value of share-based awards represent management's best estimates, but these estimates involve inherent uncertainties and the application of management judgment. As a result, if factors change, and we use different assumptions, our share-based compensation could be materially different in the future. The risk-free interest rate used for each grant is based on a zero-coupon U.S. Treasury instrument with a remaining term similar to the expected term of the share-based award. Because we do not have a sufficient history to estimate the expected term, we use the simplified method for estimating the expected term. The simplified method is based on the average of the vesting tranches and the contractual life of each grant. Because there was no public market for our common stock prior to this offering, we lacked company-specific historical and implied volatility information. Therefore, we estimate our expected stock volatility based on that of publicly-traded peer companies, and we expect to continue to use this methodology until such time as we have adequate historical data regarding the volatility of our publicly-traded stock price. For purposes of identifying publicly-traded peer companies, we selected publicly-traded companies that are in the biopharmaceutical industry, have products or product candidates in similar therapeutic areas (gastrointestinal dysfunction and pain management) and stages of preclinical and clinical development as us, have sufficient trading history to derive a historic volatility rate and have similar vesting terms as our granted options. We have not paid and do not anticipate paying cash dividends on our shares of common stock; therefore, the expected dividend yield is assumed to be zero. We also recognize compensation expense for only the portion of options that are expected to vest. Accordingly, we have estimated expected forfeitures of stock options based on our historical forfeiture rate, adjusted for known trends, and used these rates in developing a future forfeiture rate. Our forfeiture rates were 5.0%, 5.0% and 4.4% as of December 31, 2006, 2007 and 2008, respectively, and 4.4% and 4.0% as of September 30, 2008 and 2009, respectively. If our actual forfeiture rate varies from our historical rates and estimates, additional adjustments to compensation expense may be required in future periods.

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The following table presents the grant dates and related exercise prices of stock options granted and other stock awards granted since January 1, 2007:

Date of Issuance	Nature of Issuance	Number of Shares	Exercise or Purchase Price per Share	Per Share Estimated Fair Value of Common Stock[1]	Per Share Weighted Average Estimated Fair Value of Options[2]
January 23, 2007	Option grant	1,206,000	$ 2.94	$ 2.94	$ 2.06
April 24, 2007	Option grant	177,250	$ 3.05	$ 3.05	$ 2.06
July 11, 2007	Option grant	96,500	$ 3.05	$ 3.05	$ 2.08
October 23, 2007	Option grant	67,500	$ 3.62	$ 3.62	$ 2.36
February 1, 2008	Option grant	1,633,500	$ 3.76	$ 3.76	$ 2.35
April 30, 2008	Option grant	114,300	$ 4.33	$ 4.33	$ 2.53
July 29, 2008	Option grant	139,000	$ 4.67	$ 4.67	$ 2.84
November 25, 2008	Option grant	149,300	$ 4.98	$ 4.98	$ 3.03
November 25, 2008	Stock award	5,000	$ 0.00	$ 4.98	$ 0.00
February 12, 2009	Option grant	1,485,000	$ 4.89	$ 4.89	$ 2.95
May 5, 2009	Option grant	35,000	$ 5.00	$ 5.00	$ 3.06
July 22, 2009	Option grant	69,000	$ 5.48	$ 5.48	$ 3.51
July 29, 2009	Option grant	900,000[3]	$ 5.48	$ 5.48	$ 3.38
August 4, 2009	Option grant	29,000	$ 5.48	$ 5.48	$ 3.38
September 8, 2009	Option grant	360,000[4]	$ 5.48	$ 5.48	$ 3.38
September 18, 2009	Restricted stock award	470,686[5]	$ 0.00	$ 5.48	$ 0.00
October 20, 2009	Option grant	18,000	$ 7.36	$ 7.36	$ 4.35
October 22, 2009	Restricted stock award	44,863[5]	$ 0.00	$ 7.36	$ 0.00
October 26, 2009	Option grant	15,000	$ 7.36	$ 7.36	$ 4.35

(1) The per share estimated fair value of common stock represents the determination by our board of directors of the fair value of our common stock as of the date of grant, taking into account various objective and subjective factors and including the results, if applicable, of valuations of our common stock as discussed in the pages that follow.

(2) Our estimate of the per share weighted average fair value for stock option grants was computed based upon the Black-Scholes option-pricing model with the assumptions through September 30, 2009 as disclosed in our consolidated financial statements.

(3) Comprises stock options subject to performance-based milestone vesting. The vesting of these performance-based milestone stock options will occur upon the achievement of certain performance-based milestones, such as the filing of a second NDA with the FDA, the first commercial sale of our product, or achieving a specified sales target. Management has concluded that the performance-based milestones are not probable of achievement, as such, no compensation expense has been recorded related to these options.

(4) Comprises stock options granted to an executive officer hired September 8, 2009.

(5) Comprises shares of common stock sold to independent members of the board of directors under restricted stock agreements in accordance with the terms of our 2005 Stock Incentive Plan and consistent with our current director compensation program (see "Director Compensation" section). A total of 115,549 shares of restricted common stock will vest on December 31, 2009 and the remainder vest ratably over four years beginning in January 2010. In the event that a member of the board of directors ceases to serve on our board prior to December 31, 2013, the member will forfeit all unvested shares in accordance with the terms of the restricted stock agreement.

We have historically granted stock options at exercise prices not less than the fair value of our common stock as determined by our board of directors, with input from management. Our board of

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directors has historically determined, with input from management, the estimated fair value of our common stock on the date of grant based on a number of objective and subjective factors, including:

- the prices at which we sold shares of convertible preferred stock;
- the superior rights and preferences of securities senior to our common stock at the time of each grant;
- the likelihood of achieving a liquidity event such as an initial public offering or sale of our company;
- our historical operating and financial performance and the status of our research and product development efforts;
- achievement of enterprise milestones, including our entering into collaboration and license agreements; and
- external market conditions affecting the biotechnology industry sector.

Beginning in March 2006, our board of directors also considered valuations provided by management in determining the fair value of our common stock. Such valuations were prepared as of March 1, June 1, October 31 and December 31, 2006, April 24, June 30, September 30 and December 31, 2007, March 31, June 30, October 28 and December 31, 2008, and March 31, June 30 and September 30, 2009, and valued our common stock at $1.56, $1.56, $1.61, $2.94, $3.05, $3.05, $3.62, $3.76, $4.33, $4.67, $4.98, $4.89, $5.00, $5.48 and $7.36 per share, respectively. The valuations, as described in detail below for each option grant date beginning January 2007, have been used to estimate the fair value of our common stock as of each option grant date listed and in calculating share-based compensation expense. Our board of directors has consistently used the most recent quarterly valuation provided by management for determining the fair value of our common stock unless a specific event occurs that necessitates an interim valuation.

The valuations were prepared consistent with the American Institute of Certified Public Accountants Practice Aid, *Valuation of Privately-Held Company Equity Securities Issued as Compensation*, or the Practice Aid. We used the guideline company method and the similar transaction method of the market approach, which compare our company to similar publicly-traded companies or transactions, and an income approach, which looks at projected future cash flows, to value our company from among the alternatives discussed in the Practice Aid. In addition, as we have several series of convertible preferred stock outstanding, it was also necessary to allocate our company's value to the various classes of stock, including stock options. As provided in the Practice Aid, there are several approaches for allocating enterprise value of a privately-held company among the securities held in a complex capital structure. The possible methodologies include the probability-weighted expected return method, the option-pricing method and the current value method.

We used the probability-weighted expected return method described in the Practice Aid to allocate the enterprise values to the common stock. Under this method, the value of our common stock is estimated based upon an analysis of future values for our company assuming various future outcomes, the timing of which is based on the plans of our board of directors and management. Under this approach, share value is based on the probability-weighted present value of expected future investment returns, considering each of the possible outcomes available to us, as well as the rights of each share class. We estimated the fair value of our common stock using a probability-weighted analysis of the present value of the returns afforded to our stockholders under each of four possible future scenarios. Three of the scenarios assumed a shareholder exit, either through an initial public offering, or IPO, or a sale of our company. The fourth scenario assumed a sale of our company at a value that is less than the cumulative amounts invested by our preferred stockholders.

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In March 2006, when we began utilizing the Practice Aid to allocate enterprise values to the various possible outcomes, we assumed two separate IPO scenarios based on our company's profile at the time. In 2006, we were advancing the linaclotide program in human clinical trials as well as a second early stage clinical product candidate. Given the relative risk of these two programs, one IPO scenario included both programs advancing in the clinic at the time of an IPO. Based on the relative risks of both programs and the significant effect on the potential value of a liquidity event if one program failed, a second IPO scenario was added, which included only linaclotide advancing in the clinic at the time of an IPO. This second scenario was included to better reflect the potential outcomes for our company. Beginning with the March 31, 2008 valuation, due to the suspension in March 2008 of the second product candidate program, we eliminated the two product IPO scenario and we utilized a one product IPO scenario reflecting only linaclotide advancing in the clinic at the time of an IPO. Beginning with the October 28, 2008 valuation, we again included two separate IPO scenarios to better reflect our company's risk profile at that time. The linaclotide program was by then advancing in two indications, CC and IBS-C. We believe that the IBS-C indication has a significantly higher market value and higher clinical risk for Ironwood. To better reflect the potential liquidity outcomes for linaclotide, the first IPO scenario included an assumption of successful Phase 3 clinical trials for both the CC and IBS-C indications at the time of an IPO, and the second IPO scenario reflected successful Phase 3 clinical trials in only the CC indication at the time of the IPO. For both IPO scenarios and the sale scenario, the estimated future values of our common stock were calculated using assumptions including: the expected pre-money or sale valuations based on the market approach, and beginning in September 2007, the income approach using the discounted cash flow method, and the expected dates of the future expected IPO or sale. For the sale at an assumed price less than the liquidation preference scenario, the estimated future and present values of our common stock were calculated using assumptions including the estimated aggregate enterprise value that could be attained through such a sale and the estimated expected date of the future sale. The present values of our common stock under each scenario were then calculated using a risk-adjusted discount rate. Finally, the calculated present values for our common stock were probability-weighted based on our estimate of the relative occurrence of each scenario to derive the concluded value of our common stock.

Stock Option Grants on January 23, 2007

Our board of directors granted stock options on January 23, 2007, with each having an exercise price of $2.94 per share. In addition to considering the objective and subjective factors listed above, the board of directors considered the valuation as of December 31, 2006 provided by management.

As of December 31, 2006, linaclotide had completed Phase 2a clinical trials and the second product candidate had completed Phase 1 clinical trials and was expected to proceed further in clinical trials in early 2007. Additionally, Microbia had recently entered into a five-year product development agreement with a customer.

In the December 31, 2006 valuation, we used the market approach to estimate the aggregate future enterprise value of our company under the two separate IPO scenarios, as described above, one in which both product candidates successfully completed Phase 2 clinical trials, and one where only linaclotide successfully completed Phase 2 clinical trials. In both IPO scenarios, we assumed the liquidity event would occur in February 2008. In applying the market approach to the IPO scenarios, we used the Guideline Public Company Method as described in the Practice Aid. Under this method, we analyzed market data on pre-money IPO valuations for approximately 50 biotechnology companies that went public in the period 2003 to 2006. From this set of data we selected a sub-set of companies that had either one or two drugs in Phase 2 clinical trials. We used the median and high end of the range, $200.0 million to $350.0 million in the one-product IPO scenario and $150.0 million to $700.0 million in the two-product IPO scenario, to estimate the enterprise values of our company under the two IPO scenarios. We used $250.0 million for the one-product scenario and $600.0 million for the two-product IPO scenario. We used these values as the

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estimated enterprise values in the respective IPO scenarios of the probability-weighted expected return method.

In applying the market approach in the sale scenario, we analyzed sale transactions of similar biotechnology companies. The value used was supported by published transaction values of companies with product candidates in various stages of drug development ranging from discovery stage to Phase 3 clinical trials. In the sale scenario, we estimated our company's enterprise value using transactions for companies that were in a comparable stage of development as we anticipated we would be as of February 2008, which was the estimated date a sale or merger would be consummated.

In the sale at an assumed price less than the liquidation preference scenario, we assumed a sale in February 2008 of our company's existing research and intellectual property at a value that would not allow our preferred stockholders to realize their liquidation preference at December 31, 2006.

Under the IPO scenarios, the fair value of our common stock was calculated using the expected aggregate enterprise valuations and a risk-adjusted discount rate of 16% based on the estimated timing of a potential IPO with no lack of marketability discount. The risk-adjusted discount rate was based on the inherent risk of a hypothetical investment in our common stock. An appropriate rate of return required by a hypothetical investor was determined based on our cost of capital. Our calculated cost of capital was developed based upon a quantitative and qualitative analysis of factors that would impact the discount rate.

The fair value of our common stock under the sale at an assumed price less than the liquidation preference scenario was determined by reducing the total estimated enterprise value by the liquidation preferences of our convertible preferred shares, all of which would receive more value based on their liquidation preferences, as opposed to converting to common stock.

In our December 31, 2006 valuation, we used a probability weight of 35% for the two-product IPO scenario and a probability weight of 15% for the one-product IPO scenario. The greater probability of an IPO in a two-product scenario versus a one-product scenario was the basis for the higher two-product probability weight. The sale scenario had a probability weight of 45% and the sale at an assumed price less than the liquidation preference scenario had a probability weight of 5%. The probability weights assigned to the respective scenarios were primarily based on the industry average of the clinical success rates given the stage of development of our product candidates as of the valuation date as well as our assessment of the current financing and biotechnology industry environments at the time of the valuation. The resulting value, which represented the estimated fair value of our common stock at December 31, 2006, was $2.94 per share. No events or other circumstances occurred between December 31, 2006 and January 23, 2007 such that there was a change in the common stock fair value during that period.

Stock Option Grants on April 24, 2007

Our board of directors granted stock options on April 24, 2007, with each having an exercise price of $3.05 per share. In addition to considering the objective and subjective factors listed above, the board of directors considered the valuation as of April 24, 2007 provided by management.

As of April 24, 2007, we had sold 8.0 million shares of our Series F convertible preferred stock at a per share price of $6.25 from which we received approximately $50.0 million of net proceeds. With the exception of the sale of the Series F convertible preferred stock, there had not been any material changes in our business or operating results since the December 31, 2006 valuation. We used the same valuation methodologies as were used in the December 31, 2006 valuation. The increase in the estimated fair value of our common stock to $3.05 per share in the April 24, 2007 valuation as compared to the December 31, 2006 valuation was primarily related to the decrease in the time to the expected liquidity event as the sale of the Series F convertible preferred stock was already taken into consideration in the December 31, 2006 valuation.

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Stock Option Grants on July 11, 2007

Our board of directors granted stock options on July 11, 2007, with each having an exercise price of $3.05 per share. In addition to considering the objective and subjective factors listed above, the board of directors considered the valuation as of June 30, 2007 provided by management.

As of June 30, 2007, linaclotide had advanced into Phase 2b clinical trials while the second product candidate had not advanced as quickly as our previous projections. We used the same valuation methodologies as were used in the April 24, 2007 valuation, updated for the advancement of linaclotide to Phase 2b clinical trials and the delay in the second product candidate. The probability weight assigned to the two-product IPO scenario was reduced to 25% and the probability weight assigned to the one-product IPO scenario was increased to 50% compared to 15% in the April 24, 2007 valuation. The probability weight assigned to the sale scenario was reduced to 20% and the probability weight assigned to the sale at an assumed price less than the liquidation preference scenario remained the same compared to the April 24, 2007 valuation. The changes in the respective probability weights reflect linaclotide's further progress in the clinic and the delay in the second product candidate's development. Based on later clinical timelines and a reduced need for funding because of our Series F convertible preferred stock financing, the June 30, 2007 valuation reflected a revised liquidity event date of September 30, 2008 for the two IPO scenarios and the sale scenario. The resulting estimated fair value of our common stock of $3.05 per share at June 30, 2007 was the same as at April 24, 2007 because of the combined effect of the change in the probability weights assigned the two IPO scenarios and the sale scenario and the approximately seven month delay in the date of a liquidity event.

Stock Option Grants on October 23, 2007

Our board of directors granted stock options on October 23, 2007, with each having an exercise price of $3.62 per share. In addition to considering the objective and subjective factors listed above, the board of directors considered the valuation as of September 30, 2007 provided by management.

As of September 30, 2007, we suspended the clinical trials and related development activity associated with our second product candidate. After further evaluating the clinical results and market opportunity for our second product candidate, we decided not to pursue further development activities for it. However, we did assume that an earlier stage third product candidate based on an existing back-up compound could be in Phase 2 clinical trials at the time of an IPO. Additionally, in September 2007, we entered into the Forest collaboration agreement for linaclotide whereby we anticipated receiving a $70.0 million up-front license fee as well as various clinical milestone payments and a commercial milestone payment for the achievement of a certain sales level. The Forest collaboration agreement included a clinical milestone, which would trigger an equity investment in our company by Forest. Also, under the Forest collaboration agreement, all development and commercialization costs, as well as all profits and losses related to linaclotide, were to be shared equally by the parties.

We used the same valuation methodologies as were used in the June 30, 2007 valuation, updated for two material changes in our business. The first change was the suspension of all development activity associated with our second product candidate and its replacement with an earlier stage product candidate utilizing a backup compound. The second change was the execution of the Forest collaboration agreement which, among other benefits, made additional financial resources available to us in the form of milestone payments in addition to the up-front licensing fee of $70.0 million and cost sharing. At the time of this valuation, the two-product IPO scenario was updated to project linaclotide in Phase 3 clinical trials and a new third product candidate in Phase 2 clinical trials at the time of a liquidity event. The one-product IPO scenario was also updated to reflect only linaclotide in Phase 3 clinical trials at the time of a liquidity event. The sale scenario was updated to reflect linaclotide success in only one indication and under the assumption that a sale of Ironwood would be executed only in the absence of available equity financing. The probability weight assigned to the two-product IPO scenario was reduced to 15% and the probability

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weight assigned to the one-product IPO scenario was increased to 65% compared to the June 30, 2007 valuation based on our assessment that the CC indication posed lower clinical risk than IBS-C due to the different endpoints being tested and thus CC was more likely to be successful at the time of a liquidity event than the combination of both CC and IBS-C. The sale scenario's probability weight was reduced to 15% and the probability weight assigned to the sale at an assumed price less than the liquidation preference scenario remained the same compared to the June 30, 2007 valuation. The changes in the respective probability weights reflect the changes in the business described above. Additionally, the September 30, 2007 valuation reflected a delayed liquidity event date of June 30, 2009 for all the scenarios based on a decreased need for capital due to the additional funding provided to us by the Forest collaboration. The risk-adjusted discount rate for all scenarios was revised to 20% to reflect the overall increase in business risk associated with our increased reliance on linaclotide due to the setbacks and delays in our second product candidate program. The higher estimated enterprise value now associated with the one-product IPO scenario and its greater probability weight, driven by decreased clinical risk in CC and additional payments for the CC indication from the Forest collaboration, were the primary reasons for the increase in the estimated fair value of our common stock to $3.62 per share as compared to $3.05 per share in the June 30, 2007 valuation.

Stock Option Grants on February 1, 2008

Our board of directors granted stock options on February 1, 2008, with each having an exercise price of $3.76 per share. In addition to considering the objective and subjective factors listed above, the board of directors considered the valuation as of December 31, 2007 provided by management.

As of December 31, 2007, there had not been any material changes in our business or operating results since the September 30, 2007 valuation. We used the same valuation methodologies as were used in the September 30, 2007 valuation, updated to reflect the shorter time to the liquidity event date of June 30, 2009 for all the scenarios. As a result, the estimated fair value of our common stock increased to $3.76 per share in the December 31, 2007 valuation as compared to $3.62 in the September 30, 2007 valuation.

Stock Option Grants on April 30, 2008

Our board of directors granted stock options on April 30, 2008, with each having an exercise price of $4.33 per share. In addition to considering the objective and subjective factors listed above, the board of directors considered the valuation as of March 31, 2008 provided by management.

As of March 31, 2008, there were two material changes in our business. On March 4, 2008, we announced favorable Phase 2b results for linaclotide. We also terminated all efforts in our early stage clinical product candidate as well as the related backup compound based on the current marketing and regulatory environment for similar drugs. As a result of these changes, we eliminated the two-product IPO scenario. The focus of our clinical development was now solely on linaclotide, which became the primary value driver in our analysis. Additionally, the methodology for estimating the enterprise value for the remaining one-product IPO scenario was changed from the market approach to the income approach using the discounted cash flow method. This change in method incorporated the agreed upon deal terms with Forest, including all expected milestone payments and future profit sharing, which we assessed to be a better reflection of our enterprise value. Under the discounted cash flow method, our equity value is equal to the projected future free cash flows and expected terminal value of Ironwood, adjusted for cash, net of debt, and the probability of linaclotide completing successful Phase 3 clinical trials. The present value of our projected free cash flow is determined by discounting our projected future cash flows back to the valuation date. The discount rate used in the analysis was 16%. In determining the appropriate discount rate, we determined our weighted average cost of capital based on comparable biotechnology companies. We then adjusted this weighted average cost of capital for company specific risk based on the reduced risk profile of our company at the time of an IPO. Also, we increased the discount rate used to discount the per share values from the event date to the valuation date for all the scenarios to 22% from 20%. One primary

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reason for the increase in the discount rate was the change in the set of comparable companies primarily due to the elimination of the second product candidate. The change to the set of comparable companies along with updates in the market data increased the cost of equity for the scenarios.

Because we no longer considered a two-product IPO scenario viable at this time, the probability weight assigned to the one-product IPO scenario was increased to 70%. The probability weight assigned to the sale scenario was increased to 25% based on the concentration of company risk, the availability of equity financing, and increased merger and sale activity in the biotechnology industry at that time. The sale at an assumed price less than the liquidation preference scenario remained at 5%. The impact of the changes in risk-adjusted discount rates and probability weights resulted in an estimated fair value of our common stock of $4.33 per share as of March 31, 2008.

Stock Option Grants on July 29, 2008

Our board of directors granted stock options on July 29, 2008, with each having an exercise price of $4.67 per share. In addition to considering the objective and subjective factors listed above, the board of directors considered the valuation as of June 30, 2008 provided by management.

As of June 30, 2008, there had not been any material changes in our business or operating results since the March 31, 2008 valuation. We used the same valuation methodologies as were used in the March 31, 2008 valuation; however, we refined our comparable biotechnology companies to reflect anticipated progress of linaclotide into Phase 3 clinical trials by adding other companies with significant potential Phase 3 programs. The revised publicly traded comparable biotechnology companies were (1) focused on the development of gastrointestinal drugs, (2) had drug candidates in Phase 2 or Phase 3 clinical trials or a combination of both, or (3) had comparable market opportunities for their drug candidates. As a result of the change in comparable biotechnology companies, the risk-adjusted discount rate decreased to 19%. The expected liquidity event date remained June 30, 2009. These changes resulted in an increase in the estimated fair value of our common stock to $4.67 per share as of June 30, 2008.

Stock Option Grants and Stock Award on November 25, 2008

Our board of directors granted stock options and a stock award on November 25, 2008, with each stock option having an exercise price of $4.98 per share and the stock award having a fair value of $4.98 per share. In addition to considering the objective and subjective factors listed above, the board of directors considered the valuation as of October 28, 2008 provided by management.

As of October 28, 2008, we had sold 4.1 million shares of our Series H convertible preferred stock at a per share price of $12.00 from which we received approximately $49.6 million of net proceeds. This financing also included a change in our capital structure to reflect a limited dual class common stock structure whereby any shares then owned or owned prior to a public offering have a super-majority vote in certain circumstances. Also, shortly after the close of our Series H convertible preferred stock financing, the general financial market conditions substantially deteriorated as a result of the global credit and liquidity crisis, which lead to a significant increase in the cost of capital. This credit crisis substantially lowered our expectations for additional financing for the foreseeable future which had the effect of lowering our valuation primarily as a result of a delay in our assessed timeline to a liquidity event.

We used the same valuation methodologies as were used in the June 30, 2008 valuation; however, we updated them to reflect an adjustment to the IPO scenario based on the deterioration in the financial markets. The IPO scenario was also split into two linaclotide scenarios: (1) a two-indication IPO whereby both the IBS-C and CC indications achieved favorable Phase 3 clinical trials at the time of a liquidity event, and (2) a one-indication IPO whereby only the CC indication had favorable Phase 3 clinical trials at the time of a liquidity event. This split in IPO scenarios was made to reflect the difference in clinical risk associated with successful Phase 3 data in the CC indication, which relied primarily on clinical endpoints that we assessed were easier to achieve than the endpoints required in our IBS-C clinical trials. We also

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determined there was higher commercial value associated with the IBS-C market in relation to the CC market based on assessments of the size of each opportunity. The discount rate used in both IPO scenarios to discount the cash flows was 19%. The funding received in the Series H convertible preferred financing round, combined with aggressive cash management, was deemed sufficient to fund linaclotide through Phase 3 clinical trials, which, along with the current financial crisis, resulted in the moving of the expected IPO date to June 30, 2010 from June 30, 2009. Since we estimated that the IPO would occur after some Phase 3 clinical trial results for linaclotide were known, a higher probability of success was applied to the future estimated cash flows. These changes in assumptions resulted in larger estimated enterprise values in all IPO and sale scenarios. The combination of the aforementioned events and the deterioration in the condition of the financial markets balanced out the impact on the discount rate used to discount the per share values from the event date to the valuation date and left it unchanged at 19%.

We assigned a probability weight of 45% to the two-indication IPO scenario and 30% to the one-indication IPO scenario. The total probability weight of 75% assigned to an IPO liquidity event was an increase from 70% in the June 30, 2008 valuation. The increase in the total IPO probability weight reflected the greater likelihood that linaclotide would succeed in clinical trials for at least one, if not both, of the indications. The probability weight assigned to the sale scenario was reduced to 20% compared to the June 30, 2008 valuation based on the implementation of a limited dual class common stock structure and the potential of a super-majority blocking vote by any existing stockholders in certain circumstances. The probability weight assigned to the sale at an assumed price less than the liquidation preference scenario remained the same compared to the June 30, 2008 valuation. The higher estimated enterprise values now associated with the two IPO scenarios and the sale scenario combined with the greater total probability weight assigned to the IPO scenarios were the primary reasons for the increase in the estimated fair value of our common stock to $4.98 per share as compared to $4.67 per share in the June 30, 2008 valuation.

Stock Option Grants on February 12, 2009

Our board of directors granted stock options on February 12, 2009, with each having an exercise price of $4.89 per share. In addition to considering the objective and subjective factors listed above, the board of directors considered the valuation as of December 31, 2008 provided by management.

As of December 31, 2008, there had not been any material changes in our business or operating results since the October 28, 2008 valuation. We used the same valuation methodologies as were used in the October 28, 2008 valuation, except a later liquidity event date of September 30, 2010 was used for all the scenarios as compared to June 30, 2010 in the October 28, 2008 valuation. This liquidity date change resulted from the continued deterioration in the condition of the financial markets, which was assumed to have a sustained limiting effect on the IPO market for the foreseeable future. As a result, the estimated fair value of our common stock decreased to $4.89 per share in the December 31, 2008 valuation as compared to $4.98 in the October 28, 2008 valuation.

Stock Option Grants on May 5, 2009

The compensation and HR committee of our board of directors, or the compensation committee, granted stock options on May 5, 2009, with each having an exercise price of $5.00 per share. In addition to considering the objective and subjective factors listed above, the board of directors considered the valuation as of March 31, 2009 provided by management.

As of March 31, 2009, there had not been any material changes in our business or operating results since the December 31, 2008 valuation. We used the same valuation methodologies as were used in the December 31, 2008 valuation, updated to reflect an increase in the risk-adjusted discount rate from 19% to 20% for all the scenarios based on changes in market data, reflecting the additional return investors would expect from an equity investment made during the turbulent economic conditions existing at this time. Despite this increased cost of capital, no liquidity dates were changed and we were three months closer to our assumed liquidity events and as a result, the estimated fair value of our common stock increased to $5.00 per share in the March 31, 2009 valuation as compared to $4.89 in the December 31, 2008 valuation.

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Stock Option Grants on July 22, July 29, August 4 and September 8, 2009 and Restricted Stock Awards on September 18, 2009

Our board of directors or the compensation committee granted stock options on July 22 and 29, August 4 and September 8, 2009 and restricted stock awards on September 18, 2009, with each having an exercise price of $5.48 per share. In addition to considering the objective and subjective factors listed above, the board of directors considered the valuation as of June 30, 2009 provided by management.

As of June 30, 2009, linaclotide had entered Phase 3 clinical trials for CC and had not yet entered Phase 3 clinical trials for IBS-C. In April 2009, we completed the Almirall license agreement for the development and distribution of linaclotide for the European market. Under the Almirall license agreement, we anticipated receiving a net $38.0 million up-front license fee, a clinical milestone, a commercial milestone payment and royalties based on Almirall's annual sales in the licensed territory. Additionally, the Almirall license agreement includes a clinical milestone, which would trigger an equity investment in our company by Almirall.

We used the same valuation methodologies as were used in the March 31, 2009 valuation; however, we updated the discounted cash flow analyses to reflect the additional value we anticipated receiving from the completed Almirall license agreement. As a result of the revisions, the estimated enterprise value of Ironwood in both the two-indication IPO scenario and the one-indication IPO scenario increased. The estimated enterprise values under the sale scenario and sale at an assumed price less than the liquidation preference scenario remained the same as in the March 31, 2009 valuation. The probability weights assigned to each scenario, the expected liquidity event date, and the risk-adjusted discount rate all remained the same as in the March 31, 2009 valuation. As a result, the estimated fair value of our common stock increased to $5.48 per share in the June 30, 2009 valuation as compared to $5.00 per share in the March 31, 2009 valuation.

Stock Option Grants on October 20 and October 26, 2009 and Restricted Stock Award on October 22, 2009

The compensation committee granted stock options on October 20 and October 26, 2009 and a restricted stock award on October 22, 2009, with each having an exercise price of $7.36 per share. In addition to considering the objective and subjective factors listed above, our board of directors considered the valuation as of September 30, 2009 provided by management.

As of September 30, 2009, linaclotide had entered Phase 3 clinical trials for IBS-C as well as progressing in its Phase 3 clinical trials for CC. In July 2009, we achieved a clinical milestone included in the Forest collaboration agreement and as a result received a $20.0 million milestone payment from Forest and sold 2.1 million shares of our Series G convertible preferred stock to Forest at a contractually-agreed per share price of $12.00 from which we received approximately $25.0 million of net proceeds.

We used the same valuation methodologies as were used in the June 30, 2009 valuation, however, we updated them to reflect an earlier liquidity event date of March 31, 2010 for the one-indication IPO scenario based on our belief that if we received successful data from our Phase 3 clinical trials for CC, they could potentially support a public offering. In addition, the market for IPOs had become more active, thereby increasing the likelihood of an IPO based on successful Phase 3 CC data. As a result, we increased the probability weight of the one-indication IPO scenario to 45% and decreased the probability weight of the two-indication IPO scenario to 30%. The increase in the probability weight of the one-indication IPO scenario reflected the greater likelihood that linaclotide would succeed in Phase 3 clinical trials for CC at the time of an IPO. The total probability weight of 75% assigned to the combination of the one-indication and two-indication IPO scenarios remained the same as the June 30, 2009 valuation. The estimated enterprise values in both the one-indication and two-indication IPO scenarios were also updated to reflect the feedback we received from investment advisors as to the value of our potential IPO in both the one-indication and two-indication IPO scenarios. The risk-adjusted discount rate was adjusted from 20%

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to 19% for all the scenarios to reflect the initiation of the IBS-C trials and the modest improvement in the economic environment. The higher estimated enterprise values now associated with the two IPO scenarios and the sale scenario combined with the increase in probability weight and shorter timeline assigned to the one-indication IPO scenario were the primary reasons for the increase in the estimated fair value of our common stock to $7.36 per share in the September 30, 2009 valuation as compared to $5.48 in the June 30, 2009 valuation.

On November 2, 2009, we became aware of and announced favorable efficacy and safety results in two Phase 3 CC trials, meeting all 32 primary and secondary endpoints across both doses evaluated in these independent trials involving 1,287 subjects. Due to the materiality of this result for Ironwood and a favorable outcome above our expectations, management prepared a common stock valuation to reflect a significant change in value although no additional stock option grants were made or contemplated.

We used the same valuation methodologies as were used in the September 30, 2009 valuation, however, we updated them to reflect the significant change to our business that resulted from the favorable clinical trial results in CC. First, we determined that it was highly likely that we would be able to complete a successful public offering on the strength of our CC clinical trial data, and as a result we increased the probability weight of our one-indication IPO scenario to 65%. We also moved the liquidity event date to February 28, 2010 from March 31, 2010 based on higher confidence that we could complete a public offering earlier. The probability weight of the two-indication IPO remained at 30% to continue to reflect the possibility that the IBS-C trial could enroll more quickly and could persuade us to wait for IBS-C Phase 3 results before completing a public offering. The total combined probability weight of 95% assigned to the one-indication and two-indication IPO scenarios increased from 75% in the previous valuation based on our determination of a higher likelihood of completing an IPO sometime in 2010. The risk-adjusted discount rate was also lowered from 19% to 15% for all the scenarios to reflect a decrease in company risk as a result of a higher likelihood of obtaining financing required to fund Ironwood further into the future. The sale scenario was decreased to 5% to reflect the lower likelihood in light of our CC trial results. The sale at an assumed price less than the liquidation preference scenario previously assigned a 5% likelihood was decreased to zero. As a result of these changes, the estimated fair value of our common stock increased to $11.75 per share in the November 2, 2009 valuation as compared to $7.36 per share in the September 30, 2009 valuation.

On January 15, 2010, we and the underwriters determined the range set forth on the cover page of this prospectus. The midpoint of the range is $15.00 as compared to $11.75, management's determination of the estimated fair value of our common stock on November 2, 2009, the date we became aware of and announced favorable efficacy and safety results in two Phase 3 CC trials for linaclotide. This estimated fair value represents a discount of 22% from the midpoint of the range and an increase of 28% from the estimated fair value of our common stock on November 2, 2009. We note that, as is typical in initial public offerings, the range set forth on the cover page of this prospectus was not derived using a formal determination of fair value, but was determined based upon discussions between us and the underwriters. Among the factors considered in setting this range were prevailing market conditions and estimates of our business potential. In addition to this difference in purpose and methodology, we believe that the difference in value reflected between the midpoint of the range and management's determination of the estimated fair value of our common stock on November 2, 2009 is primarily the result of the following factors:

- The stock price of our publicly-traded peer companies increased, on average, approximately 17% during the period from November 2, 2009 to January 13, 2010. The NASDAQ biotechnology index increased approximately 15%, and the NASDAQ composite index increased approximately 13% during the same period.

- During the period from November 2, 2009 to January 13, 2010, four biopharmaceutical companies filed registration statements for initial public offerings in the U.S. as compared to just four

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biopharmaceutical companies that priced their initial public offerings in the 12 months preceding November 2, 2009, demonstrating a significant improvement in the market for initial public offerings in the U.S. in the biopharmaceutical industry.

Our early January 2010 discussions with the underwriters took into account our and the underwriters' perceptions of significantly increased optimism regarding the market for initial public offerings, as well as our and our underwriters' increased expectations that we would complete our initial public offering in the first quarter of 2010.

We performed a preliminary valuation to estimate the fair value of our common stock immediately before the earliest anticipated effective date of the offering of February 5, 2010, in which we held all assumptions, with the exception of the liquidity date for a one-indication IPO scenario, consistent with our November 2, 2009 valuation. The liquidity date for the one-indication IPO scenario was accelerated from February 28, 2010 to February 5, 2010. As a result of both the accelerated liquidity date for the one-indication IPO scenario and the passage of time from the November 2, 2009 valuation to the February 5, 2010 anticipated effective date, management's estimated fair value of our common stock at February 5, 2010 would be $12.18, a 19% discount from the midpoint of the range.

History has shown that it is reasonable to expect that the completion of an initial public offering will increase the value of stock as a result of the significant increase in the liquidity and ability to trade/sell such securities. However, it is not possible to measure such increase in value with precision or certainty.

Based on the $15.00 midpoint of the range, the intrinsic value of the options outstanding at October 26, 2009, the last date we granted stock options, was $176.3 million, of which $95.1 million related to vested options and $81.2 million related to unvested options.

There are significant judgments and estimates inherent in the determination of these valuations. These judgments and estimates include assumptions regarding our future performance, the time to completing an IPO or other liquidity event, and the timing of and probability of launching our product candidate as well as determinations of the appropriate valuation methods. If we had made different assumptions, our share-based compensation expense, net loss and net loss per share could have been significantly different.

We have also granted performance-based stock options with terms that allow the recipients to vest in a specific number of shares based upon the achievement of performance-based goals as specified in the grants. Share-based compensation expense associated with these performance-based stock options is recognized if the performance condition is considered probable of achievement using management's best estimates of the time to vesting for the achievement of the performance milestones. If the actual achievement of the performance milestones varies from our estimates, share-based compensation expense could be materially different than what is recorded in the period. The cumulative effect on current and prior periods of a change in the estimated time to vesting for performance-based stock options will be recognized as compensation cost in the period of the revision, and recorded as a change in estimate.

We have also granted time-accelerated stock options with terms that allow the acceleration in vesting of the stock options upon the achievement of performance-based milestones specified in the grants. Share-based compensation expense associated with these time-accelerated stock options is recognized over the requisite service period of the awards or the implied service period, if shorter.

While the assumptions used to calculate and account for share-based compensation awards represents management's best estimates, these estimates involve inherent uncertainties and the application of management's judgment. As a result, if revisions are made to our underlying assumptions and estimates, our share-based compensation expense could vary significantly from period to period.

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The total estimated compensation cost related to non-vested stock options and stock awards not yet recognized was approximately $2.2 million, $3.9 million, $6.4 million and $11.2 million as of December 31, 2006, 2007 and 2008 and September 30, 2009, respectively. The weighted-average period over which this expense is expected to be recognized is approximately 3.96 years. See Notes 2 and 15 to our consolidated financial statements located in this prospectus for further discussion of share-based compensation.

Fair Value of Financial Instruments

In September 2007, we entered into a collaboration agreement with Forest, which included a contingent equity investment in the form of a forward purchase contract, which required Forest to purchase 2,083,333 shares of our Series G convertible preferred stock at a price of $12.00 per share if we achieved a specific clinical milestone. This preferred stock, which was issued to Forest in September 2009, has rights and conditions substantially identical to our outstanding preferred stock prior to the issuance.

In April 2009, we entered into a license agreement with Almirall, which also included a contingent equity investment in the form of a forward purchase contract, which required Almirall to purchase 681,819 shares of our Series I convertible preferred stock, if a specific clinical milestone is met, at a price of $22.00 per share. The milestone in this agreement is a different milestone from the one contained in the Forest collaboration agreement. This preferred stock, which was issued to Almirall and for which we received $15.0 million of cash proceeds on November 13, 2009, has rights and conditions substantially identical to our outstanding preferred stock.

We evaluated both of these financial instruments and determined that because we may be required to settle these instruments by transferring assets to Forest and Almirall due to "deemed liquidation" provisions of the preferred stock, these instruments should be considered assets or liabilities. Each contingent equity investment was assessed at fair market value at its inception. A significant input in the valuation of the forward purchase contracts is the fair value of our convertible preferred shares which are estimated using the probability-weighted expected return method. Under the probability-weighted expected return method, the value of our convertible preferred shares is calculated based on an analysis of potential future values of our company assuming various future liquidity events, the timing and amount of which are based on estimates from our company's management. The resulting preferred share value was based on the probability-weighted present value of the expected future returns, considering each of the possible outcomes as well as the rights of each preferred share class. At each measurement date, assumptions used in the probability-weighted expected return model, including future values, liquidity dates and scenario weightings, were consistent with the assumptions used in our common stock valuations at such time, as described above. The calculated discount or premium from the pre-determined price paid by Forest and Almirall for their shares in excess of the estimated fair value of our convertible preferred stock at the expected time of meeting the respective milestone was then discounted using a company risk-adjusted rate consistent with the common stock valuations being performed at the time to arrive at the present value of the respective forward purchase contract.

At the inception of the Forest collaboration agreement, the fair value of our convertible preferred stock to be issued upon the achievement of the milestone was equal to the sum of the probability-weighted present values for the four identified possible exit scenarios initial public offering (either one-product IPO or two-product IPO or later a one-indication IPO and two-indication IPO), sale and sale at an assumed price below the liquidation preference, all with June 30, 2009 as the expected milestone achievement date. The probability weight assigned to the two-product IPO scenario was 20% and the probability weight assigned to the one-product IPO scenario was 70%. The probability weight assigned to the sale scenario was 5% and the probability weight assigned to the sale at an assumed price less than the liquidation preference scenario was 5%. The resulting enterprise values for each scenario were discounted to an estimated investment date of October 31, 2008, using a risk-adjusted discount rate of 20%. Based on this calculation, the fair value of the convertible preferred stock to be issued upon achievement of the Forest milestone was valued at $5.32 per share. The resulting difference of $6.68 per share between the fair

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value of $5.32 and the purchase price of $12.00 per share represented the estimated premium Forest would pay above the fair value of the convertible preferred stock. This per share premium was then adjusted by the probability of achieving the milestone, which was estimated at 80%, based on clinical risk, resulting in a probability adjusted premium of $5.34 per share. The resulting total premium was then discounted as of September 12, 2007 using a company risk-adjusted discount rate of 20%. As a result, the Forest contingent equity investment was valued at the inception of the agreement to be $9.0 million, which represents the fair value of the premium that Forest would pay for shares of our stock should the milestone be achieved.

The fair value of our convertible preferred stock to be issued upon the achievement of the Almirall milestone at the inception of the license agreement in April 2009 was equal to the sum of the probability-weighted present values for the four identified possible exit scenarios one-indication IPO, two-indication IPO, sale and sale at an assumed price less than the liquidation preference, all with September 30, 2010 as the expected event date. The resulting enterprise values for each scenario were discounted as of the investment date which was estimated to be October 15, 2009. Based on this calculation, the fair value of the convertible preferred stock to be issued upon achievement of the Almirall milestone was estimated at $9.23 per share. The resulting difference of $12.77 per share between the estimated fair value of $9.23 and the purchase price of $22.00 per share is the estimated premium Almirall will pay above the fair value of the convertible preferred stock. This per share premium was then adjusted by the probability of achieving the milestone, which was estimated at 75%, resulting in a probability adjusted premium of $9.58 per share. The resulting total premium was then discounted as of April 30, 2009 at 20%. As a result, the Almirall contingent equity investment was valued at the inception of the agreement to be $6.0 million, which represents the fair value of the premium that Almirall would pay for shares of our stock should the milestone be achieved.

In addition to valuing these instruments at their inception, we are also required to remeasure the fair value of our contingent equity investments at each reporting period, using current assumptions, with changes in value recorded as other income or expense. At December 31, 2007, we remeasured the fair value of the Forest contingent equity investment using valuation methodologies consistent with those used at inception, updated for current assumptions. Based on these calculations, the fair value of the convertible preferred stock to be issued upon achievement of the milestone was valued at $5.28 per share. The resulting difference of $6.72 per share was then adjusted by the probability of achieving the milestone, which was again estimated as 80%, resulting in a probability adjusted premium of $5.38 per share. The resulting total premium was then discounted as of December 31, 2007 using an appropriate risk-adjusted discount rate of 21%. As a result, the Forest contingent equity investment was valued at December 31, 2007 to be $9.6 million.

At September 30, 2008, we remeasured the fair value of the Forest contingent equity investment using valuation methodologies consistent with those used at December 31, 2007, updated for current assumptions. Based on these calculations, the fair value of the convertible preferred stock to be issued upon achievement of the Forest milestone was valued at $9.63 per share. The resulting difference of $2.37 per share was then adjusted by the probability of achieving the milestone, which was again estimated as 80%, resulting in a probability adjusted premium of $1.90 per share. The resulting total premium was then discounted as of September 30, 2008 using a risk-adjusted discount rate of 14%. As a result of these assumptions, the contingent equity investment was valued at September 30, 2008 to be $3.7 million. At December 31, 2008, we remeasured the fair value of the Forest contingent equity investment using valuation methodologies consistent with those used at September 30, 2008, updated for current assumptions. Based on these calculations, the fair value of the convertible preferred stock to be issued upon achievement of the Forest milestone was estimated at $7.16 per share. The resulting difference of $4.84 per share was then adjusted by an updated probability of achieving the milestone, which was now estimated at 90%, resulting in a probability adjusted premium of $4.35 per share. The resulting total premium was then discounted as of December 31, 2008 using a risk-adjusted discount rate of 19%. As a result, the Forest contingent equity investment was valued at December 31, 2008 to be $8.7 million.

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On July 22, 2009, we achieved the Forest milestone, thus triggering the Forest equity investment. As a result, we remeasured the fair value of the equity investment as of July 22, 2009 using valuation methodologies consistent with those used at December 31, 2008, updated for current assumptions including a change to the investment date to July 22, 2009. Based on these calculations, the fair value of the convertible preferred stock to be issued upon achievement of the Forest milestone was calculated at $7.76 per share. The resulting difference of $4.24 per share was not adjusted by a probability discount as the milestone was achieved. The resulting total premium was then discounted as of July 22, 2009 using a risk-adjusted discount rate of 20%. As a result, the Forest contingent equity investment was valued at July 22, 2009 to be $8.8 million and at that time we reclassified the forward purchase contract as a reduction to convertible preferred stock. On September 1, 2009, we received from Forest $25.0 million for the 2,083,333 shares of Series G convertible preferred stock.

At September 30, 2009, we remeasured the fair value of the Almirall contingent equity investment using valuation methodologies consistent with those used at December 31, 2008, updated for current assumptions. Based on these calculations, the fair value of the convertible preferred stock to be issued upon achievement of the Almirall milestone increased to $10.51 per share. This per share premium was then adjusted by the probability of achieving the milestone, which remained at 75%, resulting in a probability adjusted premium of $8.62 per share. The resulting total premium was then discounted as of September 30, 2009 using a risk-adjusted discount rate of 19%. As a result, the Almirall contingent equity investment was valued at September 30, 2009 to be $5.8 million.

On November 2, 2009, we achieved the Almirall milestone, thus triggering the Almirall equity investment. As a result, we remeasured the fair value of the equity investment as of November 2, 2009 using valuation methodologies consistent with those used at September 30, 2009, updated for current assumptions including a change to the investment date to November 2, 2009. Based on these calculations, the fair value of the convertible preferred stock to be issued upon achievement of the Almirall milestone was estimated at $12.41 per share. The resulting difference of $9.59 per share was not adjusted by a probability discount as the milestone was achieved. The resulting total premium was then discounted as of November 2, 2009 using a risk-adjusted discount rate of 15%. As a result, the Almirall contingent equity investment was valued at November 2, 2009 to be $6.5 million and at that time we reclassified the forward purchase contract as a reduction to convertible preferred stock and recognized in other income a $0.7 million gain on remeasurement. On November 13, 2009, we received from Almirall $15.0 million for the 681,819 shares of Series I convertible preferred stock.

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Results of Operations

The following discussion summarizes the key factors our management believes are necessary for an understanding of our consolidated financial statements.

	December 31,			Nine Months Ended September 30,	
	2006	2007	2008	2008	2009
				(unaudited)	
		(in thousands)			
Revenue:					
Collaborative arrangements	$	$ 4,608	$ 18,383	$ 13,933	$ 25,917
Services	3,140	5,856	3,833	3,309	1,581
Total revenue	3,140	10,464	22,216	17,242	27,498
Operating expenses:					
Research and development	35,543	57,246	59,809	43,309	58,824
General and administrative	7,192	10,833	18,328	13,054	17,309
Total operating expenses	42,735	68,079	78,137	56,363	76,133
Loss from operations	(39,595)	(57,615)	(55,921)	(39,121)	(48,635)
Other income (expense):					
Interest expense	(217)	(263)	(334)	(253)	(370)
Interest and investment income	2,533	4,118	2,124	1,901	214
Remeasurement of forward purchase contracts		600	(900)	(5,900)	(100)
Other income (expense), net	2,316	4,455	890	(4,252)	(256)
Loss before income tax benefit	(37,279)	(53,160)	(55,031)	(43,373)	(48,891)
Income tax benefit					(153)
Net loss	(37,279)	(53,160)	(55,031)	(43,373)	(48,738)
Net loss attributable to noncontrolling interest	99	408	1,157	726	1,483
Net loss attributable to Ironwood Pharmaceuticals, Inc.	$ (37,180)	$ (52,752)	$ (53,874)	$ (42,647)	$ (47,255)

Nine Months Ended September 30, 2009 Compared to Nine Months Ended September 30, 2008

Revenue

	Nine Months Ended September 30,		Change	
	2008	2009	$	%
	(unaudited)			
	(dollars in thousands)			
Revenue:				
Collaborative arrangements	$ 13,933	$ 25,917	$ 11,984	86.0%
Services	3,309	1,581	(1,728)	(52.2)%
Total revenue	$ 17,242	$ 27,498	$ 10,256	59.5%

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Collaborative Arrangements. The increase in revenue from collaborative arrangements for the nine months ended September 30, 2009 compared to the nine months ended September 30, 2008 was primarily due to increases in revenue from the Forest collaboration and the Almirall license agreement. During the nine month period ended September 30, 2009, we recognized approximately $8.2 million in deferred revenue related to a $20.0 million Forest milestone payment we received in July 2009, and a total of approximately $4.4 million in deferred revenue related to the $38.0 million up-front license payment received from Almirall in May 2009 and the amortization of the deferred revenue resulting from recording the initial $6.0 million valuation of the Almirall forward purchase contract. In both the nine months ended September 30, 2008 and 2009, we recognized a total of approximately $11.9 million in deferred revenue related to the amortization of the up-front license payment from Forest and the initial $9.0 million valuation of the Forest forward purchase contract. In the nine months ended September 30, 2008, we recognized approximately $2.1 million in deferred revenue related to a clinical milestone achieved in September 2008 for which we received a $10.0 million payment and, in the nine months ended September 30, 2009, we recognized approximately $1.5 million of deferred revenue related to the same milestone.

Services. Services revenue decreased primarily due to the receipt of a one-time $1.2 million payment in March 2008 as settlement of a contract dispute and the winding down of service contracts amounting to $0.4 million.

Operating Expenses

	Nine Months Ended September 30,		Change	
	2008	2009	$	%
	(unaudited)			
	(dollars in thousands)			
Operating expenses:				
Research and development	$ 43,309	$ 58,824	$ 15,515	35.8%
General and administrative	13,054	17,309	4,255	32.6%
Total operating expenses	$ 56,363	$ 76,133	$ 19,770	35.1%

Research and Development Expense. The increase in research and development expense for the nine months ended September 30, 2009 compared to the nine months ended September 30, 2008 was primarily due to an increase of $11.1 million in expenses associated with the initial Phase 3 clinical trials for linaclotide, an increase of $3.5 million in spending for compensation, benefits and other employee related expenses resulting from an increase in headcount to support our linaclotide program, and increased facilities and depreciation costs of $1.2 million associated with new research and development space.

General and Administrative Expense. The increase in general and administrative expense for the nine months ended September 30, 2009 compared to the nine months ended September 30, 2008 was primarily due to increased compensation, benefits and other employee related expenses of $3.3 million related to an increase in headcount to support our overall growth, increased facilities' costs of $0.9 million associated with new office space and increased legal costs of $0.7 million associated with intellectual property and other corporate legal matters, partially offset by a $0.4 million decrease in professional fees associated with marketing related activities.

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Other Income (Expense), Net

	Nine Months Ended September 30,		Change	
	2008	2009	$	%
	(unaudited)			
	(dollars in thousands)			
Other income (expense):				
Interest expense	$ (253)	$ (370)	$ (117)	(46.2)%
Interest and investment income	1,901	214	(1,687)	(88.7)%
Remeasurement of forward purchase contracts	(5,900)	(100)	5,800	98.3%
Total other income (expense), net	$ (4,252)	$ (256)	$ 3,996	94.0%

Interest Expense. The increase in interest expense for the nine months ended September 30, 2009 compared to the nine months ended September 30, 2008 was a result of additional borrowings in 2009 under our debt facility as well as two new capital leases that we entered into in 2008.

Interest and Investment Income. The decrease in interest and investment income for the nine months ended September 30, 2009 compared to the nine months ended September 30, 2008 was due to lower prevailing interest rates during the period combined with lower average cash and investment balances.

Remeasurement of Forward Purchase Contracts. The smaller decline in the fair value of the forward purchase contracts for the nine months ended September 30, 2009 compared to the nine months ended September 30, 2008 resulted from changes in the fair value of the Forest and Almirall forward purchase contracts at the time of remeasurement. The valuation of the Forest forward purchase contract for the nine months ended September 30, 2009 increased $0.1 million as compared to a decrease of $5.9 million for the nine months ended September 30, 2008. The large decrease in the valuation of the Forest forward purchase contract was primarily a result of an increase in the fair value of our convertible preferred stock at the time of remeasurement. This increase was driven by higher estimated enterprise values and a lower risk-adjusted interest rate assumption used in our valuation. These changes in the underlying valuation assumptions reflected the close of our Series H convertible preferred stock financing which occurred prior to the sustained deterioration of the financial markets. As a result, at September 30, 2008, the valuation of the Forest forward purchase contract decreased. The Almirall forward purchase contract valuation decreased $0.2 million in the nine months ended September 30, 2009 without a corresponding change in the nine months ended September 30, 2008 as we entered into the license agreement with Almirall in April 2009.

Income Tax Benefit. The $0.2 million increase in income tax benefit for the nine months ended September 30, 2009 was related to a refundable research and development tax credit which we received in October 2009.

Net Loss Attributable to Noncontrolling Interest. The $0.8 million increase in net loss attributable to noncontrolling interest was due to the larger net loss for Microbia as a result of lower revenue and increased expenses during the nine months ended September 30, 2009 compared to the nine months ended September 30, 2008.

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Year Ended December 31, 2008 Compared to Year Ended December 31, 2007

Revenue

	Years Ended December 31,		Change	
	2007	2008	$	%
	(dollars in thousands)			
Revenue:				
Collaborative arrangements	$ 4,608	$ 18,383	$ 13,775	298.9%
Services	5,856	3,833	(2,023)	(34.6)%
Total revenue	$ 10,464	$ 22,216	$ 11,752	112.3%

Collaborative Arrangements. The increase in revenue from collaborative arrangements for the year ended December 31, 2008 compared to the year ended December 31, 2007 was due to the amortization of $11.2 million of deferred revenue from the Forest up-front license payment and the amortization of the deferred revenue related to the initial $9.0 million valuation of the Forest forward purchase contract over the estimated development period. In the year ended December 31, 2007 we recognized a total of approximately $4.6 million of deferred revenue related to the Forest up-front license payment and the amortization of the initial valuation of the Forest forward purchase contract as compared to a total of approximately $15.8 million in the year ended December 31, 2008. Additionally, in September 2008 we achieved a clinical milestone under the Forest collaboration agreement and recognized revenue of $2.6 million related to the milestone.

Services. The decrease in services revenue for the year ended December 31, 2008 compared to the year ended December 31, 2007 was primarily due to the winding down of service contracts amounting to $3.2 million which was partially offset by the receipt of a one-time $1.2 million payment in March 2008 as settlement of a contract dispute.

Operating Expenses

	Years Ended December 31,		Change	
	2007	2008	$	%
	(dollars in thousands)			
Operating expenses:				
Research and development	$ 57,246	$ 59,809	$ 2,563	4.5%
General and administrative	10,833	18,328	7,495	69.2%
Total operating expenses	$ 68,079	$ 78,137	$ 10,058	14.8%

Research and Development Expense. The increase in research and development expense for the year ended December 31, 2008 compared to the year ended December 31, 2007 was primarily a result of increased compensation, benefits and other employee related expenses of $5.8 million related to the hiring of additional employees to support the linaclotide program; increased facility costs of $9.0 million due to the expansion of our research facility in 2008; and a $12.6 million credit to research and development expense due to a full year of reimbursement of costs under the Forest collaboration agreement for the year ended December 31, 2008 as compared to approximately three months for the year ended December 31, 2007.

General and Administrative Expense. The increase in general and administrative expense for the year ended December 31, 2008 compared to the year ended December 31, 2007 was primarily a result of increased compensation, benefits and other employee related expenses of $4.9 million resulting from an increase in headcount to support our overall growth; increased consulting costs of $1.3 million related to our pre-commercialization activities; and increased facility costs of $1.3 million associated with the additional office space we leased in 2008.

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Other Income (Expense), Net

	Years Ended December 31,		Change	
	2007	2008	$	%
	(dollars in thousands)			
Other income (expense):				
Interest expense	$ (263)	$ (334)	$ (71)	(27.0)%
Interest and investment income	4,118	2,124	(1,994)	(48.4)%
Remeasurement of forward purchase contracts	600	(900)	(1,500)	(250.0)%
Total other income (expense), net	$ 4,455	$ 890	$ (3,565)	(80.0)%

Interest Expense. The increase in interest expense for the year ended December 31, 2008 compared to the year ended December 31, 2007 was a result of additional borrowings under our debt facility in 2008 as well as entering into two new capital leases.

Interest and Investment Income. The decrease in interest and investment income for the year ended December 31, 2008 compared to the year ended December 31, 2007 was due to lower prevailing interest rates during 2008 partially offset by higher average cash and investment balances resulting from the cash received under the Forest collaboration agreement.

Remeasurement of Forward Purchase Contracts. The decrease in the valuation of the Forest forward purchase contract for the year ended December 31, 2008 compared to December 31, 2007 resulted from change in the fair value of the Forest forward purchase contract at the time of remeasurement related to changes in the underlying valuation assumptions including, but not limited to, the clinical status of linaclotide, our enterprise values, timing and likelihood of the different liquidity events and the appropriate risk-adjusted discount rate.

Net Loss Attributable to Noncontrolling Interest. The increase of $0.7 million in net loss attributable to noncontrolling interest was a result of a larger net loss for Microbia as a result of lower revenue and increased expenses for the year ended December 31, 2008 compared to the year ended December 31, 2007.

Year Ended December 31, 2007 Compared to Year Ended December 31, 2006

Revenue

	Years Ended December 31,		Change	
	2006	2007	$	%
	(dollars in thousands)			
Revenue:				
Collaborative arrangements	$	$ 4,608	$ 4,608	100.0%
Services	3,140	5,856	2,716	86.5%
Total revenue	$ 3,140	$ 10,464	$ 7,324	233.3%

Collaborative Arrangements. The increase in revenue from collaborative arrangements for the year ended December 31, 2007 compared to the year ended December 31, 2006 resulted from the recognition of a total of $4.6 million of deferred revenue related to the amortization of the initial $9.0 million valuation of the Forest forward purchase contract and the $70.0 million up-front license payment received from Forest.

Services. The increase in services revenue for the year ended December 31, 2007 compared to the year ended December 31, 2006 resulted from additional services under existing contracts.

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Operating Expenses

	Years Ended December 31,		Change	
	2006	2007	$	%
	(dollars in thousands)			
Operating expenses:				
Research and development	$ 35,543	$ 57,246	$ 21,703	61.1%
General and administrative	7,192	10,833	3,641	50.6%
Total operating expenses	$ 42,735	$ 68,079	$ 25,344	59.3%

Research and Development Expense. The increase in research and development expense for the year ended December 31, 2007 compared to the year ended December 31, 2006 was primarily a result of increased compensation, benefits and other employee related expenses of $5.3 million related to the hiring of additional employees to support the linaclotide program; an increase of $19.9 million in spending related to our Phase 2 linaclotide trials; and increased facility costs of $1.3 million related to additional research and development space leased in October 2006. These increases were partially offset by $5.0 million for reimbursable research costs shared with Forest in accordance with the Forest collaboration agreement executed in 2007.

General and Administrative Expense. The increase in general and administrative expense for the year ended December 31, 2007 compared to the year ended December 31, 2006 was primarily a result of increased consulting costs of $1.2 million related to our pre-commercialization activities; increased legal costs of $0.9 million primarily for patent related work; and other general and administrative costs of $1.0 million related to the development of our administrative infrastructure.

Other Income (Expense), Net

	Years Ended December 31,		Change	
	2006	2007	$	%
	(dollars in thousands)			
Other income (expense):				
Interest expense	$ (217)	$ (263)	$ (46)	(21.2)%
Interest and investment income	2,533	4,118	1,585	62.6%
Remeasurement of forward purchase contracts		600	600	100.0%
Total other income (expense), net	$ 2,316	$ 4,455	$ 2,139	92.4%

Interest Expense. The increase in interest for the year ended December 31, 2007 compared to the year ended December 31, 2006 was primarily a result of additional borrowings under our debt facility.

Interest and Investment Income. The increase in interest and investment income for the year ended December 31, 2007 compared to the year ended December 31, 2006 was primarily related to higher average cash, cash equivalents and investment balances resulting from the sale in February 2007 of 8.0 million shares of our Series F convertible preferred stock at a per share price of $6.25 from which we received approximately $50.0 million of net proceeds.

Remeasurement of Forward Purchase Contracts. The increase in the valuation of the Forest forward purchase contract for the year ended December 31, 2007 compared to the year ended December 31, 2006 resulted from change in the fair value of the Forest forward purchase contract at the time of remeasurement related to changes in the underlying valuation assumptions including, but not limited to,

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the clinical status of linaclotide, our enterprise values, timing and likelihood of the different liquidity events and the appropriate risk adjusted discount rate.

Net Loss Attributable to Noncontrolling Interest. The increase of $0.3 million in the loss attributable to noncontrolling interest was primarily a result of twelve months of losses in 2007 compared to four months of losses in 2006 since Microbia was not created until September 2006.

Liquidity and Capital Resources

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

	December 31,			Nine Months Ended September 30,	
	2006	2007	2008	2008	2009
				(unaudited)	
			(in thousands)		
Net cash provided by (used in):					
Operating activities	$ (33,532)	$ (6,759)	$ (28,195)	$ (16,466)	$ (14,249)
Investing activities	(5,615)	(27,609)	(15,073)	(12,026)	965
Financing activities	80,090	50,718	48,563	49,465	26,831
Net increase in cash and cash equivalents	$ 40,943	$ 16,350	$ 5,295	$ 20,973	$ 13,547

We have incurred losses since our inception on January 5, 1998 and, as of September 30, 2009, we had a cumulative deficit of approximately $290.6 million. We have financed our operations to date primarily through the sale of preferred stock and common stock, payments received under collaborative arrangements, including reimbursement of certain expenses, debt financings and interest earned on investments. Through September 30, 2009, we have received aggregate gross proceeds of approximately $322.2 million from financings, of which approximately $306.1 million was from the issuance of preferred stock, approximately $1.0 million was from the issuance of common stock and approximately $15.1 million was from debt financings. Through September 30, 2009, we have received aggregate gross proceeds of approximately $138.0 million from up-front licensing and milestone payments. At September 30, 2009, we had $98.9 million of cash, cash equivalents and available-for-sale securities. Our cash and cash equivalents include amounts held in money market funds, stated at cost plus accrued interest, which approximates fair market value. We invest cash in excess of immediate requirements in accordance with our investment policy which limits the amounts we may invest in any one type of investment and requires all investments held by us to be A+ rated so as to primarily achieve liquidity and capital preservation.

On November 13, 2009, as a result of achieving a clinical milestone under the Almirall license agreement, we received cash proceeds of approximately $15.0 million from the sale of 681,819 shares of our Series I convertible preferred stock at a price of $22.00 per share to Almirall. On a pro forma basis, after giving effect to the license fee from Astellas and the equity investment by Almirall, at September 30, 2009, we have $143.9 million of cash, cash equivalents and available-for-sale securities.

Cash Flows From Operating Activities

The decrease of $2.2 million in net cash used in operations for the nine months ended September 30, 2009 compared to the nine months ended September 30, 2008 was primarily associated with an increase of $9.1 million in the net changes in working capital relating to operations, partially offset by an increase in the net loss of $5.4 million combined with an increase of $1.6 million in the change in non-cash items such as depreciation, share-based compensation expense, remeasurement of the forward purchase contracts and accretion of the discount/premium on investment securities. The net change in working capital items relating to operations between the nine months ended September 30, 2009 and the nine months ended

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September 30, 2008 was primarily due to the receipt in the nine months ended September 30, 2009 of a $38.0 million up-front payment from Almirall and a $20.0 million milestone payment from Forest compared to the receipt in the nine months ended September 30, 2008 of a $20.0 million up-front license fee from Forest, a $10.0 million milestone payment from Forest, as well as $4.6 million in cash reimbursements for tenant improvements which were recorded as deferred rent.

Net cash used in operations for the year ended December 31, 2008 compared to the year ended December 31, 2007 increased by $21.4 million. This increase was primarily the result of a $1.9 million increase in the net loss, a $5.0 million increase in non-cash items such as depreciation, share-based compensation expense, remeasurement of the forward purchase contract and accretion of the discount/premium on investment securities and a $24.6 million decrease in net changes in working capital items relating to operations. The net changes in working capital items were primarily driven by cash receipts and the recognition of deferred revenue under the Forest collaboration agreement as well as cash reimbursements for tenant improvements which were recorded as deferred rent.

Net cash used in operations for the year ended December 31, 2007 compared to the year ended December 31, 2006 decreased by $26.8 million. This change was primarily a result of a $43.1 million increase in net changes in working capital items relating to operations. The net changes in working capital items were primarily driven by the receipt of the Forest up-front license payment and the recognition of deferred revenue under the Forest collaboration agreement. This was partially offset by a $15.9 million increase in the net loss and a $0.4 million decrease in non-cash items such as depreciation, remeasurement of the forward purchase contract, share-based compensation expense and accretion of the discount/premium on investment securities.

Cash Flows From Investing Activities

The increase of $13.0 million in net cash provided by investing activities for the nine months ended September 30, 2009 compared to the nine months ended September 30, 2008 was primarily the result of $13.4 million less cash used for the purchase of property and equipment and $35.9 million less cash used for the purchase of investments, partially offset by a $36.4 million decrease in the cash received from the sales and maturities of investments.

Net cash used in investing activities decreased by $12.5 million for the year ended December 31, 2008 compared to the year ended December 31, 2007. This decrease was primarily a result of a $27.6 million increase in cash received from the sales and maturities of investments and a $5.2 million decrease in the cash used for the purchase of investments; offset by a $20.3 million increase in purchases of property and equipment primarily related to the leasehold improvements for our new facility and the purchase of laboratory equipment for the new facility.

Net cash used in investing activities increased by $22.0 million for the year ended December 31, 2007 compared to the year ended December 31, 2006. This increase in cash used for investing activities was primarily a result of a $50.8 million increase in purchases of investments; offset by a $28.7 million increase in cash received from the sales and maturities of investments and a $0.2 million decrease in purchases of property and equipment.

Cash Flows From Financing Activities

The decrease of $22.6 million in net cash provided by financing activities for the nine months ended September 30, 2009 compared to the nine months ended September 30, 2008 was primarily due to lower proceeds from the sale of our convertible preferred stock, partially offset by higher proceeds from borrowings on our debt facility, net of payments made. During the nine months ended September 30, 2008 we received $49.6 million of proceeds from the sale of 4,141,586 shares of our Series H convertible preferred stock while in the nine months ended September 30, 2009 we received $25.0 million of proceeds from the sale of 2,083,333 shares of our Series G convertible preferred stock to Forest.

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Net cash provided by financing activities decreased by $2.2 million for the year ended December 31, 2008 compared to the year ended December 31, 2007. This decrease was primarily the result of a $1.2 million decrease in borrowings in 2008 and a $0.8 million increase in payments on borrowings. Additionally, there was a decrease of $0.4 million in the cash received from the issuance of Series H convertible preferred stock in 2008 compared to the issuance of Series F convertible preferred stock in 2007.

Net cash provided by financing activities decreased by $29.4 million for the year ended December 31, 2007 compared to the year ended December 31, 2006. This decrease was primarily a result of a $25.0 million decrease in proceeds from the issuance of our Series F convertible preferred stock offering in 2007 compared to the proceeds of our Series E convertible preferred stock offering in 2006, a $7.0 million decrease in capital contributions from noncontrolling interest in 2006 and a $0.3 million decrease in proceeds from borrowings, offset by a $3.0 million decrease in payments on borrowings.

Funding Requirements

To date, we have not commercialized any products and have not achieved profitability. We anticipate that we will continue to incur substantial net losses for the next several years as we further develop and prepare for the potential commercial launch of linaclotide, continue to invest in our pipeline, develop the organization required to sell our product candidates and operate as a publicly traded company.

We have generated revenue from services, up-front license fees and milestones, but have not generated any product revenue since our inception and do not expect to generate any product revenue from our collaborative arrangements or the sale of products unless we receive regulatory approval for commercial sale of linaclotide. We believe the net proceeds from this offering, together with our existing cash, cash equivalents and investment balances, interest income we earn on these balances, and amounts we expect to receive from our collaborators under existing contractual obligations will be sufficient to meet our anticipated cash requirements to complete development and commercialize linaclotide with our partner Forest for the U.S. market, and to fund our currently contemplated research and development efforts for at least the next five years, based on our current business plan. However, it is difficult to predict the actual rate of product sales and related collaborative arrangement revenue until the product is approved by the FDA and the specific language allowed by the FDA on the label is known. If our available cash, cash equivalents and investment balances, net proceeds from this offering, and amounts we expect to receive from our collaborators are insufficient to satisfy our liquidity requirements or if sales are less than anticipated, we may seek to sell additional equity or debt securities or secure new collaborative agreements. The sale of additional equity may result in dilution to our stockholders. If we raise additional funds through the issuance of debt securities, these securities would have rights senior to those of our common stock and could contain covenants that would restrict our operations. Any required additional capital may not be available on reasonable terms, if at all. If we are unable to obtain additional financing, we may be required to reduce the scope of, delay, or eliminate some or all of, our planned research, development and commercialization activities, or attempt to obtain funds through arrangements that may require us to relinquish rights to certain of our technologies or drug candidates, which could materially harm our business.

Our forecast of the period of time through which our financial resources will be adequate to support our operations, the costs to obtain regulatory approval, and the costs to commercialize our product candidates are forward-looking statements and involve risks and uncertainties, and actual results could vary materially and negatively as a result of a number of factors, including the factors discussed in the "Risk Factors" section of this prospectus. We have based these estimates on assumptions that may prove to be wrong, and we could utilize our available capital resources sooner than we currently expect.

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Due to the numerous risks and uncertainties associated with the development of our products, we are unable to estimate precisely the amounts of capital outlays and operating expenditures necessary to complete the development of, and to obtain regulatory approval for, linaclotide and our other product candidates for all of the indications for which we believe each product candidate is suited. Our funding requirements will depend on many factors, including, but not limited to, the following:

- the time and costs involved in obtaining regulatory approvals for our product candidates;
- the rate of progress and cost of our commercialization activities;
- the success of our research and development efforts;
- the expenses we incur in marketing and selling our product candidates;
- the revenue generated by sales of our product candidates;
- the emergence of competing or complementary technological developments;
- the costs of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights;
- the terms and timing of any additional collaborative, licensing or other arrangements that we may establish; and
- the acquisition of businesses, products and technologies (although we currently have no commitments or agreements relating to any of these types of transactions).

Contractual Commitments and Obligations

Under our collaborative agreement with Forest, we share equally with Forest all development and commercialization costs related to linaclotide in the U.S. The actual amounts that we pay Forest will depend on numerous factors outside of our control, including the success of our clinical development efforts with respect to linaclotide, the content and timing of decisions made by the FDA, the reimbursement and competitive landscape around linaclotide and our other product candidates, and other factors described under the heading "Risk Factors."

Our most significant clinical trial expenditures are to CROs. The contracts with CROs generally are cancellable, with notice, at our option and do not have any cancellation penalties. These items are not included in the table below.

The following table summarizes our contractual obligations at December 31, 2008 (excluding interest).

	Payments Due by Period				
	Total	Less Than 1 Year	1 3 Years	3 5 Years	More Than 5 Years
	(in thousands)				
Long-term debt	$ 1,815	$ 943	$ 872	$	$
Capital lease obligations	306	117	189		
Operating lease obligations	60,322	8,769	20,053	16,691	14,809
Total contractual obligations	$ 62,443	$ 9,829	$ 21,114	$ 16,691	$ 14,809

As of September 30, 2009, we did not incur any additional obligations that materially change the disclosure of our contractual obligations as shown in the table above.

Our commitment for long-term debt relates to our master loan agreement for the financing of purchases of laboratory and other equipment. As of December 31, 2008, there were no funds available under the master loan agreement to finance future equipment purchases. Not shown in the table above are

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commitments related to a new master loan and security agreement entered into in January 2009 with the same financing company that provided the prior financing to purchase our laboratory, computer, and other equipment. The new master loan and security agreement provides us up to $6.0 million of available funding through December of 2009. At September 30, 2009, approximately $2.6 million of borrowings have been made under the new master loan and security agreement. Borrowings under the new master loan and security agreement are being repaid with interest over periods of either 36 or 48 months. The new master loan and security agreement requires interest and principal payable in monthly installments on the outstanding borrowings ranging from $2,000 to $27,000 through July 2013. Outstanding borrowings under the new master loan and security agreement bear interest at a fixed rate of 12.5% for the duration of the term, and are collateralized by the laboratory and other equipment. At September 30, 2009, approximately $3.4 million was outstanding under all loan and security agreements.

Our commitment for capital lease obligations relates to leased computer equipment.

Our commitments for operating leases relate to our lease of office and laboratory space in Cambridge, Massachusetts and Microbia's office and laboratory space in Lexington, Massachusetts.

Related Party Transactions

We have and currently obtain legal services from a law firm that is an investor of ours. We paid approximately $0.3 million, $0.1 million, $0.1 million, $0.1 million and $0 in legal fees to this investor during the years ended December 31, 2006, 2007 and 2008 and the nine months ended September 30, 2008 and 2009, respectively.

In September 2006, Tate & Lyle Investments, Ltd. ("T&L") became a related party when we sold to them 1,823,529 shares of common stock of Microbia at the aggregate purchase price of approximately $2,000, and sold 7,000,000 shares of convertible preferred stock of Microbia at the aggregate purchase price of $7.0 million. T&L accounted for approximately 7%, 29%, 10%, 10% and 6% of our revenue for the years ended December 31, 2006, 2007 and 2008 and for the nine months ended September 30, 2008 and 2009, respectively.

In September 2009, Forest became a related party when we sold to them 2,083,333 shares of our convertible preferred stock at a price of $12.00 per share for cash proceeds of $25.0 million. Forest accounted for approximately 0%, 44%, 83%, 81% and 78% of our revenue for the years ended December 31, 2006, 2007 and 2008 and for the nine months ended September 30, 2008 and 2009, respectively.

In November 2009, Almirall became a related party when we sold to them 681,819 shares of our convertible preferred stock at a price of $22.00 per share for cash proceeds of $15.0 million. Almirall accounted for approximately 16% of our revenue for the nine months ended September 30, 2009.

Off-Balance Sheet Arrangements

We do not have any relationships with unconsolidated entities or financial partnerships, such as entities often referred to as structured finance or special purpose entities, that would have been established for the purpose of facilitating off-balance sheet arrangements (as that term is defined in Item 303(a)(4)(ii) of Regulation S-K) or other contractually narrow or limited purposes. As such, we are not exposed to any financing, liquidity, market or credit risk that could arise if we had engaged in those types of relationships. We enter into guarantees in the ordinary course of business related to the guarantee of our own performance and the performance of our subsidiaries.

New Accounting Pronouncements

From time to time, new accounting pronouncements are issued by the Financial Accounting Standards Board, or FASB, or other standard setting bodies that are adopted by us as of the specified effective date.

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Unless otherwise discussed, we believe that the impact of recently issued standards that are not yet effective will not have a material impact on our consolidated financial position or results of operations upon adoption.

Recently Issued Accounting Standards

In August 2009, the FASB issued Accounting Standards Update No. 2009-05, *Measuring Liabilities at Fair Value*, or ASU 2009-05. ASU 2009-05 amends Accounting Standards Codification Topic 820, *Fair Value Measurements*. Specifically, ASU 2009-05 provides clarification that in circumstances in which a quoted price in an active market for the identical liability is not available, a reporting entity is required to measure fair value using one or more of the following methods: (1) a valuation technique that uses (a) the quoted price of the identical liability when traded as an asset or (b) quoted prices for similar liabilities or similar liabilities when traded as assets and/or (2) a valuation technique that is consistent with the principles of Topic 820 of the Accounting Standards Codification, or Codification, (e.g. an income approach or market approach). ASU 2009-05 also clarifies that when estimating the fair value of a liability, a reporting entity is not required to adjust to include inputs relating to the existence of transfer restrictions on that liability. The adoption of this standard did not have an impact on our financial position or results of operations.

In October 2009, the FASB issued ASU No. 2009-13, *Multiple-Deliverable Revenue Arrangements*, or ASU 2009-13. ASU 2009-13, amends existing revenue recognition accounting pronouncements that are currently within the scope of FASB Accounting Standards Codification, or ASC, Subtopic 605-25 (previously included within EITF 00-21, *Revenue Arrangements with Multiple Deliverables*, or EITF 00-21). The consensus to ASU 2009-13 provides accounting principles and application guidance on whether multiple deliverables exist, how the arrangement should be separated, and the consideration allocated. This guidance eliminates the requirement to establish the fair value of undelivered products and services and instead provides for separate revenue recognition based upon management's estimate of the selling price for an undelivered item when there is no other means to determine the fair value of that undelivered item. EITF 00-21 previously required that the fair value of the undelivered item be the price of the item either sold in a separate transaction between unrelated third parties or the price charged for each item when the item is sold separately by the vendor. This was difficult to determine when the product was not individually sold because of its unique features. Under EITF 00-21, if the fair value of all of the elements in the arrangement was not determinable, then revenue was deferred until all of the items were delivered or fair value was determined. This new approach is effective prospectively for revenue arrangements entered into or materially modified in fiscal years beginning on or after June 15, 2010 and allows for retroactive application. We are currently evaluating the potential impact of this standard on our financial position and results of operations.

Recently Adopted Accounting Standards

Effective January 1, 2009, we adopted new accounting guidance related to accounting for uncertainty in income taxes. This accounting standard clarifies the recognition threshold and measurement attribute for the financial statement recognition and measurement of a tax position taken or expected to be taken in a tax return. This accounting standard also provides guidance on recognition, classification, interest and penalties, accounting in interim periods, disclosure and transition. We have not identified any material uncertain tax positions for which reserves would be required and the adoption of this accounting standard did not have an effect on our consolidated financial statements.

Effective January 1, 2009, we adopted a newly issued accounting standard for business combinations. This standard requires an acquiring company to measure all assets acquired and liabilities assumed, including contingent considerations and all contractual contingencies, at fair value as of the acquisition date. In addition, an acquiring company is required to capitalize in-process research and development and either amortize it over the life of the product, or write it off if the project is abandoned or impaired. This guidance is applicable to acquisitions completed after January 1, 2009 and as we did not have any business

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combinations in the first nine months of 2009, the adoption did not impact our financial position or results of operations. The standard also amended accounting for uncertainty in income taxes as required by the *Income Tax* Topic of the Codification. Previously, accounting standards generally required post-acquisition adjustments related to business combination deferred tax asset valuation allowances and liabilities for uncertain tax positions to be recorded as an increase or decrease to goodwill. This new standard does not permit this accounting and, generally, requires any such changes to be recorded in current period income tax expense. Thus, all changes to valuation allowances and liabilities for uncertain tax positions established in acquisition accounting, whether the business combination was accounted for under this guidance, will be recognized in current period income tax expense.

Effective January 1, 2009, we adopted new guidance for the accounting, reporting and disclosure of noncontrolling interests which requires, among other things, that noncontrolling interests be recorded as equity in the consolidated financial statements. The adoption of this new guidance resulted in the reclassification of noncontrolling interests (previously referred to as minority interests) to a separate component of stockholders' equity (deficit) on the consolidated balance sheet. Additionally, net loss attributable to noncontrolling interests is now shown separately from parent net loss in the consolidated statement of operations. Prior periods have been restated to reflect the presentation and disclosure requirements of the new guidance. Refer to Note 2, *Summary of Significant Accounting Policies* of this Form S-1 for additional information on the adoption of the new accounting standard for noncontrolling interests.

In April, 2009, the FASB issued a new accounting standard providing guidance for the accounting of assets acquired and liabilities assumed in a business combination that arise from contingencies. This guidance amends and clarifies previous accounting standards to address application issues regarding the initial recognition and measurement, subsequent measurement and accounting, and disclosure of assets and liabilities arising from contingencies in a business combination. This guidance is applicable to acquisitions completed after January 1, 2009. As we did not have any business combinations in the first nine months of 2009, the adoption did not impact our financial position or results of operations.

In May 2009, the FASB established general standards of accounting for and disclosures of events that occur after the balance sheet date but before financial statements are issued or are available to be issued. It requires the disclosure of the date through which an entity has evaluated subsequent events and the basis for selecting that date, that is, whether that date represents the date the financial statements were issued or were available to be issued. Our adoption of these standards had no material impact on our financial position, results of operations and cash flows.

Quantitative and Qualitative Disclosures about Market Risk

Interest Rate Risk

We are exposed to market risk related to changes in interest rates. We invest our cash in a variety of financial instruments, principally deposits, securities issued by the U.S. government and its agencies and money market instruments. The goals of our investment policy are preservation of capital, fulfillment of liquidity needs and fiduciary control of cash and investments. We also seek to maximize income from our investments without assuming significant risk.

Our primary exposure to market risk is interest income sensitivity, which is affected by changes in the general level of interest rates, particularly because our investments are in short-term marketable securities. Due to the short-term duration of our investment portfolio and the low risk profile of our investments, an immediate 10% 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.

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Recently, there has been concern in the credit markets regarding the value of a variety of mortgage-backed and auction rate securities and the resulting effect on various securities markets. We do not currently have any auction rate securities. We do not believe our cash, cash equivalents and available-for-sale investments have significant risk of default or illiquidity. While we believe our cash, cash equivalents and available-for-sale investments 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. Given the current instability of financial institutions, we cannot be assured that we will not experience losses on these deposits.

Our long-term debt and capital lease obligations bear interest at a fixed rate and therefore have minimal exposure to changes in interest rates.

Foreign Currency Risk

We have no operations outside the U.S. and do not have any foreign currency or other derivative financial instruments.

Effects of Inflation

We do not believe that inflation and changing prices over the years ended December 31, 2007 and 2008 had a significant impact on our results of operations.

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BUSINESS

Our Company

We are an entrepreneurial pharmaceutical company that discovers, develops and intends to commercialize innovative medicines targeting important therapeutic needs. Our goal is to build the next great pharmaceutical company, an outstanding business that will thrive and endure well beyond our lifetimes and generate substantial returns for our shareholders. In order to be successful, we will need to overcome the enormous challenges inherent in the pharmaceutical product development model. Developing a novel therapeutic agent can take a decade or more and cost hundreds of millions of dollars, and most drug candidates fail to reach the market. We recognize that most companies undertaking this endeavor fail, yet despite the significant risks and our own experiences with multiple failed drug candidates, we are enthusiastic and passionate about our mission to deliver differentiated medicines to patients. To achieve our mission, we are building a sustainable culture centered on creating and marketing important new drugs. If we are successful, we plan to reinvest a portion of our future cash flows into our research and development organization in order to accelerate and enhance our ability to bring new products to market. Our experienced team of researchers is currently focused on a portfolio of internally discovered drug candidates that includes one Phase 3 drug candidate (linaclotide), one Phase 1 pain drug candidate, and multiple preclinical programs.

We believe that linaclotide could present patients and healthcare practitioners with a unique therapy for a major medical need not yet met by existing therapies. Linaclotide is a first-in-class compound currently in confirmatory Phase 3 clinical trials evaluating its safety and efficacy for the treatment of patients with irritable bowel syndrome with constipation (IBS-C) or chronic constipation (CC). IBS-C and CC are gastrointestinal disorders that affect millions of sufferers worldwide, according to our analysis of studies performed by N.J. Talley (published in 1995 in the *American Journal of Epidemiology*), P.D.R. Higgins (published in 2004 in the *American Journal of Gastroenterology*) and A.P.S. Hungin (published in 2003 in *Alimentary Pharmacology and Therapeutics*) as well as 2007 U.S. census data. Linaclotide recently achieved favorable efficacy and safety results in two Phase 3 CC trials, meeting all 32 primary and secondary endpoints, including the improvement of abdominal symptoms such as bloating and discomfort as well as constipation symptoms, across both doses evaluated in these independent trials involving 1,287 subjects. We expect to have data from our Phase 3 IBS-C trials in the second half of 2010. If those trials are successful, we intend to file a New Drug Application, or NDA, with the Food and Drug Administration, or FDA, in the first half of 2011, seeking approval to market linaclotide to IBS-C and CC patients age 18 and older in the U.S. If linaclotide is approved for those indications, we may seek to expand linaclotide's market opportunity by exploring its utility in other gastrointestinal indications and in the pediatric population.

Linaclotide was designed by Ironwood scientists to target the defining attributes of IBS-C: abdominal pain, discomfort, bloating and constipation. Linaclotide acts locally in the gut with no detectable systemic exposure in humans at therapeutic doses. In the six Phase 2 and Phase 3 clinical trials we have completed to date in over 2,000 IBS-C and CC patients, linaclotide has demonstrated rapid and sustained improvement of the multiple symptoms of IBS-C and CC, with good tolerability and convenient once-daily oral dosing.

In a Phase 2b study in patients with IBS-C, linaclotide rapidly reduced abdominal pain, abdominal discomfort and bloating, and improved constipation symptoms, throughout the 12-week treatment period of the trial, with improvements noted for all symptoms assessed within the first week of initiation of therapy. In particular, abdominal pain was reduced 37% to 47%, and pain reduction was observed within the first week following initiation of therapy and was sustained throughout the treatment period, even among patients with severe or very severe abdominal pain.

In a Phase 2b study in patients with CC, linaclotide rapidly reduced abdominal discomfort and bloating, and improved constipation symptoms, throughout the 4-week treatment period of the trial.

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In five of the six Phase 2 and Phase 3 studies, diarrhea was the most common adverse event (seen in 5% to 20% of subjects), and the most common cause for discontinuation in 1% to 7% of the patients in the trials. Diarrhea has generally been mild to moderate.

We have pursued a partnering strategy for commercializing linaclotide that has enabled us to retain significant control over linaclotide's development and commercialization, share the costs with high-quality collaborators whose capabilities complement ours, and retain approximately half of linaclotide's future long-term value in the major pharmaceutical markets, should linaclotide meet our sales expectations. To date, licensing fees, milestone payments, related equity investments and development costs received from our linaclotide partners total greater than $250 million.

In September 2007, we entered into a partnership with Forest Laboratories, Inc., or Forest, to co-develop and co-market linaclotide in the U.S. Under the terms of the collaboration agreement, we and Forest are jointly and equally funding the development and commercialization of linaclotide in the U.S., with equal share of any profits. Forest also has exclusive rights to develop and commercialize linaclotide in Canada and Mexico, and will pay us royalties in the mid-teens on any net sales in these countries. In addition to having reimbursed us for half of linaclotide's development costs since September 2007, Forest has paid us $100 million in license fees and milestone payments to date and has purchased $25 million of our convertible preferred stock pursuant to the collaboration agreement. Remaining pre-commercial milestone payments could total up to $105 million. If linaclotide is successfully developed and commercialized in the U.S., total licensing, milestone payments and related equity investments to us under the Forest collaboration agreement could total up to $330 million, including the $125 million that has already been paid to us. Unless terminated by either us or Forest for material breach, violation of law, bankruptcy or certain adverse changes of control of the other party, or by Forest for convenience, the collaboration agreement will continue in full force and effect with respect to each of the U.S., Canada and Mexico as long as we and Forest are developing or commercializing a product under the agreement.

In April 2009, we entered into a license agreement with Almirall, S.A., or Almirall, to develop and commercialize linaclotide in Europe (including the Commonwealth of Independent States countries and Turkey) for the treatment of IBS-C and other gastrointestinal conditions. Under the terms of the license agreement, Almirall has paid us $38 million in license fees and milestone payments and has purchased $15 million of our convertible preferred stock. Remaining pre-commercial milestone payments could total up to $40 million. Almirall is responsible for activities and expenses relating to regulatory approval and commercialization in the European market. If Almirall receives approval to market and sell linaclotide in Europe, we will receive gross royalties which escalate based on sales volume in the territory, beginning in the mid-twenties, less the transfer price paid for the active pharmaceutical ingredient. Unless terminated by either us or Almirall for material breach, violation of law or bankruptcy, by Almirall for convenience, or by us in the event of an adverse change of control of Almirall, the license agreement will continue in full force and effect on a country-by-country basis until Almirall is no longer developing or commercializing linaclotide in such country.

In November 2009, we entered into a license agreement with Astellas Pharma Inc., or Astellas, to develop and commercialize linaclotide for the treatment of IBS-C and other gastrointestinal conditions in Japan, South Korea, Taiwan, Thailand, the Philippines and Indonesia. Under the terms of the license agreement, Astellas paid us a $30 million up-front licensing fee. Remaining pre-commercial milestone payments could total up to $45 million. Astellas is responsible for activities and expenses relating to regulatory approval and commercialization in those markets. If Astellas receives approval to market and sell linaclotide, we will receive gross royalties which escalate based on sales volume in the territory, beginning in the low-twenties, less the transfer price paid for the active pharmaceutical ingredient. Unless terminated in all or certain countries by either us or Astellas for material breach or bankruptcy, by Astellas for convenience, or by us in the event of an adverse change of control of Astellas, the license agreement will continue in full force and effect until the later of (a) the last-to-expire valid claim of our patent rights for linaclotide in the countries listed above has expired or (b) Astellas is no longer developing or commercializing linaclotide in all of the countries listed above.

We have retained all rights to linaclotide outside of the territories discussed above.

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In addition to five years of exclusivity under the Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Act, that would be granted if linaclotide is approved by the FDA, linaclotide is covered by a U.S. composition of matter patent that expires in 2025, subject to possible patent term extension. Linaclotide is also covered by an European Union composition of matter patent that expires in 2024, subject to possible patent term extension. A patent application is pending in Japan, and if issued, would expire in 2024.

We have multiple product candidates in earlier stages of development and are pursuing various therapeutic opportunities. We invest carefully in our pipeline, and the commitment of funding for each subsequent stage of our development programs is dependent upon the receipt of clear, positive data. In addition to linaclotide, our other clinical stage candidate is IW-6118, an inhibitor of Fatty Acid Amide Hydrolase, or FAAH, being evaluated for the treatment of pain and inflammation. In a Phase 1 study, IW-6118 demonstrated favorable pharmacokinetics and dose-related elevation of biomarkers suggesting that IW-6118 inhibits FAAH in humans. We are also conducting early stage, preclinical research on approximately eight therapeutic targets in gastrointestinal pain, inflammation and cardiovascular indications.

In addition, we are actively engaged in identifying externally-discovered drug candidates at various stages of clinical development and accessing them through in-licensing or acquisition. In evaluating potential assets, we apply the same criteria as those used for investments in internally-discovered assets. To date, we have not in-licensed any drug candidates, but we do expect to do so from time to time.

Owner-related Business Principles

Before investing in Ironwood, we encourage all potential new co-owners to read the owner-related business principles below that guide our overall strategy and decision making.

1. We view our shareholders as partners and co-owners in our business.

With our cash on hand and up to $190 million in pre-commercial milestone payments payable to us from linaclotide partners, the anticipated proceeds from this offering should be sufficient to enable us to launch and commercialize linaclotide in the U.S. together with our partner Forest, and to fund our currently contemplated research and development efforts for at least the next five years, based on our current business plan. Since it is possible that we will not offer additional equity capital for a number of years, a priority for this offering is to augment our current shareholder group by adding additional, long-term focused co-owners.

2. We believe we can best maximize long-term shareholder value by building a great pharmaceutical franchise.

We believe that Ironwood has the potential to deliver outstanding long-term returns to shareholders who: (i) are sober to the risks inherent in the pharmaceutical product development model and to the potential dramatic highs and lows along the way, and (ii) are comfortable with management's focus on superior long-term cash flows, instead of the steadiness or consistency of our short-term growth in accounting earnings.

Since the pharmaceutical product development cycle is lengthy and unpredictable, we believe it is critical to have a long-term strategic horizon. We work hard to embed our long-term focus into our policies and practices, which may give us a competitive advantage in attracting like-minded shareholders and the highest caliber researchers. Our current and future employees may perceive both financial and qualitative advantages in having their inventions or hard work result in marketed drugs that they and their fellow shareholders continue to own. Some of our key policies and practices that are aligned with this imperative include:

a. Our dual class equity voting structure (which applies only in the event of change of control votes) is designed to concentrate change of control decisions in the hands of long-term focused owners

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who have a history of experience with us. Please read the "Description of Capital Stock" for additional information regarding our capital structure.

b. Compensation is weighted to equity over salary for all of our employees, and many employees have a significant portion of their incentive compensation in milestone-based equity grants that reward achievement of major value-creating events a number of years out from the time of grant.

c. We have adopted a change of control severance plan for all of our employees that is intended to encourage them to bring forward their best ideas by providing them with the comfort that if a change of control occurs and their employment is terminated, they will still have an opportunity to share in the economic value that they have helped create for shareholders.

d. Many of the members of our board of directors are substantial investors in the company. Furthermore, each director is required to hold all shares of stock acquired as payment for his or her service as a director throughout his or her term on the board.

e. Our partnerships with Forest, Almirall and Astellas all include standstill agreements, which serve to protect us from an unwelcome acquisition attempt by one of our partners. In addition, we have change of control provisions in our partnership agreements in order to protect the economic value of linaclotide should the acquirer of one of our partners be unable or unwilling to devote the time and resources required to make the program successful.

3. We are and will remain careful stewards of our shareholders' capital.

We work intensely to allocate capital carefully and prudently, continually reinforcing a lean, cost-conscious culture.

While we are mindful of the declining productivity and inherent challenges of pharmaceutical research and development, we intend to invest in discovery research for many years to come. Our singular passion is to create and develop novel drug candidates, seeking to integrate the most successful drugmaking practices of the past and the best of today's cutting-edge technologies and basic research advances. While we hope to improve the productivity and efficiency of our drug creation efforts over time, our discovery process revolves around small, highly interactive, cross-functional teams. We believe that this is one area where our relatively small size is a competitive advantage, so for the foreseeable future, we do not expect our drug discovery team to grow beyond 100-150 scientists. We will continue to prioritize constrained resources and maintain organizational discipline. Once internally- or externally-derived candidates advance into development, compounds follow careful stage-gated plans, with further advancement depending on clear data points. Since most pharmaceutical research and development projects fail, it is critical that our teams are rigorous in driving to early go/no go decisions, following the data, terminating unsuccessful programs, and allocating scarce dollars and talent to the most promising efforts, thus enhancing the likelihood of late phase development success.

4. We believe commercializing our drugs is a crucial element of our long-term success.

For the foreseeable future, we intend to play an active role in the commercialization of our products in the U.S., and to outlicense commercialization rights for other territories. We believe in the long-term value of our drug candidates, so we seek collaborations that provide meaningful economics and incentives for us and any potential partner. Furthermore, we seek partners who share our values, culture, processes, and vision for our products, which we believe will enable us to work with those partners successfully for the entire potential patent life of our drugs.

5. Our financial goal is to maximize long-term per share cash flows.

Our goal is to maximize long-term cash flows per share, and we will prioritize this even if it leads to uneven short-term financial results from an accounting perspective. If and when we become profitable, we expect and accept uneven earnings growth. Our underlying product development model is risky and

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unpredictable, and we will not advance marginal development candidates or consummate suboptimal in-license transactions in an attempt to fill anticipated gaps in revenue growth. Successful drugs can be enormously beneficial to patients and highly profitable and rewarding to shareholders, and we believe strongly in our ability to occasionally (but not in regular or predictable fashion) create and commercialize great medicines that make a meaningful difference in patients' lives.

If and when we reach profitability, we do not intend to issue quarterly or annual earnings guidance, however we plan to be transparent about the key elements of our performance, including near-term operating plans and longer-term strategic goals.

Our Strategy

Our goal is to build the next great pharmaceutical company by discovering, developing and commercializing innovative and differentiated medicines that target important unmet needs. Key elements of our strategy include:

attract and incentivize a team with a singular passion for creating and commercializing medicines that can make a significant difference in patients' lives;

successfully commercialize linaclotide in collaboration with Forest in the U.S.;

support our international partners to commercialize linaclotide outside of the U.S.;

if approved for IBS-C and CC, develop linaclotide for the treatment of other gastrointestinal disorders and for the pediatric population;

invest in our pipeline of novel product candidates and evaluate candidates outside of the company for in-licensing or acquisition opportunities;

participate in a meaningful way in the economics of the drugs that we bring to the market; and

execute our strategy with our shareholders' long-term interests in mind by seeking to maximize long-term per share cash flows.

Linaclotide

Overview

The gastrointestinal tract has many roles in human physiology, including the intake, breakdown and absorption of vital nutrients and fluids as well as the elimination of waste. In healthy individuals, waste is formed into stools and eliminated by the process of bowel movements. Bowel movements in healthy individuals cause minimal pain or discomfort and occur at various frequencies ranging from three times daily to three times weekly. IBS-C and CC are functional gastrointestinal disorders that afflict millions of sufferers worldwide. IBS-C is characterized by frequent and recurrent abdominal pain and/or discomfort and constipation symptoms (*e.g.* infrequent bowel movements, hard/lumpy stools, straining during defecation). CC is primarily characterized by constipation symptoms, but a majority of these patients report experiencing bloating and abdominal discomfort as among their most bothersome symptoms. Available treatment options primarily improve constipation, leading healthcare providers to diagnose and manage IBS-C and CC based on stool frequency. However, patients view these conditions as multi-symptom disorders, and while laxatives can be effective at relieving constipation symptoms, they do not necessarily improve abdominal pain, discomfort or bloating, and can often exacerbate these symptoms. This disconnect between patients and physicians, amplified by patients' embarrassment to discuss all of their gastrointestinal symptoms, often delays diagnosis and may compromise treatment, possibly causing additional suffering and disruption to patients' daily activities.

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IBS-C and CC are chronic conditions characterized by frequent and bothersome symptoms that dramatically affect patients' daily lives. We believe that gastro esophageal reflux disease, or GERD, serves as a reasonable analogue to illustrate the potential for a treatment that effectively relieves chronic gastrointestinal symptoms. Based on a study performed by M. Camilleri published in 2005 in *Clinical Gastroenterology and Hepatology* and 2007 U.S. census data, we estimate that in 2007, approximately 40 million people in the U.S. suffered from GERD. The typical GERD sufferer, who experiences frequent episodes of heartburn poorly controlled by over the counter products, will commonly seek medical care and is generally treated with a proton pump inhibitor, such as Prilosec (omeprazole), Nexium (esomeprazole magnesium), Prevacid (lansoprazole), or Protonix (pantoprazole). According to IMS Health, peak sales of the proton pump inhibitor class reached $12.8 billion in November 2007. The proton pump inhibitors generally provide relief of key heartburn symptoms within the first week of treatment and have a favorable safety and tolerability profile. Once GERD patients experience relief of heartburn, they tend to be highly adherent to therapy, taking a proton pump inhibitor for approximately 200 days a year, according to IMS Health. The relief of bothersome symptoms and the recurrence of symptoms following discontinuation, serve to reinforce patient adherence to chronic therapy for functional disorders, like GERD, IBS-C and CC.

U.S. IBS-C and CC Opportunity

Based on the Talley and Higgins studies, studies performed by F.A. Luscombe (published in 2000 in *Quality of Life Research*) and J.F. Johanson (published in 2007 in *Alimentary Pharmacology and Therapeutics*), and 2007 U.S. census data, we estimate that in 2007, approximately 35 million to 46 million people in the U.S. suffered from symptoms of IBS-C and CC, of whom between 9 million to 15.5 million patients sought medical care. As a result of the less than optimal treatment options currently available, patients seeking care experienced a very low level of satisfaction. Due to patients' lack of satisfaction with existing treatment options, about 70% of patients stop prescription therapy within one month, according to IMS Health. It is estimated that patients seek medical care from five or more different healthcare providers over the course of their illness with limited or no success, as shown in a 2009 study by D.A. Drossman in the *Journal of Clinical Gastroenterology*. Many of the remaining patients are too embarrassed to discuss the full range of their symptoms, or for other reasons do not see the need to seek medical care and continue to suffer in silence while unsuccessfully self-treating with fiber, OTC laxatives and other remedies which improve constipation, but often exacerbate pain and bloating.

Irritable Bowel Syndrome with Constipation. Based on the Talley study and 2007 U.S. census data, we estimate that in 2007, approximately 12 million people or 5.2% of the U.S. adult population suffered from symptoms associated with IBS-C. As shown in a study conducted by the International Foundation of Functional Gastrointestinal Disorders, or IFFGD, in 2002, almost 35% of all IBS-C patients report suffering from some related symptoms daily. Based on this data and the Luscombe study, we estimate that up to 7 million of these patients sought medical attention for their symptoms. Based on the Talley, Luscombe and Johanson studies and 2007 U.S. census data, we estimate that between 5 million to 9 million sufferers have not consulted a physician and attempt to manage their symptoms with over the counter fiber and laxatives. Patients with IBS-C who seek medical care receive either a recommendation from their physician for an over the counter product or a prescription medication. As shown in a study conducted by the IFFGD in 2007, for all treated IBS-C patients, there continues to be a low rate of satisfaction with relief of their symptoms, with 92% of patients reporting that they are not fully satisfied with their treatments; and 77% of patients reporting that they were unsatisfied with overall care by their physician.

Chronic Constipation. Based on the Higgins study and 2007 U.S. census data, we estimate that in 2007, 23 million to 34 million people, or 10% to 15% of the U.S. adult population, were suffering from CC. Based on this data and the Johanson study, we estimate that of the total CC sufferers, only 6 million to 8.5 million patients suffering from CC sought medical care. Almost all of these patients, whether or not seeking medical care for their symptoms, took an over the counter or prescription treatment, or both. Similar to IBS-C, there continues to be a low rate of treatment satisfaction, with over 70% of those taking

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over the counter and prescription laxatives reporting that they are not fully satisfied with their treatment results as shown in the Johanson study.

As shown in the figure below, according to L.E. Brandt in a study published in 2005 in the *American Journal of Gastroenterology*, the symptoms underlying both disorders can be viewed on a continuum. During a consultation, patients will often discuss only the predominant symptom making it difficult for physicians to effectively diagnose and treat. For most patients, constipation is also accompanied by a set of symptoms broader than straining and infrequency of bowel movements. Given the limitations of available treatment options in addressing multiple symptoms, physicians tend to focus on the most easily treatable symptom, constipation. Our market research suggests that most physicians view abdominal pain and bloating as difficult to treat. We believe that linaclotide's profile could offer health care providers the opportunity to identify, diagnose, and treat the other important symptoms experienced by IBS-C and CC patients.

IBS-C and CC Opportunity Outside of U.S. We believe that the prevalence rates of IBS-C in Europe and Japan are similar to the prevalence rates in the U.S.

Burden of Illness. Both IBS-C and CC adversely affect the quality of life of patients, leading to increased absenteeism from work or school and increased costs to the healthcare system. According to both a study by A.P.S. Hungin published in 2005 in *Alimentary Pharmacology & Therapeutics* and the Johanson study, patients with IBS-C and CC reportedly suffer from their symptoms on average 166 and 97 days per year, respectively, and, according to the Drossman study, over one third have experienced their symptoms for more than ten years. In a typical month, IBS-C and CC patients will miss an average of one to three days of school or work, according to Johanson's study and a study by B. Cash published in 2005 in *The American Journal of Medical Care*, and their productivity will be disrupted an additional four to five days per month, according to the Cash study. When the level of suffering becomes acutely overwhelming for patients, they seek care at an ambulatory care facility. In 2004, CC was the second most common cause for ambulatory care visits after GERD, according to a 2008 article by J.E. Everhart published in *Functional Intestinal Disorders*. According to the Everhart article, CC accounted for 6.3 million ambulatory care visits (when considered as part of any listed diagnosis) and IBS accounted for 3 million ambulatory care visits. Estimates of the indirect and direct costs associated with these conditions range upwards of $25 billion, according to a study published in 2000 by M. Camilleri and D.E. Williams in *Pharmacoeconomics*.

Treatment Options for IBS-C and CC. By the time patients seek care from a physician, they have typically tried a number of available remedies and remain unsatisfied. Most IBS-C and CC patients initially attempt self-treatment with over the counter medications such as laxatives, stool softeners or fiber supplementation, as well as attempts to modify their diet. While some of these therapies offer limited success in transit-related symptoms, they offer little to no effect on other bothersome symptoms from which patients are suffering. Unfortunately, physicians have very limited treatment options beyond what is readily available to the patient alone. Physicians typically rely on fiber and laxatives, which can exacerbate bloating and abdominal pain, the same symptoms from which many patients are seeking relief and which are the most troubling to treat. In an attempt to help alleviate the more severe abdominal symptoms associated with IBS-C and CC, healthcare providers sometimes prescribe medications that have not been approved by the FDA for these indications, such as anti-depressant or antispasmodic agents.

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Polyethylene glycol, or PEG (such as Miralax), and lactulose, account for the majority of prescription and over the counter laxative treatments. Both agents demonstrate an increase in stool frequency and consistency but do not improve bloating or abdominal discomfort. Clinical trials and product labels document several adverse effects with PEG and lactulose, including exacerbation of bloating, cramping and, according to the Brandt study, up to a 40% incidence of diarrhea. Overall, up to 75% of patients taking prescription laxatives report not being completely satisfied with the predictability of when they will experience a bowel movement on treatment, and 50% were not completely satisfied with relief of the multiple symptoms associated with constipation, according to the Johanson study.

In 2002, the FDA approved Zelnorm, the first new drug for the treatment of IBS-C, and in 2004, Zelnorm was approved for the treatment of CC. Zelnorm is a serotonin 5-HT4 receptor agonist, with a mechanism of action completely separate and distinct from the mechanism of action underlying linaclotide's activity. As a newly available treatment option to potentially address some of the symptoms beyond the scope of laxatives and fiber, Zelnorm achieved great success in raising patient and physician awareness of IBS-C and CC. During the five years that Zelnorm was promoted, total prescriptions in the category grew three fold, and in 2006, there were more than 16 million total prescriptions written for treating patients with IBS-C and CC, according to IMS Health. Prior to its withdrawal, in 2006, Zelnorm total sales were approximately $561 million. In 2007, Zelnorm was withdrawn from the market by its manufacturer due to an analysis that found a higher chance of heart attack, stroke and chest pain in patients treated with Zelnorm as compared to placebo. Despite modest effectiveness relieving abdominal pain (1% to 10% of patients responding to treatment as compared to placebo) and bloating (4% to 11% of patients responding to treatment as compared to placebo) as described on the Zelnorm product label, Zelnorm succeeded in establishing a symptom-based approach highlighting the need to recognize and treat, on a chronic basis, both the abdominal and constipation symptoms afflicting these patients.

Currently, the only available prescription therapy for IBS-C and CC is Amitiza, which was approved for the treatment of CC in 2006, and for IBS-C in 2008. Amitiza sales have been modest in comparison to Zelnorm sales prior to its withdrawal from the market, according to IMS Health.

Although a significant unmet need exists for better treatments for IBS-C and CC, we believe that there are very few treatments in late-stage clinical development. The most recent entrant to the CC marketplace, solely in Europe, is Resolor (prucalopride). Resolor was recently approved by the European Medicines Agency and is indicated for the treatment of CC in women for whom laxatives have failed to provide adequate relief. Resolor, which will be marketed by Movetis, is a serotonin 5-HT4 receptor agonist like Zelnorm. Johnson & Johnson has U.S. rights to prucalopride. Currently, we believe there is only one compound in late stage clinical development, velusetrag (being developed by Theravance), which is also a serotonin 5-HT4 receptor agonist like Zelnorm, and which has completed Phase 2 trials for CC. We believe that there are a number of earlier stage compounds in development.

The Linaclotide Opportunity. Based on the Talley, Luscombe, Johanson and IFFGD studies and 2007 U.S. census data, we believe that there are over 10 million IBS-C and CC patients in the U.S. who suffer from multiple symptoms, are actively seeking therapy and are dissatisfied with current treatment options. Moreover, physicians overwhelmingly report a need for an efficacious treatment with demonstrated safety that can provide rapid, convenient, and effective multi-symptom relief, relieving abdominal pain and discomfort, bloating and constipation symptoms.

Linaclotide is a unique and promising potential treatment for patients suffering from both abdominal and constipation symptoms related to IBS-C and CC. Based on the clinical profile we have observed to date, we believe linaclotide is well positioned to provide IBS-C and CC patients with much needed reduction in abdominal and constipation symptoms, with a low incidence of adverse events, and a convenient once daily, oral dosing regimen.

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Preclinical Pharmacology, Safety, and Toxicology

Pharmacology: Unique Mechanism of Action

The underlying causes of the abdominal pain, discomfort and bloating suffered by patients with lower gastrointestinal disorders like IBS-C and CC are poorly understood. Further, because current therapeutic agents offer limited improvement in these symptoms, there has been limited medical research in this area. Since our clinical studies indicate that linaclotide provides rapid and sustained improvement of these symptoms, we have invested significant effort to define the mechanisms of linaclotide's physiological effects.

Linaclotide is a 14 amino acid peptide agonist of guanylate cyclase type-C, or GC-C, a receptor found on the epithelial cells that line the intestine. Activation of GC-C leads to increases in intracellular and extracellular cyclic guanosine monophosphate, or cGMP, levels. cGMP is a well characterized "second messenger" that relays and amplifies signals received at receptors on the cell surface to target molecules in the cytosol and/or nucleus of a cell. We believe increased cGMP has dual effects on intestinal function. First, as the figure below shows, cGMP can exit the epithelial cells to block pain signaling by inhibiting the pain-sensing neurons that carry signals from the gastrointestinal tract to the central nervous system (afferent pain fibers). Second, cGMP can remain inside the epithelial cell to activate protein kinase GII, or PKGII, which activates the protein Cystic Fibrosis Transmembrane conductance Regulator, or CFTR, by phosphorylation, or P, to stimulate electrolyte (Na^+ = sodium, Cl^- = chloride, and HCO_3^- = bicarbonate) and fluid (H_2O = water) secretion into the intestinal lumen. The resulting increase in intestinal fluid volume accelerates intestinal transit.

Our preclinical work supports the above model for the actions of linaclotide. Regarding the effect on pain sensation, we have found that increased extracellular cGMP inhibited noxious-stimulus-induced firing of afferent pain fibers. In addition, oral dosing with either linaclotide or directly with cGMP significantly reduced abdominal pain responses in a number of preclinical models. While much work remains to be done, we hypothesize that the reduction in abdominal pain, abdominal discomfort, and visceral hypersensitivity seen both preclinically and clinically is a result of increased extracellular cGMP, which may reduce firing of pain-sensing neurons and thus decrease sensitivity to otherwise painful stimuli.

Additionally, in other preclinical studies, linaclotide was shown to increase intracellular cGMP, leading to activation of channels in intestinal cell membranes that resulted in the secretion of ions and fluid out of intestinal cells and into the intestinal lumen. Increased fluid in the intestinal lumen causes accelerated intestinal transit.

Importantly, linaclotide's effects on pain sensation and gastrointestinal transit/secretion are dependent on the presence of the GC-C receptor; in preclinical experiments where the GC-C receptor was genetically deleted, the effects of linaclotide on pain sensation and secretion were eliminated.

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The binding and activity of linaclotide at the GC-C receptor is highly specific. Linaclotide has no effect on the serotonin system, unlike Zelnorm, Resolor, cisapride (Propulsid, which was approved for heartburn caused by GERD), or alosetron (Lotronex, which was approved for irritable bowel syndrome with diarrhea), each of which work through serotonin receptors in the intestine. Zelnorm, Propulsid and Lotronex were all withdrawn from the market because of safety concerns.

Preclinical Safety

Linaclotide exhibits very limited oral bioavailability in all species tested, and it does not require absorption into the bloodstream to exert its pharmacological effect. This very limited exposure is due to minimal absorption of linaclotide through the intestinal epithelium. We believe that linaclotide's limited systemic exposure may reduce the likelihood of side effects.

We have investigated the intestinal fate and metabolism of linaclotide. Linaclotide is processed by the enzyme carboxypeptidase, which removes a single amino acid (tyrosine) from the end of linaclotide. The resulting 13 amino acid metabolite has similar activity to linaclotide in all assays tested. Both linaclotide and this active metabolite are degraded in the intestine by a sequential process of disulfide bond disruption, cleavage to inactive peptide fragments, and ultimate digestion to natural amino acids.

We consider linaclotide to have a highly favorable preclinical safety profile. Linaclotide's preclinical safety profile has been evaluated in both safety pharmacology and general toxicology studies following single intravenous and oral doses and repeat oral doses in rodent and non-rodent species. Linaclotide exhibits its desired pharmacological effects at doses that are much lower than those that could cause an adverse effect in toxicology studies, with the no-observed-adverse-effect level in these preclinical studies being at least 1,000 times higher than the highest human dose in any Phase 3 trial. Intravenous administration of up to five milligrams per kilogram of linaclotide had no effect on cardiovascular or respiratory function. In a 26-week chronic toxicity study, the no-observed-adverse-effect level was greater than or equal to 4,000-times the highest human dose for any Phase 3 study. In a 39-week chronic toxicity study, the-no-observed-adverse-effect level was 1,000-times the highest human dose for any Phase 3 study.

In reproductive toxicity studies, the no-observed-adverse-effect level was determined to be 1,000-times the maximum dose studied in Phase 3 clinical studies.

We have also completed dosing for two years in carcinogenicity studies, and expect to have the final analysis in the first quarter of 2010.

Clinical

We are conducting a comprehensive clinical program consisting of 13 studies in over 4,600 people. Nine of the studies have been completed; three in healthy volunteers, two in IBS-C patients, and four in CC patients. Additionally, two Phase 3 studies in IBS-C patients and two long-term safety studies are ongoing.

Healthy Volunteer Studies

Three Phase 1 studies conducted in healthy volunteers were completed to obtain an understanding of linaclotide's safety and pharmacodynamic effects, to determine whether co-administration of linaclotide with food modulates linaclotide's pharmacodynamic effects, and to determine whether linaclotide showed minimal systemic exposure after oral administration as was observed in preclinical studies.

In the first two Phase 1 studies, single doses of up to 3,000 micrograms, or mcg, of linaclotide in 30 healthy male and female subjects, and once daily doses of up to 1,000 mcg over a seven-day period in 48 healthy male and female subjects, were generally well tolerated. Linaclotide was administered as an oral solution in this study. Linaclotide and its active metabolite were not measurable in the plasma of any subject at any dose level or time point, despite the ability of methods to measure as little as three nanograms of linaclotide or its metabolite in a milliliter of plasma. There were no dose-related increases in

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the number of subjects reporting treatment-emergent adverse events, or TEAEs, after linaclotide administration,

In a Phase 1 food-effect study in 19 healthy non-constipated volunteers, linaclotide administration in the fed state resulted in more frequent and looser stools as compared to linaclotide administration in the fasted state. In this study, despite the use of improved methods that can measure as little as 0.2 nanograms of linaclotide or 2 nanograms of its metabolite in a milliliter of plasma, there were no measurable levels of either compound in individuals dosed with 300 mcg of linaclotide in either the fed or fasted state. In this same study, a single supratherapeutic dose of 3,000 mcg (10 times higher than the highest Phase 3 dose) was administered immediately following seven consecutive days of administration of 300 mcg linaclotide once daily. Linaclotide was detected in the plasma of two of 18 subjects following administration of the 3,000 mcg dose, and the active metabolite of linaclotide was not detected in any subject. Exposure levels of linaclotide in these two subjects were not high enough or sufficiently sustained to allow calculation of pharmacokinetic parameters. The majority of subjects experienced gastrointestinal-related TEAEs during the study (primarily diarrhea), which were mild or moderate in severity and resolved following treatment.

Studies in CC and IBS-C Patients

In Phase 2 and Phase 3 studies in CC and IBS-C patients, the following key symptoms were measured:

Spontaneous Bowel Movements (SBMs): Bowel movements that occur in the absence of laxative, enema, or suppository usage within the preceding 24 hours

Complete SBMs (CSBMs): SBMs accompanied by the patient self-reporting a feeling of complete evacuation

Stool Consistency using the Bristol Stool Form Scale: a 7-point ordinal scale (1=separate hard lumps like nuts [difficult to pass]; 2=sausage shaped but lumpy; 3=like a sausage but with cracks on surface; 4=like a sausage or snake, smooth and soft; 5=soft blobs with clear-cut edges [passed easily], 6=fluffy pieces with ragged edges, a mushy stool; 7=watery, no solid pieces [entirely liquid])

Straining (during bowel movements): a 5-point ordinal severity scale (1=not at all, 2=a little bit, 3=a moderate amount, 4=a great deal, 5=an extreme amount)

Abdominal Pain: a 5-point ordinal severity scale (1=none, 2=mild, 3=moderate, 4=severe, and 5=very severe)

Abdominal Discomfort: a 5-point ordinal severity scale (1=none, 2=mild, 3=moderate, 4=severe, and 5=very severe)

Bloating: a 5-point ordinal severity scale (1=none, 2=mild, 3=moderate, 4=severe, and 5=very severe)

Constipation Severity: a 5-point ordinal severity scale (1=none, 2=mild, 3=moderate, 4=severe, and 5=very severe)

IBS Symptom Severity: a 5-point ordinal severity scale (1=none, 2=mild, 3=moderate, 4=severe, and 5=very severe)

Phase 2

We conducted four Phase 2 studies, two in patients with IBS-C and two in patients with CC, to evaluate linaclotide's safety, efficacy, and dose response.

Phase 2 IBS-C Studies

Phase 2a IBS-C Study. A single-center Phase 2a motility study was conducted in 36 female patients with IBS-C. The study evaluated doses of 100 and 1,000 mcg for effects on upper and lower gastrointestinal motility when administered orally in solution once daily for five days. Bowel symptoms and safety

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parameters were also measured. In this study, the 1,000 mcg dose of linaclotide significantly accelerated lower gastrointestinal motility, as measured as ascending colonic emptying and overall colonic transit at 48 hours. No effect of linaclotide 1,000 mcg dose on upper gastrointestinal motility, as measured by gastric emptying or small bowel transit, was observed in this study. There was also a dose-dependent improvement in bowel symptoms. Headache was the most common TEAE.

Phase 2b IBS-C Study. A randomized, double-blind, placebo-controlled study was conducted in 420 IBS-C patients at 92 sites in the U.S. and Canada. The study enrolled IBS-C patients age 18 years or older with at least mild abdominal pain/discomfort, fewer than three CSBMs per week, and no more than six SBMs per week during the pre-treatment period. The study had a two-week pre-treatment baseline period, a 12-week treatment period, and a two-week post-treatment period. Four doses of linaclotide were evaluated: 75 mcg, 150 mcg, 300 mcg and 600 mcg, administered once daily as oral capsules. The primary endpoint of the study was the change from baseline in weekly CSBM frequency in the evaluable population. However, data are shown below for the more inclusive intent-to-treat, or ITT, population, as that is the primary endpoint population for Phase 3. Additional endpoints included the change from baseline in other bowel symptoms (SBMs, stool consistency, straining), daily abdominal symptoms (pain, discomfort, and bloating), and weekly global severity assessments (IBS symptom severity, constipation severity).

During the baseline period, the average CSBM frequency was 0.3 CSBMs per week, and 68% of patients had no CSBMs during this period. The change from baseline in weekly CSBM frequency versus placebo was statistically significant (p-value < 0.01) in all linaclotide dosing arms compared to the placebo group. The p-value is a measure of probability that the difference between the placebo group and the linaclotide group is due to chance (*e.g.,* p = 0.01 means that there is a 1% (0.01 = 1.0%) chance that the difference seen between the placebo and linaclotide group is the result of random chance as opposed to the linaclotide treatment). A p-value less than or equal to 0.05 (0.05 = 5%) is commonly used as a criterion for statistical significance.

Phase 2b IBS-C Primary Endpoint: Change from Pre-treatment in CSBM Frequency

*p<0.05, **p<0.01, ***p<0.001
Note: ITT population

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Linaclotide treatment decreased abdominal pain, abdominal discomfort, bloating and global measures of IBS severity and constipation severity in the study. The pretreatment baseline values on the five-point ordinal severity scale (1=none, 2=mild, 3=moderate, 4=severe, and 5=very severe) ranged from 2.87 to 3.13 for abdominal pain, 3.11 to 3.34 for abdominal discomfort, 3.32 to 3.56 for bloating, 3.56 to 3.73 for IBS severity and 3.47 to 3.80 for constipation severity. Improvement in the abdominal symptoms and global measurements of severity ranged from 25.5% to 53.8% compared to placebo rates of 16.1% to 25.6% across the dose groups as shown in the table below. In particular, the 300 mcg dose (the dose level being evaluated in Phase 3 IBS-C trials) demonstrated a 46.8% relative reduction in the mean abdominal pain score versus 25.6% in the placebo arm.

Phase 2b IBS-C: Improvement as Percent Change from Baseline*

Endpoint	Placebo	75 mcg	150 mcg	300 mcg	600 mcg
Abdominal pain	25.6%	37.1%	36.9%	46.8%	44.4%
Abdominal discomfort	22.1%	31.3%	32.5%	42.7%	38.6%
Bloating	16.1%	27.3%	25.5%	37.3%	31.6%
IBS severity	22.2%	35.0%	34.1%	42.1%	41.0%
Constipation severity	23.3%	42.3%	41.1%	53.8%	48.8%

* ITT population. Improvement as percent change from baseline calculated as the percent difference in the treatment group's mean change from baseline value relative to the mean baseline score.

Abdominal pain improved within the first week of treatment and the effect was sustained over the 12-week treatment period as shown below.

Abdominal Pain

Note: ITT population

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Linaclotide also demonstrated a significant reduction in abdominal pain frequency as measured by an increase in the median percentage of pain-free days in the 300 mcg group compared to the placebo group (18.5% vs. 2.0%). At the 75 mcg, 150 mcg, and 600 mcg dose groups, there was a numerical but not statistically significant increase in the percentage of pain-free days relative to placebo.

Significant improvements in other bowel habits, including frequency of SBMs, straining and stool consistency (*i.e.,* less hard stools) were also demonstrated, and were seen within the first week of treatment. The percentages of patients reporting a CSBM within 24 hours of initial dosing ranged from 27% to 37% for the linaclotide dose groups compared to 13% for the placebo group ($p<0.05$ for all linaclotide dose groups compared to placebo). All improvements were statistically significant for at least three of the four linaclotide dose groups for each endpoint. The 300 mcg dose, which is currently being assessed in Phase 3 IBS-C trials, demonstrated statistically significant effects across all secondary endpoints. Effects were seen within the first week of dosing, often within the first three days, and continued over the 12 weeks of treatment. Linaclotide provided statistically significant improvement in multiple symptoms of IBS-C in this study.

We analyzed the Phase 2b IBS-C data utilizing the Phase 3 primary efficacy parameters (see *"Phase 3 IBS-C Trials"* below). Responder rates for the placebo group, the pooled linaclotide-treated group (75, 150, 300, and 600 mcg aggregated), and the 300 mcg group (the Phase 3 IBS-C dose) were determined. The responder rate for the 12-week abdominal pain and CSBM (APC) responder was 10% in the placebo group, 20% for the pooled linaclotide-treated group, and 27% for the 300 mcg group. The responder rate for the 12-week CSBM responder was 13% in the placebo group, 26% for the pooled linaclotide-treated group, and 31% for the 300 mcg group. The responder rate for the 12-week abdominal pain responder was 30% in the placebo group, 44% for the pooled linaclotide-treated group, and 48% for the 300 mcg group.

The most common TEAE in the linaclotide-treated groups was diarrhea (occurring in 11% to 18% of patients), which was the primary cause of discontinuation for 1% to 7% of patients. Most reports of diarrhea were mild to moderate; nine linaclotide-treated patients reported severe diarrhea. Other TEAEs occurred with similar frequency across the placebo and linaclotide dose groups.

Phase 2b IBS-C: Treatment-emergent Adverse Events

TEAEs occurring in ≥ 3% of patients in any of the linaclotide groups and > placebo

		Linaclotide			
Treatment-emergent adverse event (TEAE)	**Placebo n=85**	**75 mcg n=79**	**150 mcg n=82**	**300 mcg n=85**	**600 mcg n=89**	**All n=335**
Any TEAE	**35 (41%)**	**41 (52%)**	**40 (49%)**	**50 (59%)**	**61 (69%)**	**192 (57%)**
Diarrhea	1 (1%)	9 (11%)	10 (12%)	14 (16%)	16 (18%)	49 (15%)
Abdominal pain	3 (4%)	4 (5%)	3 (4%)	4 (5%)	7 (8%)	18 (5%)
Urinary tract infection	2 (2%)	7 (9%)	1 (1%)	5 (6%)	1 (1%)	14 (4%)
Nausea	5 (6%)	1 (1%)	8 (10%)	1 (1%)	3 (3%)	13 (4%)
Nasopharyngitis	5 (6%)	3 (4%)	6 (7%)	1 (1%)	1 (1%)	11 (3%)
Upper respiratory tract infection	3 (4%)	0	2 (2%)	4 (5%)	5 (6%)	11 (3%)
Sinusitis	2 (2%)	3 (4%)	2 (2%)	3 (4%)	2 (2%)	10 (3%)
Bronchitis	0	2 (3%)	1 (1%)	1 (1%)	3 (3%)	7 (2%)
Back pain	1 (1%)	0	4 (5%)	1 (1%)	1 (1%)	6 (2%)
Fecal incontinence	0	0	1 (1%)	0	3 (3%)	4 (1%)

Phase 2 CC Studies

Phase 2a CC Study. A randomized, placebo-controlled study was conducted in 42 CC patients at 14 sites. The study evaluated doses of 100, 300 and 1,000 mcg administered orally once daily as an oral solution for 14 days. Bowel and abdominal symptoms as well as safety parameters were measured. In this

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study, linaclotide increased SBM frequency and CSBM frequency compared to placebo. Linaclotide also improved stool consistency (*i.e.,* decreased stool hardness), decreased straining severity and decreased abdominal discomfort when compared to placebo. The most common TEAE was diarrhea.

Phase 2b CC Study. A randomized, double-blind, placebo-controlled study was conducted in 310 CC patients at 57 sites in the U.S. The study enrolled patients age 18 years or older who had fewer than three CSBMs per week and no more than six SBMs per week in the pre-treatment period. The study had a two-week pre-treatment baseline period, a four-week treatment period and a two-week post-treatment period. Four doses of linaclotide were evaluated: 75 mcg, 150 mcg, 300 mcg, and 600 mcg, administered once daily as oral capsules. The primary endpoint of the study was the change from baseline in weekly SBM frequency in the evaluable population. However, data are shown for the more inclusive ITT population as that is the primary endpoint population for Phase 3. Additional endpoints included the change from baseline in other bowel symptoms (CSBMs, stool consistency, training) and daily abdominal symptoms (discomfort and bloating), as well as the global assessment of constipation severity.

The change from baseline versus placebo for weekly SBM frequency increased from a baseline of 2.3 per week in all treatment groups and was statistically significant in all linaclotide dosing arms compared to the placebo group. Weekly SBM frequency increased with the dose of linaclotide administered. Linaclotide improved all other bowel habits, including frequency of CSBMs, straining, and stool consistency (*i.e.,* less hard stools). All improvements were statistically significant for each endpoint and for all four linaclotide dose groups, except straining at the 75 mcg dose level. Improvements were sustained over the four-week treatment period.

Phase 2b CC: Primary Endpoint: Change from Pre-treatment in SBM Frequency

*p<0.05, **p<0.01, ***p<0.001
Note: ITT population

The percentages of patients reporting a CSBM within 24 hours of initial dosing ranged from 14% to 36% for the linaclotide dose groups compared to 7% for the placebo group (p<0.05 for the 75, 300 and 600 mcg dose groups compared to placebo).

Linaclotide treatment decreased abdominal discomfort, bloating and constipation severity in the study. The pretreatment baseline values ranged from 2.36 to 2.50 for abdominal discomfort, 2.69 to 2.83 for bloating and 3.25 to 3.58 for constipation severity. Improvement of these symptoms ranged from 17.2%

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to 40.9% compared to placebo rates of 2.5% to 6.6% (see table below). Onset of improvement in these symptoms generally ocurred within the first week of treatment.

Phase 2b CC: Improvement as Percent Change from Baseline*

Endpoint	Placebo	75 mcg	150 mcg	300 mcg	600 mcg
Abdominal discomfort	3.8%	25.0%	23.4%	18.2%	21.8%
Bloating	2.5%	24.6%	25.9%	17.6%	17.2%
Constipation severity	6.6%	35.2%	38.6%	38.3%	40.9%

* ITT population. Improvement as percent change from baseline calculated as the percent difference in the treatment group's mean change from baseline value relative to the mean baseline score.

The most common and only dose-dependent TEAE in the linaclotide-treated groups was diarrhea (occurring in 5% to 14% of patients), which was the primary cause of discontinuation for 2% to 5% of patients. Most reports of diarrhea were of mild or moderate severity, with two linaclotide-treated patients reporting severe diarrhea (both in the 600 mcg group). Other TEAEs occurred with similar frequency across the placebo and linaclotide dose groups (see table below).

Linaclotide Phase 2b CC: Treatment-emergent Adverse Events

TEAEs occurring in ≥ 3% of patients in any of the linaclotide groups and > placebo

Treatment-emergent adverse event (TEAE)	Placebo n=69	75 mcg n=59	150 mcg n=56	Linaclotide 300 mcg n=62	600 mcg n=63	All n=240
Any TEAE	**22 (32%)**	**21 (36%)**	**18 (32%)**	**18 (29%)**	**24 (38%)**	**81 (34%)**
Diarrhea	2 (3%)	3 (5%)	5 (9%)	3 (5%)	9 (14%)	20 (8%)
Abdominal pain	3 (4%)	2 (3%)	5 (9%)	2 (3%)	2 (3%)	11 (5%)
Nausea	1 (1%)	2 (3%)	2 (4%)	1 (2%)	2 (3%)	7 (3%)
Urinary tract infection	1 (1%)	1 (2%)	2 (4%)	1 (2%)	1 (2%)	5 (2%)
Dizziness	0	0	0	1 (2%)	3 (5%)	4 (2%)
Vomiting	1 (1%)	1 (2%)	1 (2%)	0	2 (3%)	4 (2%)
Bowel sounds abnormal	0	0	1 (2%)	0	2 (3%)	3 (1%)
Bronchitis	2 (3%)	2 (3%)	0	0	0	2 (1%)
Influenza	0	0	2 (4%)	0	0	2 (1%)

Phase 1 and Phase 2 Serious Adverse Event Summary

There were no serious adverse events in the Phase 1 studies. Serious adverse events occurred in less than 1% of patients in the Phase 2 program and were similarly distributed across placebo and linaclotide treated groups.

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Phase 3

The Phase 3 program consists of two long-term safety studies and four pivotal efficacy trials: two in patients with IBS-C and two in patients with CC. The Phase 3 trials were designed based on our experience from the Phase 2 program, which provided an understanding of linaclotide's potential therapeutic effect on abdominal symptoms (*e.g.,* abdominal bloating, discomfort and pain) and constipation (frequency, straining and stool consistency) and provided insight into the appropriate methods for measuring these symptoms. The consistent results for the primary and secondary efficacy measures as well as safety parameters observed throughout the Phase 2 program were also reflected in marked improvements in global assessments (*e.g.,* constipation severity, IBS severity). With this in mind, we designed the Phase 3 trials as larger confirmatory trials targeting the same patient populations (similar inclusion and exclusion criteria) and similar endpoints. In order to increase the statistical power (>95% for the primary endpoint), we increased the size of the Phase 3 studies to 200 patients per group for CC compared to 50 patients per group in Phase 2 and 400 patients per group for IBS-C compared to 80 patients per group in Phase 2. We also extended the length of the treatment period of the CC trials to 12 weeks from four weeks in Phase 2 and extended one of the IBS-C trials to six months of treatment compared to the 12 weeks utilized in Phase 2 (the primary Phase 3 endpoint remains at 12 weeks). To better align our measurements of abdominal symptoms in the IBS-C Phase 3 studies with those preferred by regulatory authorities, we modified the measurement tool used by patients to describe their abdominal symptoms from a 5-point scale to an 11-point scale (0-10). Our experience with a similar scale in Phase 2b IBS-C study indicated that the 11-point scale provided similar responses to those observed with the 5-point scale and may detect change with greater precision.

The doses of linaclotide referenced in connection with our Phase 1 and Phase 2 studies represented the total peptide content, which, in addition to linaclotide, includes inactive linaclotide-related peptides. Beginning with Phase 3 and going forward, dose level designations refer solely to linaclotide content. Thus, the 150 mcg total peptide dose in Phase 2 has active linaclotide content equivalent to the 133 mcg dose in Phase 3 and going forward. Similarly, the 300 mcg total peptide dose in Phase 2 has active linaclotide content equivalent to the 266 mcg dose in Phase 3 and going forward. This does not reflect any change in the amounts of linaclotide delivered between the trials or the formulation, but rather an improvement in analytic methods and the way we reference the dose levels.

Phase 3 IBS-C Trials

In July 2009, we initiated two confirmatory Phase 3, multi-center, randomized, double-blind, placebo-controlled trials assessing the safety and efficacy of linaclotide in patients with IBS-C in the U.S. and Canada. Each trial will target enrollment of 800 IBS-C patients. Patients enrolled in the trials are to have fewer than three CSBMs and no more than five SBMs per week during the pretreatment period, with an average abdominal pain score of at least 3.0 on an 11-point scale (0=none, 10=very severe). Patients are being randomized to receive placebo or 266 mcg linaclotide administered once daily as an oral capsule. There are three primary efficacy parameters: 12-week abdominal pain and CSBM responder; 12-week responder; and 12-week abdominal pain responder. A 12-week CSBM responder is a patient who had three or more CSBMs per week and an increase of at least one CSBM per week over baseline for at least nine of the 12 weeks of the treatment period. A 12-week abdominal pain responder is a patient who has at least a 30% relative reduction in abdominal pain compared to baseline for at least nine out of the 12 weeks in the treatment period. Finally, a 12-week abdominal pain and constipation responder is a patient who meets both the responder criteria for abdominal pain and constipation for at least nine out of the 12 weeks in the treatment period.

We anticipate having top-line data from both trials in the second half of 2010.

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Phase 3 CC Trials

In November 2009, we announced positive top-line results from two confirmatory Phase 3 multi-center, randomized, double-blind, placebo-controlled studies assessing the safety and efficacy of linaclotide administered once daily as an oral capsule in patients with CC. In both trials, statistical significance was achieved for the primary endpoint of 12-week CSBM responder at the 2 doses studied in each trial (133 mcg/day: p-values ≤0.0012 and 266 mcg/day: p-values<0.0001). In both trials, statistical significance was achieved for all pre-specified secondary endpoints, which included measures of bloating, abdominal discomfort, and constipation severity.

As illustrated in the table below, data from the Phase 3 CC program were consistent with the Phase 2b CC study described earlier, and support the potential for linaclotide to improve the multiple symptoms associated with CC.

Phase 3 CC Trials: Statistical Significance of Linaclotide Effects as Compared to Placebo

	Trial 303 (n=642)		Trial 01 (n=630)	
Endpoint	**133 mcg**	**266 mcg**	**133 mcg**	**266 mcg**
Primary endpoint				
12-week CSBM responder	p<0.0001	p<0.0001	p=0.0012	p<0.0001
Secondary endpoints				
CSBM frequency	p<0.0001	p<0.0001	p<0.0001	p<0.0001
SBM frequency	p<0.0001	p<0.0001	p<0.0001	p<0.0001
Stool consistency	p<0.0001	p<0.0001	p<0.0001	p<0.0001
Severity of straining	p<0.0001	p<0.0001	p<0.0001	p<0.0001
Constipation severity	p<0.0001	p<0.0001	p<0.0001	p<0.0001
Abdominal discomfort	p=0.0003	p=0.0063	p=0.0006	p=0.0001
Bloating	p<0.0001	p=0.0049	p=0.0005	p<0.0001

Trial 01. Trial 01 was conducted in 630 CC patients. The trial enrolled patients age 18 years or older who had fewer than three CSBMs per week and no more than six SBMs per week during the pre-treatment period. The trial included a two-week pre-treatment baseline period and a 12-week treatment period. The primary efficacy endpoint was a 12-week CSBM responder. A 12-week CSBM responder is a patient who had three or more CSBMs per week and an increase of at least one CSBM per week over baseline for at least nine of the 12 weeks of the treatment period. During the baseline period, the average CSBM frequency was 0.3 CSBMs per week and 72% of patients had no CSBMs during this period.

The 12-week CSBM responder rate was 16.0% in the 133 mcg linaclotide group (p=0.0012), and 21.3% in the 266 mcg linaclotide group (p<0.0001), a numerical increase of 2.6 and 3.5 fold, respectively, when compared to the placebo group, which exhibited a 6.0% responder rate (see table below). The additional endpoints shown in the table below were statistically significant at both the 133 mcg and 266 mcg dose levels.

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Phase 3 CC (Trial 01): Responder Endpoints*

Endpoint	Placebo (n = 215)	133 mcg (n = 213)	266 mcg (n = 202)
Primary Endpoint			
12-week CSBM responder[1]	6.0%	16.0% *(p=0.0012)*	21.3% *(p<0.0001)*
Additional Endpoints			
CSBM rate ≥1 responder[2]	13.0%	31.0% *(p<0.0001)*	40.1% *(p<0.0001)*
CSBM rate ≥3 responder[3]	6.0%	16.0% *(p=0.0012)*	21.8% *(p<0.0001)*
12-week CSBM mean change ≥1 responder[4]	25.6%	49.3% *(p<0.0001)*	56.9% *(p<0.0001)*

*
ITT population

(1)
Patient must have had a CSBM weekly frequency rate that was three or greater and increased by one or more from baseline for at least nine of the 12 weeks of the treatment period.

(2)
Patient must have had a CSBM weekly frequency rate that was increased by one or more from baseline for at least nine of the 12 weeks of the treatment period.

(3)
Patient must have had a CSBM weekly frequency rate that was three or greater for at least nine of the 12 weeks of the treatment period

(4)
Patient must have had an overall mean CSBM frequency rate that was increased one or more from baseline over the treatment period.

Linaclotide-treated patients demonstrated a significant increase in average weekly CSBMs from baseline (0.6 for placebo; 2.0 for 133 mcg, p<0.0001; 2.7 for 266 mcg, p<0.0001) and an increase in average weekly SBMs from baseline (1.1 for placebo; 3.4 for 133 mcg, p<0.0001; 3.7 for 266 mcg, p<0.0001).

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The increase in stool frequency occurred in the first week and was sustained over the 12 weeks of treatment as shown in the figure below.

Mean Weekly CSBMs*

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* "Pre-Tx" is the pre-treatment period

In addition to the endpoints detailed above, the remaining secondary endpoints measured in this study; abdominal discomfort, bloating, constipation severity, stool consistency and straining; were statistically significant for linaclotide versus placebo at both doses.

In a post-hoc analysis, improvements in abdominal discomfort, bloating and constipation severity were observed as shown in the table below. Baseline values for these endpoints ranged from 2.47 to 2.56 for abdominal discomfort, 2.73 to 2.82 for bloating and 3.31 to 3.34 for constipation severity.

Phase 3 CC (Trial 01): Improvement as Percent Change from Baseline*

Endpoint	Placebo	133 mcg	266 mcg
Abdominal discomfort	19.5%	31.1%	33.5%
Bloating	13.0%	24.3%	27.3%
Constipation severity	14.4%	40.2%	42.7%

* ITT population. Improvement as percent change from baseline calculated as the percent difference in the treatment group's mean change from baseline value relative to the mean baseline score.

The most common TEAE associated with linaclotide treatment in Trial 01 was diarrhea (15% to 20% of patients, compared to 3% for placebo). Diarrhea led to discontinuation in 5% to 6% of linaclotide

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treated patients compared to 0.5% of patients receiving placebo. Other TEAEs were similarly distributed across the treatment groups. Serious adverse events occurred in 2% of patients and were similarly distributed across the placebo and linaclotide treatment groups. There was one death during the treatment period, and one death outside of the treatment period, both of which were deemed unrelated to treatment by the investigators.

Phase 3 CC (Trial 01): Treatment-emergent Adverse Events

TEAEs occurring in ≥ 3% of patients in any of the linaclotide groups and > placebo

Treatment-emergent adverse event (TEAE)	Placebo N=215	Linaclotide 133 mcg N=213	Linaclotide 266 mcg N=205	All N=418
Any TEAE	**116 (54%)**	**138 (65%)**	**116 (57%)**	**254 (61%)**
Diarrhea	6 (3%)	42 (20%)	30 (15%)	72 (17%)
Flatulence	13 (6%)	16 (8%)	13 (6%)	29 (7%)
Upper respiratory tract infection	14 (7%)	16 (8%)	9 (4%)	25 (6%)
Abdominal pain	5 (2%)	11 (5%)	11 (5%)	22 (5%)
Nausea	7 (3%)	8 (4%)	9 (4%)	17 (4%)
Abdominal distension	7 (3%)	7 (3%)	8 (4%)	15 (4%)
Urinary tract infection	8 (4%)	8 (4%)	6 (3%)	14 (3%)
Sinusitis	5 (2%)	8 (4%)	4 (2%)	12 (3%)
Nasopharyngitis	7 (3%)	3 (1%)	8 (4%)	11 (3%)

Trial 303. Trial 303 was conducted in 643 patients, and was identical to Trial 01 in design except Trial 303 also included a four-week randomized withdrawal period, as described below. During the baseline period, the average CSBM frequency was 0.3 CSBMs per week and 68% of patients had no CSBMs during this period.

The 12-week CSBM responder rate was 21.2% in the 133 mcg linaclotide group (p<0.0001) and 19.4% in the 266 mcg linaclotide group (p<0.0001), a numerical increase of 6.3 and 5.8 fold, respectively, when compared to the placebo group, which exhibited a 3.3% responder rate.

The additional endpoints shown in the table below were statistically significant at both the 133 mcg and 266 mcg dose levels.

Phase 3 CC (Trial 303): Responder Endpoints*

Endpoint	Placebo (N = 209)	133 mcg (N = 217)	266 mcg (N = 216)
Primary Endpoint			
12-week CSBM responder[(1)]	3.3%	21.2% *(p<0.0001)*	19.4% *(p<0.0001)*
Additional Endpoints			
CSBM rate change ≥1 responder[(2)]	11.0%	39.2% *(p<0.0001)*	37.0% *(p<0.0001)*
CSBM rate ≥3 responder[(3)]	3.8%	21.7% *(p<0.0001)*	19.4% *(p<0.0001)*
12-week CSBM mean change ≥1 responder[(4)]	22.5%	55.8% *(p<0.0001)*	52.8% *(p<0.0001)*

* ITT population

(1) Patient must have had a CSBM weekly frequency rate that was three or greater and increased by one or more from baseline for at least nine of the 12 weeks of the treatment period.

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(2) Patient must have had a CSBM weekly frequency rate that was increased by one or more from baseline for at least nine of the 12 weeks of the treatment period.

(3) Patient must have had a CSBM weekly frequency rate that was three or greater for at least nine of the 12 weeks of the treatment period

(4) Patient must have had an overall mean CSBM frequency rate that was increased one or more from baseline over the treatment period.

Linaclotide-treated patients demonstrated a significant increase in average weekly CSBMs from baseline (0.5 for placebo; 1.9 for 133 mcg, p<0.0001; 2.0 for 266 mcg, p<0.0001) and a significant increase in average weekly SBMs from baseline (1.1 for placebo; 3.0 for 133 mcg, p<0.0001; 3.0 for 266 mcg, p<0.0001). The increase in stool frequency occurred in the first week and was sustained over the 12 weeks of treatment.

In addition to the endpoints detailed above, the remaining secondary endpoints measured in Trial 303; abdominal discomfort, bloating, constipation severity, stool consistency and straining; were statistically significant for linaclotide versus placebo at both doses.

In a post hoc analysis, improvements in abdominal discomfort, bloating and constipation severity were observed as shown in the table below. Baseline values for these endpoints ranged from 2.46 to 2.52 for abdominal discomfort, 2.74 to 2.81 for bloating, and 3.25 to 3.32 for constipation severity.

Phase 3 CC (Trial 303): Improvement as Percent Change from Baseline*

Endpoint	Placebo	133 mcg	266 mcg
Abdominal discomfort	21.1%	32.9%	30.3%
Bloating	13.2%	26.9%	22.0%
Constipation severity	13.9%	40.5%	37.2%

* ITT population. Improvement as percent change from baseline calculated as the percent difference in the treatment group's mean change from baseline value relative to the mean baseline score.

As mentioned above, Trial 303 included a four-week randomized withdrawal period. During the 12-week treatment period in Trial 303, patients were randomized to placebo, 133 mcg or 266 mcg linaclotide. Following the 12-week treatment period, patients were re-randomized to either placebo or linaclotide according to five different treatment sequences as described below:

placebo to linaclotide 266 mcg;

linaclotide 133 mcg to placebo;

linaclotide 133 mcg to linaclotide 133 mcg;

linaclotide 266 mcg to placebo; or

linaclotide 266 mcg to linaclotide 266 mcg.

In the randomized withdrawal period, linaclotide-treated groups re-randomized to placebo exhibited bowel and abdominal symptoms similar to those seen in the placebo group during the treatment period, without evidence that linaclotide made the subjects' original pre-treatment symptoms worse. Additionally, the placebo group, when allocated to 266 mcg linaclotide treatment group in the randomized withdrawal period, showed improvements in symptoms similar to those observed in the groups initially treated with linaclotide. Linaclotide-treated groups who continued linaclotide following re-randomization continued to demonstrate a sustained effect over the four-week randomized withdrawal period.

This pattern is illustrated in the figures below for CSBM frequency and constipation severity.

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Mean Weekly CSBMs*

Mean Weekly Constipation Severity*

* "Pre-Tx" is the pre-treatment period

* Includes randomized withdrawal (RW) period

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The TEAEs for Trial 303 are shown in the table below. The most common adverse event associated with linaclotide treatment was diarrhea (12% to 14%, compared to 7% for placebo). Diarrhea led to discontinuation in 3% of linaclotide treated patients compared to 0.5% of patients receiving placebo. Other adverse events were similarly distributed across the treatment groups. Serious adverse events occurred in 2% of patients and were similarly distributed across placebo and linaclotide treatment groups. There were no deaths during this trial.

Phase 3 CC (Trial 303): Treatment-emergent Adverse Events

TEAEs occurring in ≥ 3% of patients in any of the linaclotide groups and > placebo

Treatment-emergent adverse events (TEAE)	Placebo N=209	Linaclotide 133 mcg N=217	Linaclotide 266 mcg N=217	All N=434
Any TEAE	**105 (50%)**	**122 (56%)**	**119 (55%)**	**241 (56%)**
Diarrhea	14 (7%)	27 (12%)	30 (14%)	57 (13%)
Headache	8 (4%)	7 (3%)	10 (5%)	17 (4%)
Flatulence	9 (4%)	8 (4%)	8 (4%)	16 (4%)
Nausea	8 (4%)	7 (3%)	9 (4%)	16 (4%)
Abdominal distension	3 (1%)	8 (4%)	7 (3%)	15 (3%)
Abdominal pain	8 (4%)	6 (3%)	9 (4%)	15 (3%)
Nasopharyngitis	6 (3%)	6 (3%)	9 (4%)	15 (3%)
Sinusitis	3 (1%)	5 (2%)	7 (3%)	12 (3%)
Abdominal pain upper	3 (1%)	7 (3%)	3 (1%)	10 (2%)

In a broad sample from both trials (>300 patients), using methods that can measure as little as 0.2 nanograms of linaclotide or two nanograms of its active metabolite in a milliliter of plasma, there were no measurable plasma levels of linaclotide or its active metabolite.

Pre-specified Subpopulation Analysis

In an integrated analysis of results from male patients from the two Phase 3 CC trials, a statistically significant increase in responders was observed as assessed by the primary endpoint. Likewise, in a similar integrated analysis of elderly patients (65 years or older) from the two Phase 3 CC trials, a statistically significant effect was observed. Details are depicted in the table below.

Phase 3 CC Trials: Primary Endpoint in Pre-specified Subpopulations*

Male Patients	**Placebo (N = 46)**	**133 mcg (N = 44)**	**266 mcg (N = 51)**
12-week CSBM responder[1]	4.3%	29.5%	29.4%
		(p=0.0028)	*(p=0.0014)*
Elderly Patients (≥65 years of age)	**Placebo (N = 55)**	**133 mcg (N = 51)**	**266 mcg (N = 48)**
12-week CSBM responder[1]	5.5%	33.3%	20.8%
		(p=0.0004)	*(p=0.0312)*

* ITT population, pooled across both Ph3 CC trials (Trial 01 and Trial 303)

(1) Patient must have had a CSBM weekly frequency rate that was three or greater and increased by one or more from baseline for at least nine of the 12 weeks of the treatment period.

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Long-Term Safety Studies

We are conducting two open-label long-term safety studies, or LTSS, which have been underway since September 2008. The long-term safety studies were undertaken to assess the safety and tolerability profile of linaclotide treatment over six to 12 months and longer, as required by U.S. regulatory requirements for a new chemical entity intended for long-term treatment (chronic or repeated intermittent use for longer than six months), and to provide continued linaclotide therapy to patients who have requested continued access. Patients who complete any of the linaclotide Phase 2 or Phase 3 trials are eligible to enroll in the LTSS. In addition, patients who complete the pre-treatment period of one of the Phase 3 efficacy studies, but who fail to be randomized for reasons not related to their classification as having CC or IBS-C, are also eligible to enroll in the LTSS. We expect these studies to include greater than 2,500 patients and they are designed to further evaluate the safety and tolerability of linaclotide at the 266 mcg dose. To date, we have enrolled over 1,500 patients in these studies.

Sales and Marketing

For the foreseeable future, we intend to develop and commercialize our drugs in the U.S. alone or with partners, while out-licensing commercialization rights for other territories. In executing our strategy, our goal is to retain significant control over the development process and commercial execution for our products, while participating in a meaningful way in the economics of all drugs that we bring to the market.

We plan to develop our commercial organization around linaclotide, with the intent to leverage this organization for future products. To deliver on our strategy, we intend to create a high-quality commercial organization dedicated to bringing innovative, highly-valued healthcare solutions to our customers, including patients, payors, and healthcare providers.

Maximizing the Value of Linaclotide in the U.S.

Our commercial strategy for linaclotide, if approved, will be to establish linaclotide as the prescription product of choice for both IBS-C and CC. We, together with our U.S. commercialization partner Forest, plan to build awareness that patients suffer from multiple, highly bothersome symptoms of IBS-C and CC, and that these symptoms can dramatically impair sufferers' quality of life.

Forest has demonstrated the ability to successfully launch innovative products, penetrate primary care markets and drive the growth of multiple brands in highly competitive markets. Forest brings large and experienced sales, national accounts, trade relations, operations and management teams providing ready access to primary care offices and key managed care accounts. We have strong alignment with Forest and a shared vision for linaclotide. The combined marketing team possesses a deep understanding of gastroenterology and primary care customers, and this knowledge will be leveraged to craft a compelling medical message and promotional campaign.

If linaclotide is approved, we intend to maximize its potential value in the U.S. by demonstrating linaclotide's anticipated clinical benefits and good tolerability in the treatment of the multiple symptoms relating to IBS-C and CC. Based on its unique mechanism of action and its clinical data, we believe linaclotide:

- could offer rapid, multi-symptom reduction of IBS-C and CC symptoms;
- could address the needs of many of the patients who currently are not fully satisfied with prescription treatment options;
- could address the needs of many patients who are treated by healthcare providers with over the counter options, or who are self-medicating with over the counter options;
- could enhance patient compliance due to its favorable tolerability; and

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may ease some lingering safety concerns caused by the withdrawal of several prior drugs in this category, because linaclotide has limited systemic exposure and does not impact serotonin receptors, unlike prior drugs indicated for IBS-C and/or CC.

We intend to build strong ties with the medical community by efficiently providing disease awareness information, product information and treatment solutions to enable physicians to more effectively identify, diagnose and manage patient care in these patient populations. We intend to:

- educate healthcare providers and provide patient assessment tools to diagnose and monitor treatment response;
- establish the importance of pain and discomfort as a driver for patients to seek therapy, and a cause of dissatisfaction with current therapies;
- introduce linaclotide's novel mechanism of action, which may provide a rationale for the efficacy and safety of linaclotide; and
- position linaclotide as a viable treatment for the effective relief of the multiple symptoms of IBS-C and CC.

We plan to educate patients suffering from symptoms relating to IBS-C and CC to enable them to recognize that they have a real medical disorder and could possibly benefit from treatment. We intend to:

- raise patient awareness through the use of symptom awareness messages and outreach to patient advocacy groups, because we believe, as demonstrated in the GERD market, that patients can easily self-identify with symptomatic disorders and can be motivated to demand improvement in care;
- improve the patient-physician dialogue, helping physicians to appreciate the significant level of patient suffering, alleviate the embarrassment that can inhibit patients from fully disclosing the extent of their symptoms, and expose the limitations of existing prescription and over the counter therapies; and
- empower the millions of patients who previously requested prescription therapies for agents such as Zelnorm and remain frustrated with current treatment options, to demand more comprehensive care and access to linaclotide, if approved.

We believe a successful patient education strategy will be a critical component in closing the significant gap between diagnosed and effectively treated patients. We will consider the use of direct-to-consumer promotional campaigns, which have been used successfully in the past to drive patient awareness and demand for treatment. We also intend to use other efficient communication channels and point of care education solutions to educate and enable patients to discuss their symptoms and treatment response with physicians. A large scale general awareness campaign will be considered after we evaluate the impact of our targeted patient education efforts aimed at currently dissatisfied patients seeking an alternative.

We intend to build a commercial organization, including our own primary and specialty care field force in the U.S., complementing and leveraging our partner Forest's demonstrated ability and experience in successfully launching innovative products and penetrating primary care markets. In addition:

- we hope to complement the Forest selling activities with a focused effort on gastrointestinal specialists and the highest volume primary care offices;

upon any commercial launch of linaclotide, we expect to be responsible for up to 35% of the field sales effort, in a geographically distributed manner, and will be tasked with calling on primary care physicians and specialists;

we expect to be responsible for up to 35% of the medical science liaison efforts; and

we intend to develop innovative internal capabilities, utilizing state of the art technologies to reach patients in varied locations, including the doctor's office, the pharmacy and on the internet, in an effort to encourage the adoption of linaclotide and attempt to optimize patient adherence.

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We also hope to maximize patient access to treatment with linaclotide on affordable terms. We intend to:

- create a compelling evidence-based value dossier supported by key opinion leaders and patient advocates to secure payor reimbursement;
- offer linaclotide at a price that reflects its anticipated efficacy and safety profile relative to other existing therapies; and
- seek an appropriate status for linaclotide on the formularies of managed care payors.

Maximizing the Value of Linaclotide Outside the U.S.

We have out-licensed commercialization rights for territories outside of the U.S. to Almirall in Europe and Astellas in Japan, South Korea, Taiwan, Thailand, the Philippines and Indonesia.

In April 2009, we entered into a licensing agreement with Almirall to develop and commercialize linaclotide in Europe (including the Commonwealth of Independent States countries and Turkey) for the treatment of IBS-C and other gastrointestinal conditions. Under the terms of the license agreement, Almirall has paid us $53 million, which included a $38 million up-front licensing fee paid upon execution of the license agreement. Remaining pre-commercial licensing fees, milestone payments and related equity investments could total up to $40 million. In addition, we will receive escalating royalties on linaclotide sales should Almirall receive approval to market and sell linaclotide in Europe. Almirall is responsible for activities and expenses relating to regulatory approval and commercialization in the European market.

Almirall provides access to the highest potential European markets with an established sales presence in each of the United Kingdom, Italy, France, Germany and Spain, and also has a presence in Belgium, Poland, Portugal and Switzerland. Almirall plans to coordinate sales and marketing efforts from its central office in an effort to ensure consistency of the overall brand strategy and objectively assess performance. Almirall's knowledge of the local markets should help to facilitate regulatory access, reimbursement and market penetration through a customized approach to implementing promotional and selling campaigns in the European Union.

In November 2009, we entered into a licensing agreement with Astellas to develop and commercialize linaclotide for the treatment of IBS-C and other gastrointestinal conditions in Japan, South Korea, Taiwan, Thailand, the Philippines and Indonesia. Under the terms of the license agreement, Astellas paid us a $30 million up-front licensing fee. Remaining pre-commercial milestone payments could total up to $45 million. Astellas is responsible for activities and expenses relating to regulatory approval and commercialization in those markets. If Astellas receives approval to market and sell linaclotide, we will receive escalating royalties on linaclotide sales.

Astellas is one of Japan's largest pharmaceutical companies and has top commercial capabilities in both primary care and specialty categories throughout Asia. Their demonstrated ability to market innovative medicines and their growing gastrointestinal franchise in Japan make them an ideal partner for Ironwood.

Pipeline Strategy

We invest significant effort defining and refining our research and development process and teaching internally our approach to drug-making. We favor programs with early decision points, well validated targets, predictive preclinical models, initial chemical leads and clear paths to approval, all in the context of a target product profile that can address significant unmet or underserved clinical needs. We emphasize data-driven decision making, strive to advance or terminate projects early based on clearly defined go/no go criteria, prioritize programs at all stages and fluidly allocate our capital to the most promising programs. We continue to work diligently to ensure this disciplined approach is ingrained in our culture and processes

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and expect that our research productivity will continue to improve as our team gains more experience and capabilities. Moreover, we hope that as our passion and style of drug-making becomes better validated and more widely known, we will be able to attract additional like-minded researchers to join our cause.

To date, all of our product candidates have been discovered internally. We believe our discovery team has created a number of promising candidates over the past few years and has developed an extensive intellectual property estate in each of these areas. In addition we are actively seeking to identify attractive external opportunities. We utilize the same critical filters for investment when evaluating external programs as we do with our own, internally-derived candidates.

Pipeline

We aim to create differentiated, first-in-class/best-in-class medicines that provide relief and clear therapeutic benefits to patients suffering from chronic diseases. To support this vision, we have ongoing efforts to identify product candidates that strengthen our pipeline, including treatments for upper gastrointestinal disorders, pain and inflammation, asthma and allergic disease, and cardiovascular disease.

An example of one of our internally discovered candidates meeting the above criteria is IW-6118, a novel mechanism agent for the treatment of pain that acts by inhibiting the enzyme Fatty Acid Amide Hydrolase, or FAAH. There remains a substantial unmet need for drugs with improved efficacy and side-effect profiles to manage pain, and we believe few novel mechanism agents to treat pain are in clinical development. FAAH metabolizes bioactive lipid molecules, known as fatty acid amides, or FAAs, that have important analgesic and anti-inflammatory properties. Inhibition of FAAH has been shown preclinically to increase levels of FAAs, reduce pain sensation, and decrease inflammation, indicating that FAAH inhibitors could provide an innovative means to provide pain relief in humans.

IW-6118 is a novel small molecule inhibitor of FAAH, that decreased inflammation and pain and elevated FAAs in preclinical models. We have an active investigational new drug application, or IND, for IW-6118 and are currently investigating the safety, tolerability, and pharmacokinetic properties of this molecule in Phase 1 studies. In addition, the effects of IW-6118 on the plasma levels of FAAs are also being assessed. Our data indicate that IW-6118 has favorable pharmacokinetics and that IW-6118 dosing elevates FAAs, suggesting that this molecule effectively inhibits FAAH in humans.

Manufacturing and Supply

We do not have manufacturing capabilities, and we currently use contract manufacturers for the manufacturing of linaclotide and our other product candidates. Accordingly, unless or until we develop or acquire sufficient manufacturing capabilities, we will depend on third parties to manufacture linaclotide and any future products that we may develop or acquire. We are in the process of seeking long-term commercial supply contracts with two active pharmaceutical ingredient manufacturers, and we anticipate that we will be able to negotiate these third-party agreements on commercially reasonable terms. We believe both manufacturers have the capabilities to produce linaclotide in accordance with current good manufacturing practices, or GMP, on a sufficient scale to meet our commercial needs. It is a fundamental part of our commercial strategy to maintain two or more active pharmaceutical ingredient suppliers to ensure continuity in our supply chain. In addition, we have in-house expertise to manage our two contract manufacturing partners effectively.

Each of our collaboration partners, Forest, Almirall and Astellas, is responsible for completing the drug product manufacturing process of linaclotide by finishing and packaging linaclotide active pharmaceutical ingredient into capsules, and we will be dependent upon our partners' success in producing drug product for commercial sales. We believe these partners have sufficient capabilities to complete the manufacturing process successfully in-house.

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Linaclotide is a 14 amino acid peptide, manufactured via solid-phase synthesis using naturally occurring amino acids. There is little or no precedent for producing a convenient, room-temperature stable dosage form of an orally-delivered peptide drug with a significant market opportunity. Our team developed a formulation with simple, safe excipients that was shown to be stable at room temperature for at least 24 months in various development batches. In addition, we have demonstrated stability under accelerated conditions of 40°C with 75% relative humidity for six months, which, in accordance with industry standards, is predictive of stability of greater than 18 months at room temperature conditions. We optimized our formulation following the achievement of development batch stability, and prepared scale up batches and Phase 3 clinical trial material for stability testing. Both show acceptable stability under accelerated conditions for six months and have shown acceptable room temperature stability at the six and 12 month time points. We will continue to monitor those batches as well as additional drug product registration batches for stability in the coming months.

We believe our efforts to date will lead to a formulation that is both cost effective and able to meet the stability requirements for pharmaceutical products. Our work in this area has created an opportunity to seek additional intellectual property protections around the linaclotide program. In conjunction with Forest, we have filed patent applications worldwide to cover the room temperature stable linaclotide formulation as well as related formulations. If claims covering the room temperature stable formulation are allowed, they would expire in 2029 in the U.S. These patent rights would be subject to any potential patent term adjustments or extensions and/or supplemental protection certificates extending such term extensions in countries where such extensions may become available.

Microbia

We are the majority stockholder of Microbia, Inc., or Microbia, a biomanufacturing company based in Lexington, Massachusetts. Microbia was spun out of Ironwood in 2006 and focuses on building a specialty biochemicals business based on a proprietary strain-development platform. Microbia's technology platform has been designed to produce high-quality, competitively-priced specialty ingredients and industrial biomaterials from renewable resources.

Microbia designs microbes for the cost-effective biomanufacturing of products from renewable resources. This technology may be applicable to a wide array of product opportunities. Microbia's initial focus is on carotenoids, which are of a broad class of chemicals based on the 5-carbon isoprene structure. Commonly found in nature, these chemicals have traditionally been manufactured from petrochemical-derived raw materials. Current commercial applications for carotenoids include natural flavor and aroma compounds, nutritional supplements, pharmaceutical intermediates and a variety of industrial chemicals. In addition to these already developed uses, newer applications under development include high octane biofuels and other industrial chemicals such as rubber substitutes.

Patents and Proprietary Rights

We actively seek to protect the proprietary technology that we consider important to our business, including pursuing patents that cover our products and compositions, their methods of use and the processes for their manufacture, as well as any other relevant inventions and improvements that are commercially important to the development of our business. We also rely on trade secrets that may be important to the development of our business.

Our success will depend significantly on our ability to obtain and maintain patent and other proprietary protection for the technology, inventions and improvements we consider important to our business; defend our patents; preserve the confidentiality of our trade secrets; and operate without infringing the patents and proprietary rights of third parties.

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Linaclotide and GC-C Patent Portfolio

Our linaclotide patent portfolio is currently composed of two issued U.S. patents; a granted European patent (which has been validated in 31 European countries and in Hong Kong); four issued patents in other foreign jurisdictions; nine pending U.S. non-provisional patent applications; five pending U.S. provisional patent applications; two pending Patent Cooperation Treaty, or PCT, applications; and 46 pending foreign patent applications, all of which relate to issued U.S. patents, pending U.S. non-provisional patent applications or pending PCT applications. We own all of the issued patents and own or jointly own all of the pending applications.

The issued U.S. patents, which will expire in 2025, contain claims directed to the linaclotide molecule, pharmaceutical compositions thereof, methods of using linaclotide to treat gastrointestinal disorders and processes for making the molecule. If claims in our pending patent covering the room temperature stable formulation are allowed, they would expire in August 2029. The granted European patent, which will expire in 2024, contains claims directed to the linaclotide molecule, pharmaceutical compositions thereof and uses of linaclotide to prepare medicaments for treating gastrointestinal disorders. The pending PCT, U.S., foreign and provisional applications contain claims directed to linaclotide and related molecules, pharmaceutical formulations thereof, methods of using linaclotide to treat various diseases and disorders and processes for making the molecule. These patent applications, if issued, will expire between 2024 and 2030.

In addition to the patents and patent applications related to linaclotide, we currently have one issued U.S. patent, five pending U.S. non-provisional patent applications, one pending PCT application and five pending foreign non-provisional patent applications, all of which relate to the U.S. issued patent or pending U.S. non-provisional patent applications, which are directed to other GC-C agonist molecules, pharmaceutical compositions thereof, methods of using these molecules to treat various diseases and disorders and processes of synthesizing the molecules. The issued U.S. patent will expire in 2024. The patent applications, if issued, will expire between 2024 and 2029.

Additional Intellectual Property

Our pipeline patent portfolio is currently composed of three issued U.S. patents; a granted European patent (which has been validated in 31 European countries and in Hong Kong); six issued patents in other foreign jurisdictions; 15 pending U.S. non-provisional patent applications; three pending U.S. provisional applications; nine pending PCT applications; and 67 pending foreign patent applications, all of which relate to issued U.S. patents or pending U.S. non-provisional patent applications. We own all of the issued patents and own or jointly own all of the pending applications. One of the issued U.S. patents expires in 2022, and the other two patents expire in 2024. The European patent and the other foreign issued patents expire in 2024. The pending patent applications, if issued, will expire between 2024 and 2030.

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the date of filing the non-provisional application. In the U.S., a patent's term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the U.S. Patent and Trademark Office in granting a patent, or may be shortened if a patent is terminally disclaimed over an earlier-filed patent.

The patent term of a patent that covers an FDA-approved drug may also be eligible for patent term extension, which permits patent term restoration as compensation for the patent term lost during the FDA regulatory review process. The Hatch-Waxman Act permits a patent term extension of up to five years beyond the expiration of the patent. The length of the patent term extension is related to the length of time the drug is under regulatory review. Patent extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval and only one patent applicable to an approved drug may be extended. Similar provisions are available in Europe and other foreign jurisdictions to extend the term of a patent that covers an approved drug. We expect to apply for patent term extensions for some of

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our current patents, depending upon the length of clinical trials and other factors involved in the filing of an NDA.

Government Regulation

In the United States, pharmaceutical products are subject to extensive regulation by the FDA. The Federal Food, Drug, and Cosmetic Act and other federal and state statutes and regulations, govern, among other things, the research, development, testing, manufacture, storage, recordkeeping, approval, labeling, promotion and marketing, distribution, post-approval monitoring and reporting, sampling, and import and export of pharmaceutical products. The FDA has very broad enforcement authority and failure to abide by applicable regulatory requirements can result in administrative or judicial sanctions being imposed on us, including warning letters, refusals of government contracts, clinical holds, civil penalties, injunctions, restitution, disgorgement of profits, recall or seizure of products, total or partial suspension of production or distribution, withdrawal of approval, refusal to approve pending applications, and criminal prosecution.

FDA Approval Process

We believe that our product candidates, including linaclotide, will be regulated by the FDA as drugs. No manufacturer may market a new drug until it has submitted an NDA to the FDA, and the FDA has approved it. The steps required before the FDA may approve an NDA generally include:

- preclinical laboratory tests and animal tests conducted in compliance with FDA's good laboratory practice requirements;
- development, manufacture and testing of active pharmaceutical product and dosage forms suitable for human use in compliance with current good manufacturing practices, or GMP;
- the submission to the FDA of an investigational new drug application, or IND, for human clinical testing, which must become effective before human clinical trials may begin;
- adequate and well-controlled human clinical trials to establish the safety and efficacy of the product for its specific intended use(s);
- the submission to the FDA of an NDA; and
- FDA review and approval of the NDA.

Preclinical tests include laboratory evaluation of the product candidate, as well as animal studies to assess the potential safety and efficacy of the product candidate. The conduct of the pre-clinical tests must comply with federal regulations and requirements including good laboratory practices. We must submit the results of the preclinical tests, together with manufacturing information, analytical data and a proposed clinical trial protocol to the FDA as part of an IND, which must become effective before we may commence human clinical trials. The IND will automatically become effective 30 days after its receipt by the FDA, unless the FDA raises concerns or questions before that time about the conduct of the proposed trials. In such a case, we must work with the FDA to resolve any outstanding concerns before clinical trials can proceed. We cannot be sure that submission of an IND will result in the FDA allowing clinical trials to begin, or that, once begun, issues will not arise that suspend or terminate such trials. The study protocol and informed consent information for patients in clinical trials must also be submitted to an institutional review board for approval. An institutional review board may also require the clinical trial at the site to be halted, either temporarily or permanently, for failure to comply with the institutional review board's requirements or may impose other conditions.

Clinical trials involve the administration of the product candidate to humans under the supervision of qualified investigators, generally physicians not employed by or under the trial sponsor's control. Clinical trials are typically conducted in three sequential phases, though the phases may overlap or be combined. In Phase 1, the initial introduction of the drug into healthy human subjects, the drug is usually tested for

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safety (adverse effects), dosage tolerance and pharmacologic action, as well as to understand how the drug is taken up by and distributed within the body. Phase 2 usually involves studies in a limited patient population (individuals with the disease under study) to:

- evaluate preliminarily the efficacy of the drug for specific, targeted conditions;
- determine dosage tolerance and appropriate dosage as well as other important information about how to design larger Phase 3 trials; and
- identify possible adverse effects and safety risks.

Phase 3 trials generally further evaluate clinical efficacy and test for safety within an expanded patient population. The conduct of the clinical trials is subject to extensive regulation, including compliance with good clinical practice regulations and guidance.

The FDA may order the temporary or permanent discontinuation of a clinical trial at any time or impose other sanctions if it believes that the clinical trial is not being conducted in accordance with FDA requirements or presents an unacceptable risk to the clinical trial patients. We may also suspend clinical trials at any time on various grounds.

The results of the preclinical and clinical studies, together with other detailed information, including the manufacture and composition of the product candidate, are submitted to the FDA in the form of an NDA requesting approval to market the drug. FDA approval of the NDA is required before marketing of the product may begin in the U.S. If the NDA contains all pertinent information and data, the FDA will "file" the application and begin review. The FDA may "refuse to file" the NDA if it does not contain all pertinent information and data. In that case, the applicant may resubmit the NDA when it contains the missing information and data. Once the submission is accepted for filing, the FDA begins an in-depth review. The FDA has agreed to certain performance goals in the review of new drug applications. Most such applications for non-priority drug products are reviewed within 10 months. The review process, however, may be extended by FDA requests for additional information, preclinical or clinical studies, clarification regarding information already provided in the submission, or submission of a risk evaluation and mitigation strategy. The FDA may refer an application to an advisory committee for review, evaluation and recommendation as to whether the application should be approved. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions. Before approving an NDA, the FDA will typically inspect the facilities at which the product candidate is manufactured and will not approve the product candidate unless GMP compliance is satisfactory. FDA also typically inspects facilities responsible for performing animal testing, as well as clinical investigators who participate in clinical trials. The FDA may refuse to approve an NDA if applicable regulatory criteria are not satisfied, or may require additional testing or information. The FDA may also limit the indications for use and/or require post-marketing testing and surveillance to monitor the safety or efficacy of a product. Once granted, product approvals may be withdrawn if compliance with regulatory standards is not maintained or problems are identified following initial marketing.

The testing and approval process requires substantial time, effort and financial resources, and our product candidates may not be approved on a timely basis, if at all. The time and expense required to perform the clinical testing necessary to obtain FDA approval for regulated products can frequently exceed the time and expense of the research and development initially required to create the product. The results of preclinical studies and initial clinical trials of our product candidates, including linaclotide, are not necessarily predictive of the results from large-scale clinical trials, and clinical trials may be subject to additional costs, delays or modifications due to a number of factors, including difficulty in obtaining enough patients, investigators or product candidate supply. Failure by us or our collaborators, licensors or licensees, including Forest, Almirall and Astellas, to obtain, or any delay in obtaining, regulatory approvals or in complying with requirements could adversely affect the commercialization of product candidates and our ability to receive product or royalty revenues.

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Hatch-Waxman Act

The Hatch-Waxman Act established abbreviated approval procedures for generic drugs. Approval to market and distribute these drugs is obtained by submitting an Abbreviated New Drug Application, or ANDA, with the FDA. The application for generic drugs is "abbreviated" because it need not include preclinical or clinical data to demonstrate safety and effectiveness and may instead rely on the FDA's previous finding that the brand drug, or reference drug, is safe and effective. In order to obtain approval of an ANDA, an applicant must, among other things, establish that its product is bioequivalent to an existing approved drug and that it has the same active ingredient(s), strength, dosage form, and the same route of administration. A generic drug is considered bioequivalent to its reference drug if testing demonstrates that the rate and extent of absorption of the generic drug is not significantly different from the rate and extent of absorption of the reference drug when administered under similar experimental conditions.

The Hatch-Waxman Act also provides incentives by awarding, in certain circumstances, certain legal protections from generic competition. This protection comes in the form of a non-patent exclusivity period, during which the FDA may not accept or approve a generic drug, whether the application for such drug is submitted through an ANDA or a through another form of application, known as a 505(b)(2) application.

The Hatch-Waxman Act grants five years of exclusivity when a company develops and gains NDA approval of a new chemical entity that has not been previously approved by the FDA. This exclusivity provides that the FDA may not accept an ANDA or 505(b)(2) application for five years after the date of approval of previously approved drug, or four years in the case of an ANDA or 505(b)(2) application that challenges a patent claiming the reference drug (see discussion below regarding patent challenges). The Hatch-Waxman Act also provides three years of exclusivity for approved applications for drugs that are not new chemical entities, if the application contains the results of new clinical investigations (other than bioavailability studies) that were essential to approval of the application. Examples of such applications include applications for new indications, dosage forms (including new drug delivery systems), strengths, or conditions of use for an already approved product. This three-year exclusivity period protects against FDA approval of ANDAs and 505(b)(2) applications for generic drugs that include the innovation that required clinical data; it does not prohibit the FDA from accepting or approving ANDAs or 505(b)(2) NDAs for generic drugs that do not include the innovation.

Paragraph IV Certifications. Under the Hatch-Waxman Act, NDA applicants and NDA holders must provide information about certain patents claiming their drugs for listing in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations," also known as the "Orange Book." When an ANDA or 505(b)(2) application is submitted, it must contain one of several possible certifications regarding each of the patents listed in the Orange Book for the reference drug. A certification that a listed patent is invalid or will not be infringed by the sale of the proposed product is called a "Paragraph IV" certification.

Within 30 days of the acceptance by the FDA of an ANDA or 505(b)(2) application containing a Paragraph IV certification, the applicant must notify the NDA holder and patent owner that the application has been submitted, and provide the factual and legal basis for the applicant's opinion that the patent is invalid or not infringed. The NDA holder or patent holder may then initiate a patent infringement suit in response to the Paragraph IV notice. If this is done within 45 days of receiving notice of the Paragraph IV certification, a one-time 30-month stay of the FDA's ability to approve the ANDA or 505(b)(2) application is triggered. The FDA may approve the proposed product before the expiration of the 30-month stay only if a court finds the patent invalid or not infringed, or if the court shortens the period because the parties have failed to cooperate in expediting the litigation.

Patent Term Restoration. Under the Hatch-Waxman Act, a portion of the patent term lost during product development and FDA review of an NDA or 505(b)(2) application is restored if approval of the application is the first permitted commercial marketing of a drug containing the active ingredient. The patent term restoration period is generally one-half the time between the effective date of the IND and the

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date of submission of the NDA, plus the time between the date of submission of the NDA and the date of FDA approval of the product. The maximum period of restoration is five years, and the patent cannot be extended to more than 14 years from the date of FDA approval of the product. Only one patent claiming each approved product is eligible for restoration and the patent holder must apply for restoration within 60 days of approval. The U.S. Patent and Trademark Office, in consultation with the FDA, reviews and approves the application for patent term restoration.

Other Regulatory Requirements

After approval, drug products are subject to extensive continuing regulation by the FDA, which include company obligations to manufacture products in accordance with GMP, maintain and provide to the FDA updated safety and efficacy information, report adverse experiences with the product, keep certain records and submit periodic reports, obtain FDA approval of certain manufacturing or labeling changes, and comply with FDA promotion and advertising requirements and restrictions. Failure to meet these obligations can result in various adverse consequences, both voluntary and FDA-imposed, including product recalls, withdrawal of approval, restrictions on marketing, and the imposition of civil fines and criminal penalties against the NDA holder. In addition, later discovery of previously unknown safety or efficacy issues may result in restrictions on the product, manufacturer or NDA holder.

We and any manufacturers of our products are required to comply with applicable FDA manufacturing requirements contained in the FDA's GMP regulations. GMP regulations require among other things, quality control and quality assurance as well as the corresponding maintenance of records and documentation. The manufacturing facilities for our products must meet GMP requirements to the satisfaction of the FDA pursuant to a pre-approval inspection before we can use them to manufacture our products. We and any third-party manufacturers are also subject to periodic inspections of facilities by the FDA and other authorities, including procedures and operations used in the testing and manufacture of our products to assess our compliance with applicable regulations.

With respect to post-market product advertising and promotion, the FDA imposes a number of complex regulations on entities that advertise and promote pharmaceuticals, which include, among others, standards for direct-to-consumer advertising, promoting drugs for uses or in patient populations that are not described in the drug's approved labeling (known as "off-label use"), industry-sponsored scientific and educational activities, and promotional activities involving the internet. Failure to comply with FDA requirements can have negative consequences, including adverse publicity, enforcement letters from the FDA, mandated corrective advertising or communications with doctors, and civil or criminal penalties. Although physicians may prescribe legally available drugs for off-label uses, manufacturers may not market or promote such off-label uses.

Changes to some of the conditions established in an approved application, including changes in indications, labeling, or manufacturing processes or facilities, require submission and FDA approval of a new NDA or NDA supplement before the change can be implemented. An NDA supplement for a new indication typically requires clinical data similar to that in the original application, and the FDA uses the same procedures and actions in reviewing NDA supplements as it does in reviewing NDAs.

Adverse event reporting and submission of periodic reports is required following FDA approval of an NDA. The FDA also may require post-marketing testing, known as Phase 4 testing, risk minimization action plans, and surveillance to monitor the effects of an approved product or place conditions on an approval that could restrict the distribution or use of the product.

Outside the United States, our and our collaborators' abilities to market a product are contingent upon receiving marketing authorization from the appropriate regulatory authorities. The requirements governing marketing authorization, pricing and reimbursement vary widely from jurisdiction to jurisdiction. At present, foreign marketing authorizations are applied for at a national level, although

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within the European Union registration procedures are available to companies wishing to market a product in more than one European Union member state.

Corporate Information

We were incorporated in Delaware in 1998. Prior to April 7, 2008, we were named Microbia, Inc., which is now the name of our majority-owned subsidiary (formerly Microbia Precision Engineering, Inc.). Our address is 320 Bent Street, Cambridge, Massachusetts 02141. Our telephone number is 617-621-7722. Our website address is www.ironwoodpharma.com. Information contained in, and that can be accessed through, our website is not incorporated into and does not form a part of this prospectus.

Employees

As of December 31, 2009, we had 165 employees. Approximately 50 were scientists engaged in discovery research, 73 were in our drug development organization, and 42 were in sales and general and administrative functions. None of our employees are represented by a labor union, and we consider our employee relations to be good.

Property and Facilities

Our corporate headquarters and principal operations are located in Cambridge, Massachusetts, where we lease and occupy approximately 114,400 rentable square feet of office and laboratory space in two buildings located at 301 Binney Street and 320 Bent Street. Pursuant to our lease at 301 Binney Street, we will add approximately 38,800 square feet of lab and office space at this location on or before January 1, 2011. The term of our lease at 301 Binney Street expires on January 31, 2016, with our option to extend the term of the lease for two additional five year periods. The term of our lease at 320 Bent Street expires on December 31, 2010, with our option to extend the term of the lease for three additional five year periods. We believe that our facilities are suitable and adequate for our needs.

Legal Proceedings

On November 7, 2008, we filed a complaint in the United States District Court for the District of Columbia (*Ironwood Pharmaceuticals, Inc. v. Hon. Jon W. Dudas*) against the U.S. Patent and Trademark Office seeking judgment that the patent term adjustment of U.S. Patent 7,371,727 be lengthened from 411 days to 702 days. We believe that the U.S. Patent and Trademark Office miscalculated the patent term adjustment for one of our patents. The case is currently stayed pending final disposition of the appeal of *Wyeth and Elan Pharma International Ltd. v. Hon. Jon W. Dudas* regarding a similar legal issue. The Wyeth appeal is likely to be decided in 2010 and a decision in favor of either party should be dispositive of Ironwood's suit, as well as over 100 cases filed by other parties as a result of the Wyeth decision last year. We do not expect that this litigation, regardless of the decision, will have a material adverse effect on our business.

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MANAGEMENT

Executive Officers and Directors

The following table sets forth the name, age and position of each of our executive officers and directors as of December 31, 2009:

Name	Age	Position
Peter M. Hecht, Ph.D.	46	Chief Executive Officer, Director
Michael J. Higgins	47	Senior Vice President, Chief Operating Officer and Chief Financial Officer
Mark G. Currie, Ph.D.	55	Senior Vice President, R&D and Chief Scientific Officer
Thomas A. McCourt	52	Senior Vice President, Marketing and Sales and Chief Commercial Officer
Joseph C. Cook, Jr.[1][2][4]	67	Director and Chairman of the Board
George H. Conrades[1][2]	70	Director
David Ebersman[3]	40	Director
Marsha H. Fanucci[1]	56	Director
Stephen C. Knight, M.D.[1][5]	49	Director
Terrance G. McGuire[2]	53	Director
Gina Bornino Miller[2]	49	Director
Bryan E. Roberts, Ph.D.[3][6]	42	Director
David E. Shaw[3]	58	Director
Christopher T. Walsh, Ph.D.[3]	65	Director

(1) Member of audit committee.

(2) Member of governance and nominating committee.

(3) Member of compensation committee.

(4) Mr. Cook will step down as chairman of the board of directors (but will remain a director) in July 2010.

(5) Dr. Knight will be resigning from the board of directors at the time of this offering.

(6) Dr. Roberts will become the chairman of the board of directors in July 2010.

Peter M. Hecht has served as our chief executive officer since our founding in 1998. Prior to founding Ironwood, Dr. Hecht was a research fellow at Whitehead Institute for Biomedical Research. Dr. Hecht serves on the boards of directors of Whitehead Institute and Microbia, Inc., our majority-owned subsidiary. He also serves on the Leadership Council for The David H. Koch Institute for Integrative Cancer Research at the Massachusetts Institute of Technology and the advisory board of Infante Sano. Dr. Hecht earned a B.S. in mathematics and an M.S. in biology from Stanford University, and holds a Ph.D. in molecular biology from the University of California at Berkeley.

Michael J. Higgins has served as our chief operating officer and chief financial officer since joining Ironwood in 2003. Prior to 2003, Mr. Higgins held a variety of senior business positions at Genzyme Corporation, including vice president of corporate finance. He serves on the board of directors of Microbia, Inc., our majority-owned subsidiary. Mr. Higgins earned a B.S. from Cornell University and an M.B.A. from the Amos Tuck School of Business Administration at Dartmouth College.

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Mark G. Currie serves as our senior vice president of research and development and chief scientific officer, and has led our R&D efforts since joining us in 2002. Prior to joining Ironwood, he directed cardiovascular and central nervous system disease research as vice president of discovery research at Sepracor Inc. Previously, Dr. Currie initiated, built and led discovery pharmacology and also served as director of arthritis and inflammation at Monsanto Company. Dr. Currie earned a B.S. in biology from the University of South Alabama and holds a Ph.D. in cell biology from the Bowman-Gray School of Medicine of Wake Forest University.

Thomas A. McCourt has served as our senior vice president of marketing and sales and chief commercial officer since joining Ironwood in September 2009. Prior to joining Ironwood, Mr. McCourt led the U.S. brand team for denosumab at Amgen Inc. from April 2008 to August 2009. Prior to that, he was with Novartis AG from 2001 to 2008, where he directed the launch and growth of Zelnorm for the treatment of patients with IBS-C and chronic constipation and held a number of senior commercial roles, including vice president of strategic marketing and operations. Mr. McCourt was also part of the founding team at Astra Merck Inc., leading the development of the medical affairs and science liaison group and then serving as brand manager for Prilosec. Mr. McCourt has a degree in pharmacy from the University of Wisconsin.

Joseph C. Cook, Jr. has served as our chairman of the board of directors since co-founding our company in 1998. Mr. Cook is a principal and co-founder of Mountain Group Capital, LLC, a private investment company. He serves on the board of directors for Corcept Therapeutics, Inc., a biopharmaceutical company, and is a founder and serves as chairman of the board of Clinical Products Ltd., a company marketing a medical food for people with diabetes. Mr. Cook served as chairman of the board of Amylin Pharmaceuticals, Inc. from 1998 to 2009 and was chief executive officer from 1998 to 2003. He spent 28 years at Eli Lilly and Co., retiring from Lilly in 1993 after spending his last seven years there in a variety of senior management positions. In 2009, Mr. Cook received the Pinnacle Award for Life Science Leadership from the Rady School of Management at the University of California at San Diego. Mr. Cook received a B.S. in Engineering from the University of Tennessee in 1965.

George H. Conrades has served as director since December 2005. Mr. Conrades has been the executive chairman of Akamai Technologies, Inc. since 2005, prior to which he served as their chairman and chief executive officer from 1999 to 2005 and as a director from 1998 to 2005. Mr. Conrades has also been a venture partner of Polaris Venture Partners, an early stage investment company, since August 1998. From August 1997 to July 1998, Mr. Conrades served as executive vice president of GTE and president of GTE Internetworking, an integrated telecommunications services firm. Mr. Conrades served as chief executive officer of BBN Corporation, a national Internet services provider and internet technology research and development company, from January 1994 until its acquisition by GTE Internetworking in July 1997. Prior to joining BBN Corporation, Mr. Conrades was a senior vice president at International Business Machines Corporation, or IBM, a developer of computer systems, software, storage systems and microelectronics, and a member of IBM's corporate management board. Mr. Conrades is currently a director of Harley-Davidson, Inc., a motorcycle manufacturer, and Oracle Corporation, an enterprise software company.

David Ebersman has served as director since July 2009. Mr. Ebersman is currently chief financial officer of Facebook, a privately-held social utility company. Prior to joining Facebook, he worked in a number of positions at Genentech, Inc., a leading public biotechnology company, until its acquisition by Hoffmann-La Roche in March 2009. At Genentech, he was appointed executive vice president in January 2006 and chief financial officer in March 2005. Previously, he served as senior vice president, finance from January 2005 through March 2005 and senior vice president, product operations from May 2001 through January 2005. He joined Genentech in February 1994 as a business development analyst and subsequently served as manager, business development from February 1995 to February 1996, director, business development from February 1996 to March 1998, senior director, product development from March 1998 to February 1999 and vice president, product development from February 1999 to May 2001. Prior to joining Genentech, Mr. Ebersman held the position of research analyst at Oppenheimer & Company, Inc.

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Mr. Ebersman was selected as a Fellow in the Henry Crown Fellowship Program. Mr. Ebersman received a B.A. in economics and international relations from Brown University.

Marsha H. Fanucci has served as director since October 2009. Ms. Fanucci served as senior vice president and chief financial officer of Millennium Pharmaceuticals, Inc. from July 2004 through January 2009, where she was responsible for corporate strategy, treasury, financial planning and reporting and operations. While at Millennium, she also served as vice president, finance and corporate strategy and vice president, corporate development and strategy. Previously, she was vice president of corporate development and strategy at Genzyme Corporation, a biotechnology company, from 1998 to 2000. From 1987 to 1998, Ms. Fanucci was employed at Arthur D. Little, Inc. where she most recently served as vice president and director. Ms. Fanucci presently serves on the board of directors of Momenta Pharmaceuticals, Inc. She received her B.S. in pharmacy from West Virginia University and her M.B.A. from Northeastern University.

Stephen C. Knight has served as director since January 2004. Dr. Knight is currently the president and managing partner of Fidelity Biosciences. Prior to joining Fidelity in 2003, Dr. Knight was president and chief operating officer for EPIX Pharmaceuticals, Inc. in Cambridge, Massachusetts. Between 1990 and 1996 Dr. Knight worked as senior consultant at Arthur D. Little. Dr. Knight currently serves as chairman of the board of directors for EnVivo Pharmaceuticals. He also serves on the board of directors of Bikam Pharmaceuticals, CardioKine Inc., Proteostasis Therapeutics, FoldRx, NextWave Pharmaceuticals, Optegra Eyecare, Ltd., Respivert, Ltd., and U.S. Genomics. Dr. Knight holds an M.D. from the Yale University School of Medicine and an M.B.A. from the Yale School of Organization and Management. Dr. Knight received a B.S. in biology from Columbia University.

Terrance G. McGuire has served as director since 1998. Mr. McGuire was a co-founder and is currently a general partner of Polaris Venture Partners. Prior to starting Polaris Venture Partners in 1996, Mr. McGuire spent seven years at Burr, Egan, Deleage & Co., investing in early stage medical and information technology companies. He serves on the board of directors of several private companies and has served on the boards of Akamai Technologies, Inc., Aspect Medical Systems, Inc., Cubist Pharmaceuticals, Inc., deCODE genetics, Inc. and various private companies. Mr. McGuire is currently the chairman of the National Venture Capital Association, which represents ninety percent of the venture capitalists in the U.S., chairman of the board of the Thayer School of Engineering at Dartmouth College, and a member of the boards of The David H. Koch Institute for Integrative Cancer Research at the Massachusetts Institute of Technology and The Arthur Rock Center for Entrepreneurship at Harvard Business School. Mr. McGuire earned a B.S. in physics and economics from Hobart College, an M.S. in engineering from The Thayer School at Dartmouth College and an M.B.A from Harvard Business School.

Gina Bornino Miller has served as director since our founding in 1998. Prior to co-founding Ironwood, Ms. Miller was the president and general manager for Quantum Corporation's Specialty Storage Products Group between 1993 and 1996. Ms. Miller's past work experience also includes vice president of corporate development and planning for Quantum Corporation, director of strategic planning at Silicon Graphics, Inc., various engineering and management positions in the high tech industry and strategy consulting across a variety of other industries. Ms. Miller serves as chairperson of the board of directors of Microbia, Inc., our majority-owned subsidiary.

Bryan E. Roberts has served as director since 2001. Dr. Roberts joined Venrock, a venture capital investment firm, in 1997, where he serves as partner. From 1989 to 1992, Dr. Roberts worked in the corporate finance department of Kidder, Peabody & Co., a brokerage company. Dr. Roberts serves on the board of directors of several private companies, and he has previously served on the board of directors of athenahealth, Inc., XenoPort, Inc. and Sirna Therapeutics, Inc. He received a B.A. from Dartmouth College and a Ph.D. in chemistry and chemical biology from Harvard University.

David E. Shaw has served as director since 2004. Mr. Shaw is managing director of Black Point Group LLC, a private equity partnership, and a partner with Venrock, a venture capital firm. Mr. Shaw was

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formerly an advisor to New Mountain Capital, LLC from 2004 to 2007. He served as executive chairman of Ikaria Holdings, Inc., a pharmaceutical company, from 2008-2009 and was their chief executive officer from 2007-2008. Mr. Shaw also serves as chairman of the board and chief executive officer of Fetch Enterprises, Inc. He is the founder and former chief executive of IDEXX Laboratories Inc., a medical technology company, and he has been active in other life science firms. Mr. Shaw holds a B.A. from the University of New Hampshire and an M.B.A. from the University of Maine.

Christopher T. Walsh has served as director since July 2003. Dr. Walsh has been the Hamilton Kuhn Professor of Biological Chemistry and Molecular Pharmacology at Harvard Medical School since 1991 and formerly was president of the Dana-Farber Cancer Institute and chairman of the Department of Biological Chemistry and Molecular Pharmacology at Harvard Medical School. He has performed extensive research in enzyme stereochemistry, reaction mechanisms and the mechanisms of action of anti-infective and immunosuppressive agents. Dr. Walsh serves on the Scientific Advisory Board for Eisai Inc., Epizyme Corporation, LS9, Inc. and the Bioventures Group of Health Care Ventures LLC. Dr. Walsh is also a board member of Achaogen Inc. and Proteostasis Therapeutics, Inc. Dr. Walsh received an A.B. in biology from Harvard University and a Ph.D. in life sciences from The Rockefeller University, New York.

There are no family relationships among any of our directors or executive officers.

Code of Ethics

We will adopt a code of business conduct and ethics applicable to our directors, executive officers and all other employees. A copy of that code will be available on our corporate website at http://www.ironwoodpharma.com upon completion of this offering. Any amendments to the code of ethics and business conduct, and any waivers thereto involving our executive officers, also will be available on our corporate website. A printed copy of these documents will be made available upon request. The content on our website is not incorporated by reference into this prospectus.

Board Composition

Our board of directors currently consists of eleven members, ten of whom are non-employee members. Each director holds office until his or her successor is duly elected and qualified or until his or her death, resignation or removal. Pursuant to our fourth amended and restated voting agreement, each holder of our capital stock has agreed to vote all of his or her shares for a nominee to the board named by Beacon Bioventures L.P. until the completion of this offering. Dr. Knight is the current board member who was nominated by Beacon Bioventures L.P.; however, Dr. Knight will be resigning from the board of directors at the time of this offering. The fourth amended and restated voting agreement will terminate upon the completion of this offering, and there will be no further contractual obligations regarding the election of our directors following such termination.

In accordance with the terms of our certificate of incorporation and our by-laws that will become effective upon the completion of this offering, our board of directors will be divided into three classes, each of whose members will serve for staggered three year terms. Upon the completion of this offering, the members of the classes will be divided as follows:

- the class I directors will be Drs. Hecht and Roberts, Ms. Miller and Mr. Shaw, and their term will expire at the annual meeting of stockholders to be held in 2011;
- the class II directors will be Messrs. Conrades, Cook and Ebersman, and their term will expire at the annual meeting of stockholders to be held in 2012; and
- the class III directors will be Ms. Fanucci, Mr. McGuire and Dr. Walsh, and their term will expire at the annual meeting of stockholders to be held in 2013.

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Our certificate of incorporation that will become effective upon the completion of this offering will state that our board shall consist of between one and fifteen members, and the precise number of directors shall be fixed by a resolution of our board. Any vacancy in the board, including a vacancy that results from an increase in the number of directors, will be filled by a vote of the majority of the directors then in office. Any additional directorships resulting from an increase in the number of directors will be apportioned by the board among the three classes. This classification of the board of directors may have the effect of delaying or preventing changes in our control or management.

Our certificate of incorporation that will become effective upon the completion of this offering will provide that our directors may be removed only for cause by a majority of the stockholders entitled to vote on such removal. Upon the expiration of the term of a class of directors, directors in that class will be eligible to be elected for a new three-year term at the annual meeting of stockholders in the year in which their term expires.

As set forth in our corporate governance guidelines, our board of directors anticipates that its chairperson shall rotate every five years. The next rotation is scheduled to take place in July 2010, at which time Mr. Cook will step down as the chairman of the board (but will remain our director) and Dr. Roberts will assume the chairmanship.

Director Independence

Under Rules 5605 and 5615 of the NASDAQ Marketplace Rules, a majority of a listed company's board of directors must be comprised of independent directors within one year of listing. In addition, NASDAQ Marketplace Rules require that, subject to specified exceptions, each member of a listed company's audit, compensation and governance and nominating committees be independent and that audit committee members also satisfy independence criteria set forth in Rule 10A-3 under the Exchange Act. Under Rule 5605(a)(2) of the NASDAQ Marketplace Rules, a director will only qualify as an "independent director" if, in the opinion of that company's board of directors, that person does not have a relationship that would interfere with the exercise of independent judgment in carrying out the responsibilities of a director.

Based upon information requested from and provided by each director concerning their background, employment and affiliations, including family relationships, our board of directors has determined that none of Messrs. Cook, Conrades, Ebersman, McGuire and Shaw, Mss. Miller and Fanucci, and Drs. Knight, Roberts and Walsh, representing ten of our eleven directors, has a relationship that would interfere with the exercise of independent judgment in carrying out the responsibilities of a director and that each of these directors is "independent" as that term is defined under Rule 5605(a)(2) of the NASDAQ Marketplace Rules. Our board of directors also determined that Messrs. Cook and Conrades, Ms. Fanucci and Dr. Knight, who comprise our audit committee; Messrs. Conrades, Cook and McGuire and Ms. Miller, who comprise our governance and nominating committee; and Messrs. Ebersman and Shaw and Drs. Roberts and Walsh, who comprise our compensation and HR committee, all satisfy the independence standards for such committees established by Rule 10A-3 under the Exchange Act, the SEC and the NASDAQ Marketplace Rules, as applicable. In making such determination, the board of directors considered the relationships that each such non-employee director has with our company and all other facts and circumstances the board of directors deemed relevant in determining their independence.

Board Committees

Our board of directors has established an audit committee, a governance and nominating committee and a compensation and HR committee. Each committee operates under a charter that has been approved by our board. The chair of each of our committees will rotate every three to five years.

Audit Committee. The members of our audit committee are Messrs. Cook and Conrades, Ms. Fanucci and Dr. Knight. Mr. Cook presently chairs the audit committee. In July 2010, Mr. Cook will step down as

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chair of the audit committee (but will remain a member), at which time Ms. Fanucci will assume the chair. Our audit committee assists our board of directors in its oversight of the integrity of our financial statements and our independent registered public accounting firm's qualifications, independence and performance.

Our audit committee's responsibilities include:

- reviewing and discussing with management and our independent registered public accounting firm our annual and quarterly financial statements, earnings releases and related disclosures;
- reviewing and discussing with management and our independent registered public accounting firm our internal controls and internal auditing procedures, including any material weaknesses in either;
- discussing our accounting policies and all material correcting adjustments with our management and our independent registered public accounting firm;
- monitoring our control over financial reporting and disclosure controls and procedures;
- appointing, overseeing, setting the compensation for and, when necessary, terminating our independent registered public accounting firm;
- approving all audited services and all permitted non-audit, tax and other services to be performed by our independent registered public accounting firm;
- discussing with the independent registered public accounting firm its independence and ensuring that it receives the written disclosures regarding these communications required by the Public Company Accounting Oversight Board;
- reviewing and approving all transactions or series of similar transactions to which we were or are a party in which the amount involved exceeded or exceeds $120,000 and in which any of our directors, executive officers, holders of more than 5% of any class of our voting securities, or any member of the immediate family of any of the foregoing persons, had or will have a direct or indirect material interest, other than compensation arrangements with directors and executive officers;
- recommending whether the audited financial statements should be included in our annual report and preparing the audit committee report required by SEC rules;
- reviewing all material communications between our management and our independent registered public accounting firm;
- approving, reviewing and updating our code of business conduct and ethics; and
- establishing procedures for the receipt, retention, investigation and treatment of accounting related complaints and concerns.

Ms. Fanucci is our audit committee financial expert, as is currently defined in Item 407(d)(5) of Regulation S-K.

Governance and Nominating Committee. The members of our governance and nominating committee are Messrs. Cook, Conrades and McGuire and Ms. Miller. Mr. Conrades chairs the governance and nominating committee. In July 2010, Mr. Cook will step down as member of the governance and nominating committee.

Our governance and nominating committee's responsibilities include:

identifying individuals qualified to become members of our board of directors;

recommending to our board of directors the persons to be nominated for election as directors;

assisting our board of directors in recruiting such nominees;

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recommending to our board of directors qualified individuals to serve as committee members;

performing an annual evaluation of our board of directors;

evaluating the need and, if necessary, creating a plan for the continuing education of our directors; and

assessing and reviewing our corporate governance guidelines and recommending any changes to our board of directors.

Compensation and HR Committee. The members of our compensation and HR committee, or our compensation committee, are Messrs. Ebersman and Shaw and Drs. Roberts and Walsh. Dr. Roberts chairs the compensation committee. In July 2010, Dr. Roberts will step down as chair of the compensation committee (and as a member), at which time Mr. Shaw will assume the chair. As described above, each member of our compensation committee satisfies the independence standards established by Rule 10A-3 under the Exchange Act, the SEC and the NASDAQ Marketplace Rules. In addition, each member of our compensation committee qualifies as a "non-employee director" under Rule 16b-3 of the Exchange Act. Our compensation committee assists the board of directors in the discharge of its responsibilities relating to the compensation of the board of directors and our executive officers.

Our compensation committee's responsibilities include:

reviewing and approving corporate goals and objectives relevant to executive officer compensation and evaluating the performance of executive officers in light of those goals and objectives;

reviewing and approving, or recommending for approval by the independent directors, executive officer compensation, including salary, bonus and incentive compensation, deferred compensation, perquisites, equity compensation, benefits provided upon retirement, severance or other termination of employment, and any other forms of executive compensation;

reviewing and approving, or recommending for approval by the independent directors, our chief executive officer's compensation based on its evaluation of the chief executive officer's performance;

overseeing and administering our incentive compensation plans and equity-based plans and recommending the adoption of new incentive compensation plans and equity-based plans to our board of directors including the determination of the fair market value of our common stock;

making recommendations to our board of directors with respect to director compensation;

reviewing and discussing with management the compensation discussion and analysis required to be included in our filings with the SEC and recommending whether the compensation discussion and analysis should be included in such filings;

preparing the compensation committee report required by SEC; and

making recommendations to our board of directors with respect to management succession planning, including planning with respect to our chief executive officer.

Compensation Committee Interlocks and Insider Participation

None of the members of our compensation committee is or has at any time during the past fiscal year been an officer or employee of Ironwood. None of the members of the compensation committee has formerly been an officer of Ironwood. None of our executive officers serve, or in the past fiscal year has served, as a member of the board of directors or compensation committee of any other entity that has one or more executive officers serving as a member of our board of directors or compensation committee. For a description of transactions between us and members of the compensation committee and entities affiliated with such members, please see "Certain Relationships and Related Party Transactions."

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EXECUTIVE COMPENSATION

Compensation Discussion and Analysis

This section discusses the principles underlying our policies and decisions with respect to the compensation of our executive officers who are named in the "Summary Compensation Table", or our "named executive officers", and all material factors relevant to an analysis of these policies and decisions. Our named executive officers are:

- Peter M. Hecht, Ph.D., Chief Executive Officer;
- Michael J. Higgins, Chief Operating Officer and Chief Financial Officer;
- Mark G. Currie, Ph.D., Senior Vice President, Research and Development and Chief Scientific Officer; and
- Thomas A. McCourt, Senior Vice President, Marketing and Sales and Chief Commercial Officer.

Compensation Philosophy

We are an entrepreneurial pharmaceutical company dedicated to creating, developing, and commercializing innovative human medicines. The objective of our compensation policies is to provide compensation and incentives which attract, motivate and reward outstanding talent across Ironwood through well-communicated programs that are aligned with our core values and business mission, and support a positive company culture. Our core values are to:

- build a thriving and sustainable business by focusing on creating long term value;
- maintain a collaborative environment which fosters innovation;
- recognize and develop the abilities and interests of our employees, consistent with the needs of Ironwood;
- act with integrity and humanity; and
- have fun.

We are guided by the following principles with respect to our compensation determinations:

- design compensation and incentive programs that align employee actions and motivations with the interests of our stockholders, support our business objectives and reward the achievement of key goals and milestones;
- foster and support our performance-driven culture by setting clear, high-value goals, rewarding outstanding performers, and making sure our best performers know clearly how much we value their contributions;

as with all spending, serve as careful stewards of our stockholders' assets when making decisions to increase compensation or to make equity awards;

maximize our employees' sense of ownership so that they have a long-term owner's perspective, can see the impact of their efforts on our success, and can share in the benefits of that success through the opportunity to become stockholders of Ironwood via stock options and awards;

recognize that compensation is one of a number of tools to stimulate and reward productivity and great drug making, together with recognizing individual growth potential, providing a great workplace culture, and sharing in our success;

foster a strong team culture, focused on our principles of great drug making, which is reinforced through our compensation and incentive programs;

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design compensation and incentive programs that are fair, equitable and competitive; and

design compensation and incentive programs that are simple and understandable.

Basis for Historical and Future Compensation Policies and Decisions

Our compensation policies have historically been established by our board of directors, with the advice and recommendation of our compensation committee. As set forth in our compensation committee's written charter, adopted in 2008 and amended in 2009, the compensation committee has the responsibility of reviewing and approving, or recommending for approval to the full board, the compensation of our executive officers; annually reviewing and determining our chief executive officer's compensation based on the board's evaluation of his performance; recommending to the full board the adoption of new compensation plans; and administering our existing plans. In addition, the compensation committee is responsible for ensuring that our compensation policies are aligned with our compensation philosophy and guiding principles.

We do not have employment agreements with our named executive officers. Each component of each of our executive officer's initial compensation package was based on numerous factors, including:

the individual's particular background and circumstances, including prior relevant work experience and compensation paid prior to joining us;

the individual's role with us and the compensation paid to similar persons in the companies represented in the compensation data that we reviewed;

the demand for people with the individual's specific expertise and experience at the time of hire;

performance goals and other expectations for the position;

comparison to other executives within Ironwood having similar levels of expertise and experience; and

uniqueness of industry skills.

Historically, our compensation policies and individual compensation determinations have been based on an annual evaluation, and we have taken into consideration our results of operations, our long and short-term goals, individual goals, the competitive market for our executives with similar stage companies and general economic factors. In 2009, we engaged Pearl Meyer & Partners, or Pearl Meyer, to conduct a competitive assessment of compensation for selected executive positions with respect to base salary, actual total cash compensation, target total cash compensation, and long-term incentives. In addition, Pearl Meyer prepared a detailed equity dilution analysis, a review of the compensation strategy and philosophy of a group of companies we consider to be our peer group and a review of the short-term and long-term incentive practices of these peer companies. Pearl Meyer also compared our executive compensation to market compensation data from the Radford Biotechnology Executive Survey and the SIBS Executive Compensation Survey, two confidential survey sources based on revenue and executive officer position. Pearl Meyer's assessment of executive compensation showed generally that total cash compensation of our named executive officers was below the 25th percentile of the market data, but that our long-term incentive equity participation was above the median of the market data. The results of Pearl Meyer's assessment were presented to the compensation committee and will be taken into consideration when making future compensation decisions but will not be used to mandate any specific actions.

Our peer group, which was compiled by Pearl Meyer with input from us, the board of directors, and the compensation committee, is composed of the U.S. based, publicly-traded companies in the pharmaceutical, biotechnology and life sciences industries listed below, which have a median revenue of

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approximately $116.0 million, a median market capitalization of $870.3 million, a median R&D expense of $72.8 million, and a commercial drug or drug candidate in later stage development (other than Alnylam):

Alexion Pharmaceuticals, Inc.;

Alnylam Pharmaceuticals, Inc.;

AMAG Pharmaceuticals, Inc.;

Auxilium Pharmaceuticals Inc.;

Medivation, Inc.;

Onyx Pharmaceuticals, Inc.;

Optimer Pharmaceuticals, Inc.;

Regeneron Pharmaceuticals, Inc.;

Salix Pharmaceuticals, Ltd.;

Theravance, Inc.;

Vertex Pharmaceuticals Incorporated; and

Xenoport, Inc.

Elements of Executive Compensation and Determination of Amounts

In 2009, the compensation program for our executive officers consisted principally of base salary and long-term compensation in the form of stock options. Our compensation program is weighted toward long-term compensation as opposed to short-term or cash-based compensation as we believe this better aligns our employees with our core values. If we achieve our corporate goals, we expect our stock price to rise and the stock option awards currently held by our executives to become the major component of overall compensation. To date, we have not implemented any cash bonus program for named executive officers or our employees as a whole. As discussed below, in 2009 we adopted a change of control severance benefit plan, or our change of control plan, applicable to all employees.

Base Salary

Base salaries for our executive officers are determined at commencement of employment and are generally re-evaluated annually and adjusted, if warranted, to realign salaries with market levels and to reflect the performance of the executive. In determining whether to adjust an executive's base salary, our compensation committee takes into consideration factors such as our performance in prior years, individual performance, general economic factors and compensation equity among our executive officers. The compensation committee sets base salaries

primarily based on the abilities, performance and experience of our named executive officers. The compensation committee also reviews our named executive officers' past compensation and compensation data for comparable positions in our industry. The compensation committee seeks to set base salaries for our named executive officers at competitive levels, generally targeting the 50th percentile as compared to peer group and survey data, but focuses on equity-based compensation for the reasons identified below.

Equity-Based Compensation

To reward and incentivize our named executive officers in a manner that best aligns their interests with our stockholders' interests, we use stock options as the primary incentive vehicles for long-term compensation. To date, stock options have been granted with both time and performance-based vesting conditions to each of our executive officers. We believe that stock options are an effective tool for meeting

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our compensation goal of increasing long-term stockholder value by tying the value of the stock options to our future performance. Because employees are able to profit from stock options only if our stock price increases relative to the stock option's exercise price, we believe stock options provide meaningful incentives to employees to increase the value of our stock over time. All employee stock options issued prior to this offering can be exercised prior to vesting, with any shares issued upon such exercise subject to repurchase by us in the event the executive is no longer employed by us. We have not granted any equity awards other than stock options to our named executive officers to date.

We plan to adopt a new equity incentive plan in connection with this offering. Similar to our previous and current equity incentive plans, our new equity incentive plan will encompass multiple forms of equity which may be issued in the future, including stock options and stock awards.

Our compensation committee does not apply a rigid formula in allocating stock options to executives as a group or to any particular executive, but does emphasize the achievement of corporate goals in determining approximately 75% of each annual performance award for our executive officers, other than Dr. Hecht. All of Dr. Hecht's annual performance award is based on the achievement of corporate objectives. In addition, our compensation committee exercises its judgment and discretion and considers, among other things, the role and responsibility of the executive, competitive factors, the amount of share-based equity compensation already held by the executive, the non-equity compensation received by the executive and the total number of options to be granted to all participants during the year. Our compensation committee makes an initial option grant to new employees and annual grants to our employees in connection with the annual review of our employees' compensation, as further discussed below, and throughout the year may award additional grants as circumstances warrant. The compensation committee has the discretion to reprice options under our existing equity plans but has not exercised this discretion to date.

We do not currently have any security ownership requirements for our named executive officers. In addition we have never had a program or policy in place to coordinate equity grants with the release of material non-public information.

Initial Stock Option Awards

We make an initial award of stock options to all new employees in connection with the commencement of their employment. These grants have an exercise price equal to the fair market value of our common stock on the grant date, as determined by our compensation committee, and vest over four years as to 25% of the shares on the first anniversary of the date of hire and as to 1/48th of the total shares each month thereafter for the next 36 months. The initial stock option awards are intended to provide the employee with incentive to build value in the organization over an extended period of time and to maintain competitive levels of total compensation.

Annual Stock Option Awards

Our practice is to make annual stock option awards to all employees as part of our annual compensation program, and historically we have granted such awards in February of each year based on our performance in the prior year. These grants have an exercise price equal to the fair market value of our common stock on the grant date, as determined by our compensation committee, and generally vest over four years as to 1.25% of the shares on each monthly anniversary of the vesting commencement date, which is January 1 of the applicable year, for the first 36 months, and as to 4.583% of the shares each month thereafter.

Historically, our management and compensation committee has reviewed anonymous private company compensation surveys and drawn upon the experience of our compensation committee members in determining long-term equity incentive awards. Based upon these factors, our compensation committee

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determines the size of the long-term equity incentives at levels it considers appropriate to create a meaningful opportunity for reward predicated on the creation of long-term stockholder value.

Milestone-Based Stock Option Awards

Our named executive officers and many of our employees have a significant portion of their incentive compensation in milestone-based equity awards that accelerate upon the achievement of major value-creating events which may occur many years from the date of grant. We believe performance based equity awards align our employees with our stockholders' best interests and motivate our employees to apply their best efforts toward the accomplishment of these value-creating events.

Change of Control Severance Benefit Plan

In May 2009, our compensation committee adopted a change of control severance benefit plan, or our change of control plan, that applies to all of our employees and provides for certain payments and benefits in connection with or following a termination of employment associated with a "change of control" (as defined therein). We adopted this change of control plan on the premise that innovative ideas and the associated intellectual property generated from these ideas are the basis upon which economic value is created in the biopharmaceutical industry and that our employees are the source of these value-creating ideas. The potential for a change of control or other event that could substantially change the nature and structure of Ironwood could therefore adversely affect our ability to recruit and motivate employees. The change of control plan was designed to encourage employees to bring forward their best ideas by providing them with the knowledge that if a change of control occurs, and their employment is terminated as a result thereof, they will have an opportunity to share in the value that they helped create for our stockholders, regardless of their employment status at Ironwood after the change of control. The key goals of our change of control plan are to recognize the value of employees' contributions to us through the acceleration of equity awards with time-based vesting and to ensure employees have a reasonable period of time within which to locate suitable employment without undue financial hardship. We believe that our change of control plan is a positive recruitment tool in attracting top talent to Ironwood.

A further description of the change of control plan and the potential payments to our named executive officers pursuant to the plan is set forth below under the heading "Potential Payments Upon Termination or Change in Control."

Other Compensation

We maintain broad-based benefits that are provided to all employees, including health insurance, life and disability insurance, dental insurance, fitness and transportation stipends, and a 401(k) plan with a 50% matching company contribution on the first $6,000 of an employee's annual contribution. None of our named executive officers or other employees receives perquisites of any nature.

Process for Determining Individual Compensation and Role of Executive Officers

Historically, our compensation program follows a process that begins in January of each year during which the board finalizes its assessment of our corporate performance for the prior year. The compensation committee, in consultation with our chief executive officer, uses the board's assessment to determine the appropriate size of pools for salary increases and stock option awards to be awarded based on performance during the prior year compared to established goals. Each year, a target percentage of our budget is allocated toward salary increases on the basis of 100% achievement of corporate goals. Similarly, a stock option pool is established at a set percentage of our fully diluted shares, assuming 100% achievement of corporate goals. Upon completion of our goal assessment, both pools are calibrated for corporate performance. The compensation committee assigns a portion of these pools to those individuals holding positions at the vice president level or above, and designates the appropriate portion of each pool

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for allocation by management to all other employees. To assist the compensation committee in determining the size of the incentive pools, our management prepares a matrix of salary ranges and stock option awards for our positions based on industry comparisons and benchmark data from Radford surveys (that also provide the basis for determining salary offers for new hires), salary adjustments based on internal or external pay parity and promotional adjustments for the ensuing fiscal year. In February of each year, the compensation committee approves all of the annual stock option awards and salary increases.

During the first quarter of each year, the compensation committee and management assign the appropriate weights to each of our corporate and financial goals established during the prior year. Managers will subsequently conduct mid-year discussions with their direct reports on the progress of achieving individual performance goals. During the fourth quarter, the compensation committee conducts a preliminary assessment of corporate performance for the current year, employees begin conducting self-assessments, and managers begin collecting input from others within Ironwood and drafting performance reviews.

Tax and Accounting Considerations

While the compensation committee generally considered the financial accounting and tax implications of its executive compensation decisions, neither element was a material consideration in the compensation awarded to our named executive officers in 2009.

Relationship of Elements of Compensation

Our compensation structure is comprised primarily of base salary and stock options. In setting executive compensation, the compensation committee considers the aggregate compensation payable to an executive officer and the form of such compensation. We use stock options as a significant component of compensation because we believe that this best ties individual compensation to the creation of stockholder value. While we offer competitive base salaries, we believe share-based compensation is a significant motivator in attracting and motivating employees. Awards of stock options generally have either long-term vesting schedules, typically four years, or vest upon the achievement of important value-creating milestones. If an employee leaves our employ before the completion of the vesting period, then that employee does not receive any benefit from the non-vested portion of his award. We believe that this feature makes it more attractive to remain as our employee and these arrangements do not require substantial cash payments by us.

The compensation committee manages the expected impact of salary increases payable to our named executive officers by requiring that the size of any salary increases be tied to the attainment of corporate and individual goals.

The compensation committee may decide, as appropriate, to modify the mix of base salary, annual and long-term incentives to best fit an executive officer's specific circumstances or if required by competitive market conditions, to attract and motivate skilled personnel. For example, the compensation committee may decide to award additional stock options to an executive officer if the total number of stock option grants received during an individual's employment with us does not adequately reflect the executive's current position. We believe that this discretion and flexibility allows the compensation committee to better achieve our compensation objectives.

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Compensation Actions in 2009

2008 and 2009 Goals

For 2008 and 2009, allocations of cash and stock options were, in large part, dependent upon us meeting certain weighted performance objectives. These performance objectives encompassed three categories for each year: (i) clinical and business development milestones for our most advanced product candidate, linaclotide, (ii) research milestones designed to encourage efficient innovation, and (iii) financial objectives aimed at the efficient use of our capital. In addition to our core goals, we also create aggressive stretch goals, which, if accomplished, can result in overachieving our annual goals. Historically, Dr. Hecht's performance evaluation was based primarily on the achievement of our corporate objectives. In addition to the achievement of corporate goals, our other named executive officers are evaluated on the achievement of additional individual goals which contribute toward, and relate directly to, the accomplishment of our corporate objectives. Our board of directors determined that we met 80% of our corporate objectives in 2008, which consisted of the following:

Corporate Goal	Target Percentage (%)	Actual Level of Achievement (%)
Initiate linaclotide Phase 3 trials, confirm commercial formulation, define ex-U.S. commercial strategy (stretch goal included the completion of an ex-U.S. transaction)	50	50
Advance cardiovascular candidate into Phase 3	20	0
Pipeline advancement	20	15
Achieve year-end cash target of >$90 million and expense control (stretch goal included the completion of a financing)	10	15
Totals	100	80

Based on our achievement of 80% of our corporate objectives in 2008, the option pool from which the named executive officers were awarded annual stock option grants in 2009 was proportionately reduced.

In addition to the 2008 corporate goals identified above, for which each of our named executive officers is directly accountable, the following is a summary of the 2008 individual goals for our named executive officers, other than Dr. Hecht, who was compensated on the basis of the achievement of our corporate goals, and Mr. McCourt, who did not join us until 2009:

Named Executive Officer	Summary of Individual Goals
Mark Currie	Lead strategic decisionmaking in advancing linaclotide through clinical trials Build and maintain strong relationship with collaboration partner Develop linaclotide "rest-of-world" strategy Lead research and discovery group to deliver on corporate pipeline goals
Michael Higgins	Lead Ironwood strategy Develop linaclotide "rest-of-world" strategy Complete private financing Lead investor relations efforts

Both Dr. Currie and Mr. Higgins were deemed to have met their individual objectives in 2008. Accordingly, they received their full incentive award from the pool that had been proportionately reduced based on the company's achievement of 80% of its corporate objectives. No bonuses or merit increases were awarded for 2008 performance.

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Our 2009 corporate goals will be used to determine compensation awards and adjustments in early 2010. In December of 2009, our board of directors determined that we met 105% of our corporate objectives, which consisted of the following:

Corporate Goal	Target Percentage (%)	Actual Level of Achievement (%)
Advance linaclotide Phase 3 program, secure partnership for linaclotide ex-U.S, and finalize commercial manufacturing strategy	60	70
Pipeline advancement	15	10
Achieve year-end cash target of >$75 million and other financial objectives and expense control	25	25
Totals	100	105

In addition to the 2009 corporate goals identified above, for which each of our named executive officers is directly accountable, the following is a summary of the 2009 individual goals for our named executive officers, other than Dr. Hecht, who is compensated on the basis of the achievement of our corporate goals, and Mr. McCourt, who did not join us until the fourth quarter of 2009:

Named Executive Officer	Summary of Individual Goals
Mark Currie	Meet enrollment goals for linaclotide clinical studies and generate phase 3 data Complete ex-U.S. transaction for linaclotide Bring one clinical candidate through phase 1 studies Submit additional IND for a new product candidate Develop two new clinical candidates
Michael Higgins	Secure linaclotide manufacturing supply chain Complete ex-U.S. transaction for linaclotide Prepare Ironwood for an initial public offering Develop linaclotide launch strategy Manage the expenses of the company to enable it to meet its corporate cash objectives

The compensation committee will evaluate each named executive officer's individual performance in the first quarter of 2010.

Base Salary

Our named executive officers currently receive the following base salaries: Dr. Hecht $100,000, Mr. Higgins $265,000, Dr. Currie $315,000, and Mr. McCourt $325,000. None of our named executive officers or other employees received an increase in base salary either for 2008 performance or during 2009, as our chief executive officer and compensation committee determined that we should maintain our current base salaries given the general economic environment at that time. Based on management's recommendation, in lieu of salary increases, the compensation committee authorized a merit and adjustment pool representing an average of 2% of base salary that was paid to each employee in February 2009 in a one-time lump sum payment. Mr. Higgins received a one-time payment of $5,000 and Dr. Currie received $8,000. Mr. McCourt, who joined us in September 2009, was not eligible for this one-time payment. Dr. Hecht elected not to receive the one-time merit payment.

Dr. Hecht's salary of $100,000 represents the salary that he has been receiving since he began serving as chief executive officer in 1998. Dr. Hecht's compensation is reviewed annually by our compensation committee, but due to Dr. Hecht's desire to keep his cash compensation the same, the compensation committee has not recommended an increase in Dr. Hecht's cash compensation to date. Further,

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Dr. Hecht has indicated to the compensation committee that he would not expect an increase to his salary in the future.

Annual Stock Option Grants and New Hire Grant

On February 12, 2009, each of our named executive officers was awarded the following stock option grants of Class B common stock based on his performance during 2008.

Named Executive Officer	2009 Annual Option Grant for 2008 Performance (# of Shares of Class B Common Stock Subject to Option)
Peter M. Hecht, Ph.D.	110,000
Mark G. Currie, Ph.D.	175,000
Michael J. Higgins	95,000

These options were granted under our Amended and Restated 2005 Stock Incentive Plan, or our 2005 Plan, have an exercise price of $4.89 per share (which was the fair market value of our Class B common stock on the date of grant, as determined by our board of directors) and, with the exception of a portion of the option awarded to Dr. Currie, vest as to 1.25% of the award on each monthly anniversary following January 1, 2009 for the first 36 months, and as to 4.583% of the award each month thereafter. Options to purchase 50,000 shares of Class B common stock that were part of Dr. Currie's performance award vested in full on the date of the grant in recognition of the success of our Phase 2b program for our product candidate, linaclotide, due to Dr. Currie's primary responsibility for the program, and the remaining options vest in accordance with the foregoing schedule.

Mr. McCourt was not eligible for a performance grant in February of 2009 since he did not join us until September of 2009. Upon joining Ironwood, Mr. McCourt received a total of 200,000 time-based options to purchase shares of Class B common stock which vest over four years, and an additional 160,000 options to purchase Class B common stock that vest in increments of 40,000 each upon meeting certain performance milestones, including: (i) acceptance by the FDA of our first NDA; (ii) the first commercial sale of our product candidate linaclotide, (iii) acceptance by the FDA of our second NDA, and (iv) achieving a certain threshold in global pharmaceutical product sales.

Milestone Grants

In July of 2009, the board of directors granted options to purchase shares of Class B Common Stock to various employees, including Dr. Hecht, Mr. Higgins and Dr. Currie who each received options to purchase 40,000 shares of our Class B common stock, that will vest as to 50% of the shares upon our achievement of $1 billion in global pharmaceutical product sales, and as to the remaining 50% of the shares upon the acceptance by the FDA of our second NDA. These options have an exercise price of $5.48 per share and may be exercised prior to vesting, with any shares issued upon such exercise subject to repurchase by us in the event the employee terminates his employment with us. The compensation committee and the board of directors determined that these performance grants would be a strong motivational tool linked to real and value-creating events for us as a whole.

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Summary Compensation Table

The following table sets forth information regarding the compensation paid or accrued during the fiscal year ended December 31, 2009 to each of our named executive officers.

Name and Principal Position	Year	Salary ($)	Bonus ($)[1]	Option Awards ($)[2]	All Other Compensation ($)[3]	Total ($)
Peter M. Hecht, Ph.D. Chief Executive Officer	2009	100,000	0	465,684	4,410	570,094
Michael J. Higgins Chief Operating Officer and Chief Financial Officer	2009	265,000	5,000	177,771	4,410	452,181
Mark G. Currie, Ph.D. Senior Vice President, R&D and Chief Scientific Officer	2009	315,000	8,000	475,561	4,410	802,971
Thomas A. McCourt[4] Chief Commercial Officer and Senior Vice President, Marketing and Sales	2009	102,292	0	52,698	1,961	156,951

(1) Consists of a one-time payment in lieu of a pay raise.

(2) Calculated in accordance with ASC 718, *Compensation Stock Compensation*. The amount reflects the dollar amount realized by us for financial statement reporting purposes for 2009 without regard to any estimate of forfeitures related to service-based vesting conditions. For a discussion of the assumptions used in the valuation, see Note 15 to our consolidated financial statements for the nine months ended September 30, 2009 included elsewhere in this prospectus. See also our discussion of share-based compensation under "Management's Discussion and Analysis of Financial Condition and Results of Operations Critical Accounting Policies and Estimates."

(3) Consists of matching contributions made under our 401(k) plan, as well as a transportation stipend and a fitness stipend. For Mr. McCourt, this amount also includes reimbursement of his relocation expenses incurred in connection with the commencement of his employment with us in September 2009. As set forth in Mr. McCourt's offer letter, we have agreed to reimburse Mr. McCourt up to $300,000 for his relocation and other expenses incurred in connection with the commencement of his employment.

(4) Mr. McCourt began employment as our Chief Commercial Officer and Senior Vice President, Marketing and Sales on September 8, 2009. Mr. McCourt's annualized salary is $325,000.

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Grants of Plan-Based Awards (2009)

The following table sets forth information regarding equity awards granted to each of our named executive officers during the fiscal year ended December 31, 2009. All equity awards granted to our named executive officers in 2009 consisted of options to purchase shares of our Class B common stock and were granted under our 2005 Plan with an exercise price equal to the fair market value of our Class B common stock, as determined by our compensation committee, on the date of grant. The vesting schedule of each option included in the following table is described in the footnotes to the Outstanding Equity Awards at Fiscal Year-End (2009) table.

Name	Grant Date	Estimated Future Payouts Under Equity Incentive Plan Awards Target (#)	All Other Option Awards: Number of Securities Underlying Options (#)	Exercise or Base Price of Option Awards ($/Sh)	Grant Date Fair Value of Stock and Option Awards ($)[1]
Peter M. Hecht, Ph.D.	2/12/2009		110,000	4.89	324,808
	7/29/2009	40,000		5.48	135,072
Michael J. Higgins	2/12/2009		95,000	4.89	280,516
	7/29/2009	40,000		5.48	135,072
Mark G. Currie, Ph.D.	2/12/2009		50,000	4.89	147,640
	2/12/2009		125,000	4.89	369,100
	7/29/2009	40,000		5.48	135,072
Thomas A. McCourt					