IRONWOOD PHARMACEUTICALS INC
Form 10-K
March 30, 2011

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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2010

OR

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

For the transition period from to
Commission File Number 001-34620

IRONWOOD PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**04-3404176**
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification Number)
301 Binney Street Cambridge, Massachusetts	**02142**
(Address of Principal Executive Offices)	(Zip Code)

Registrant's telephone number, including area code: **(617) 621-7722**

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

Title of each class	**Name of each exchange on which registered**
Class A common stock, $0.001 par value	The NASDAQ Stock Market LLC (NASDAQ Global Select Market)

Securities registered pursuant to Section 12(g) of the Act: **None**

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes o No ý

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

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports) and (2) has been subject to such filing requirements for the past 90 days. Yes ý No o

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

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

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 definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act.

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

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

Aggregate market value of voting stock held by non-affiliates of the Registrant as of June 30, 2010: $1,004,518,914

As of March 15, 2011, there were 48,612,174 shares of Class A common stock outstanding and 50,825,074 shares of Class B common stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE:

Portions of the definitive proxy statement for our 2011 Annual Meeting of Stockholders are incorporated by reference into Part III of this report.

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PART I

Item 1. *Business*

Our Company

We are an entrepreneurial pharmaceutical company that discovers, develops and intends to commercialize differentiated medicines that improve patients' lives. 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 team, a culture and processes centered on creating and marketing important new drugs. If we are successful getting medicines to patients, we hope to earn the right to build an enduring pharmaceutical company, an outstanding business that will thrive well beyond our lifetimes and generate substantial returns for our stockholders. Furthermore, 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.

We believe that linaclotide, our guanylate cyclase type-C, or GC-C, agonist being developed for the treatment of patients with irritable bowel syndrome with constipation, or IBS-C, or chronic constipation, or CC, could present patients and healthcare practitioners with a unique therapy for a major medical need not yet met by existing therapies. 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 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.

Linaclotide recently completed the clinical efficacy portion of its development program, achieving favorable efficacy and safety results in all four of its Phase 3 IBS-C and CC clinical trials. Across these four trials, linaclotide met 66 out of 66 U.S. and European Union, or E.U., primary and secondary endpoints. In the eight Phase 2 and Phase 3 clinical studies in almost 3,700 IBS-C and CC patients, linaclotide demonstrated rapid and sustained improvement of the pain and bloating as well as the constipation symptoms that define these chronic gastrointestinal disorders, with good tolerability and convenient once-daily oral dosing. Based on the results of our development program, we intend to submit a New Drug Application, or NDA, with the Food and Drug Administration, or FDA, in the third quarter of 2011, seeking approval to market linaclotide to IBS-C and CC patients age 18 and older in the U.S. Similarly, our European partner, Almirall S.A., or Almirall, intends to submit a Market Authorization Application, or MAA, with the European Medicines Agency, or EMA, in the second half of 2011, seeking approval to market linaclotide to IBS-C patients in the E.U. If linaclotide is approved for IBS-C and CC patients age 18 and older in the U.S., we may seek to expand linaclotide's market opportunity by exploring its utility in other gastrointestinal indications and in the pediatric population.

In each of the 12-week and 26-week Phase 3 studies in patients with IBS-C, linaclotide rapidly reduced abdominal pain, abdominal discomfort and bloating, and these reductions were sustained throughout the entire treatment period. In the 12-week trial, 50% of linaclotide-treated patients had at least a 30% reduction in abdominal pain for at least six of the 12 weeks, and in the 26-week trial, 49% of linaclotide-treated patients had at least a 30% reduction in abdominal pain for at least six of the first 12 weeks of the treatment period. In each trial, the abdominal pain reduction was observed within

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the first week following initiation of therapy and was sustained throughout the treatment period. In the 26-week trial, linaclotide elicited a 40% mean decrease in abdominal pain by the sixth week, a 46% mean decrease by the twelfth week, and a 50% mean decrease at the twenty-sixth week.

As with abdominal pain, linaclotide-treated patients experienced a significant improvement in constipation symptoms during the first week of treatment in each of the Phase 3 IBS-C and CC clinical trials, and this improvement was sustained throughout the whole treatment period.

In the four Phase 3 studies, diarrhea was the most common adverse event (seen in 14% to 20% of linaclotide-treated patients), and the most common adverse event that led to study discontinuation (in 3% to 6% of linaclotide-treated patients). 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. As of December 31, 2010, licensing fees, milestone payments, related equity investments and development costs received from our linaclotide partners total approximately $307 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 capital stock pursuant to the collaboration agreement. Remaining pre-commercial milestone payments could total up to $20 million upon NDA acceptance by the FDA and up to $85 million upon NDA approval. 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 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 $57 million in license fees and milestone payments and has purchased $15 million of our capital stock. Remaining pre-commercial milestone payments could total up to $20 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, or API. 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

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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 API. 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.

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 E.U. and Japanese composition of matter patents, both of which expire in 2024, subject to possible patent term extension.

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, supportive data. Linaclotide is our only product candidate that has demonstrated clinical proof of concept. We have a pipeline of early stage, pre-proof of concept development candidates in multiple therapeutic areas, including gastrointestinal disease, pain and inflammation, and respiratory disease. We are also conducting early stage, preclinical research in these therapeutic areas, as well as in the area of cardiovascular disease. Finally, we are actively engaged in evaluating externally-discovered drug candidates at all stages of development. In evaluating potential assets, we apply the same criteria as those used for investments in internally-discovered assets.

We were incorporated in Delaware on January 5, 1998.

Owner-related Business Principles

We encourage all current and potential stockholders to read the owner-related business principles below that guide our overall strategy and decision making.

1. Ironwood's stockholders own the business; all of our employees work for them.

Each of our employees also has equity in the business, aligning their interests with their fellow stockholders. As employees and co-owners of Ironwood, our management and employee team seek to effectively allocate scarce stockholder capital to maximize the average annual growth of per share value.

Through our policies and communication, we seek to attract like-minded owner-oriented stockholders. We strive to effectively communicate our views of the business opportunities and risks over time so that entering and exiting stockholders are doing so at a price that approximately reflects our intrinsic value.

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

We believe that Ironwood has the potential to deliver outstanding long-term returns to stockholders who are sober to the risks inherent in the pharmaceutical product development model and to the potential dramatic highs and lows along the way, and who focus on superior long-term, per share cash flows.

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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 stockholders 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 stockholders 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 who have a history of experience with us.

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 stockholders.

d. All 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 stockholders' 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 out-license commercialization rights for other territories. We believe in the

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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 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 stockholders, 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 discover, develop and commercialize differentiated medicines that improve patients' lives, and to generate outstanding returns for our stockholders. 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.;

harvest the maximum value of linaclotide outside of our partnered territories;

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;

maximize the commercial potential of our drugs and participate in an important way in the economics when they reach the market; and

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

Linaclotide Overview

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

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gastrointestinal symptoms, often delays diagnosis and may compromise treatment, possibly causing additional suffering and disruption to patients' daily activities.

IBS-C and CC are chronic conditions characterized by frequent and bothersome symptoms that dramatically affect patients' daily lives. We believe that gastroesophageal 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.

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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 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

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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.

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, 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 approved in 2009 by the EMA and is indicated for the treatment of CC in women for whom laxatives have failed to provide adequate relief. Resolor, which is marketed by Shire-Movetis, is a serotonin 5-HT4 receptor agonist like Zelnorm. Resolor is currently in Phase 3 trials being studied as a potential treatment for CC in males and for opioid induced constipation (OIC). Johnson & Johnson has U.S. rights to prucalopride. The U.S. patent covering the composition of matter expires in 2015.

The Linaclotide Opportunity. Linaclotide is a 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

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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.

Annually, we estimate that over 30 million 30-day units of laxative and fiber medications are purchased in an effort to relieve chronic abdominal and constipation symptoms. Based on our analysis of data from IMS Health, The Nielsen Company and abstracts by P. Schoenfeld, et al. and W. Chey, et al. for the American College of Gastroenterology 2010 Annual Meeting and the 18th United European Gastroenterology Week, respectively, these 30 million units are comprised of 7-8 million laxative prescriptions for patients with constipation and abdominal symptoms and approximately 22 million over-the-counter (OTC) laxative and fiber units for chronic patients. Assuming a price comparable to those for branded prescription drugs for other gastrointestinal indications that are made available in Redbook and First Databank, the daily cost for linaclotide treatment per patient could range from $5.50 to $8.50 per day, with a prescription cost of $165 to $250 per month. Applying these assumptions to the potential market as a whole, these 30 million units could represent a potential U.S. commercial opportunity for a safe and effective IBS-C/CC drug in excess of $6 billion per year. Since many of these 30 million units are taken episodically or as rescue medications, there exists a potential upside in the market if the annual days of therapy increases, assuming that certain patients desire to manage and control their symptoms chronically. There is also the possibility that new patients could enter the marketplace as awareness of a new therapy increases.

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 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

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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.

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.

Clinical

Linaclotide recently completed the efficacy portion of its clinical development program, and two long-term safety studies are still ongoing. The clinical development program consists of 13 studies in over 4,600 people: three in healthy volunteers, four in IBS-C patients, four in CC patients, and two long-term safety studies in IBS-C and CC patients.

Manufacturing and Supply

It is our goal to consistently and reliably produce and supply the highest quality drugs to our patients on a worldwide basis, with redundancy built into each critical step of the manufacturing process. We currently execute our global production and delivery of linaclotide through a combination

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of independent third party organizations and our collaboration partners. We believe that we have sufficient in-house expertise to lead and manage our virtual global supply chain for linaclotide on an ongoing basis to meet worldwide patient demand, should it be approved by the regulatory authorities.

Pharmaceutical manufacturing consists of two phases manufacturing of the active pharmaceutical ingredient, or API (sometimes referred to as drug substance), and manufacturing of the final drug product. We currently use contract manufacturers for the production of linaclotide API. Linaclotide is a 14 amino acid peptide, manufactured via solid phase synthesis using naturally occurring amino acids. We and Forest entered into a commercial supply agreement with PolyPeptide Laboratories, Inc. and Polypeptide Laboratories (SWEDEN) AB for the manufacture of the linaclotide API that will be used to obtain regulatory approval of linaclotide in the U.S., Canada and/or Mexico, and, pending any such approval, that will be incorporated into the finished product for commercialization in those countries. We continue to pursue additional commercial supply agreements with other manufacturers for linaclotide API for U.S. and worldwide use. We believe our commercial suppliers will have the capabilities to produce linaclotide API in accordance with current good manufacturing practices, or GMP, on a sufficient scale to meet our commercial needs.

Each of our collaboration partners, Forest, Almirall and Astellas, is responsible for linaclotide drug product manufacturing in its respective territory. In addition, we are pursuing arrangements with other manufacturers for the drug product manufacturing of linaclotide in the parts of the world outside of our partnered territories, and to further ensure continuity of drug product supply in partnered territories. Previous to linaclotide, there was 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 in these development batches under accelerated conditions of 40°C with 75% relative humidity for six months, which, based on industry precedent, 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. These scale up batches and Phase 3 clinical trial material batches have shown acceptable room temperature stability at the six, 12 and 18 month time points. Our partners, Forest and Almirall, have prepared pre-registration and registration batches to be utilized for regulatory submissions in their respective territories. We, together with Forest, are on track to submit an NDA in the third quarter of 2011. Almirall is on track to submit an EMA in the second half of 2011. We and our partners will continue to monitor those batches going forward.

We believe our efforts to date have led 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 these claims 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.

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.

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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 utilized to develop a compelling medical message and promotional campaign in the hope of delivering an effective treatment for patients suffering with the defining symptoms of IBS-C and CC.

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.

Almirall provides access to the highest potential European markets with an established direct presence in each of the United Kingdom, Italy, France, Germany and Spain, and also has a presence in Austria, Belgium, the Nordics, 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 E.U.

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.

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

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 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.

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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 gastrointestinal disorders, pain and inflammation, respiratory disease, and cardiovascular disease. Linaclotide is our only product candidate that has demonstrated clinical proof of concept. We have a pipeline of early stage, pre-proof of concept development candidates in multiple therapeutic areas, including gastrointestinal disease, pain and inflammation, and respiratory disease. We are also conducting early stage, preclinical research in these therapeutic areas, as well as in the area of cardiovascular disease.

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.

Linaclotide and GC-C Patent Portfolio

Our linaclotide patent portfolio is currently composed of five issued U.S. patents, two granted European patents (each of which has been validated in 31 European countries and in Hong Kong), a granted Japanese patent, eight issued patents in other foreign jurisdictions, and numerous pending provisional, U.S. non-provisional, foreign and PCT patent 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 between 2024 and 2028, 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 application 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 provisional, U.S. non-provisional, foreign and PCT 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 2031.

In addition to the patents and patent applications related to linaclotide, we currently have one issued U.S. patent and a number of pending provisional, U.S. non-provisional, foreign and PCT applications directed to other GC-C agonist molecules, pharmaceutical compositions thereof, methods

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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; and numerous pending provisional, U.S. non-provisional, foreign and PCT 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 2031.

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

Government Regulation

In the U.S., 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;

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development, manufacture and testing of active pharmaceutical product and dosage forms suitable for human use in compliance with current GMP;

the submission to the FDA of an 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 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

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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.

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

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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 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.

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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, prohibitions on promoting drugs for uses or in patient populations that are not described in the drug's approved labeling (known as "off-label use"), and principles governing industry-sponsored scientific and educational activities. 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 or patients, 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 in type and quality to the clinical data supporting the original application for the original indication, and the FDA uses similar procedures and actions in reviewing such 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 to place conditions on an approval that restrict the distribution or use of the product.

Outside the U.S., 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 within the E.U. registration procedures are available to companies wishing to market a product in more than one E.U. member state.

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Employees

As of December 31, 2010, we had 217 employees. Approximately 68 were scientists engaged in discovery research, 85 were in our drug development organization, 8 were in our commercial team, and 56 were in general and administrative functions. None of our employees are represented by a labor union, and we consider our employee relations to be good.

Item 1A. ***Risk Factors***

In addition to the other information in this Annual Report on Form 10-K, any of the factors described below could significantly and negatively affect our business, financial condition, results of operations or prospects. The trading price of our Class A common stock may decline due to these risks.

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.

Our lead product candidate, linaclotide, recently completed the clinical efficacy portion of its development program. 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 an NDA from the FDA, or in any foreign jurisdictions until we receive the requisite approvals from such jurisdictions. We have not yet submitted an NDA or foreign equivalent in any jurisdiction. Obtaining regulatory approval is a lengthy, expensive and uncertain process. The FDA and foreign regulatory authorities also have substantial discretion in the drug approval process, including the ability to delay, limit or deny approval of a product candidate for many reasons. Potential risks include those that the regulatory authorities:

- may not deem linaclotide or another product candidate safe and effective;
- may not find the data from preclinical studies and clinical trials sufficient to support approval;
- may not approve of manufacturing processes and facilities;
- may not approve linaclotide for both IBS-C and CC indications;
- may require significant warnings or restrictions on use to the product label for linaclotide or another product candidate; or
- may change their approval policies or adopt new regulations.

Linaclotide is our GC-C agonist that is currently in Phase 3 clinical development for the treatment of IBS-C and CC. In September and November 2010, we announced the positive top-line results from each of the two Phase 3 clinical trials assessing the safety and efficacy of linaclotide in patients with IBS-C, and in November 2009, we announced that we achieved positive results in each of our Phase 3 CC trials. Even though linaclotide met the endpoints of the CC trials and the top-line results indicate that it met the endpoints of the IBS-C trials, it may not be approved for either or both indications or for any other indication for which we seek approval from the FDA.

Further, the FDA and any foreign regulatory authority may disagree with our trial design or our interpretation of data from clinical trials, or they may change the requirements for approval even after they have reviewed and commented on the design for our clinical trials. The FDA and any foreign regulatory authority might also approve linaclotide for fewer or more limited indications than we

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request, or may grant approval contingent on the performance of costly post-approval clinical trials. In addition, the FDA and any foreign regulatory authority 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.

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. Any 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. In the four Phase 3 clinical trials, our top-line results indicate that diarrhea was seen in 14% to 20% of linaclotide-treated patients, and was the most common adverse event that led to study discontinuation in 3% to 6% of linaclotide-treated patients. In our clinical development program, there have been no serious adverse events in any patients receiving linaclotide treatment that were deemed by a study investigator or us to be "definitely related" or "probably related" to linaclotide treatment, nor have there been any deaths in any patients receiving linaclotide treatment that were deemed by a study investigator or us 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.

If we or our collaboration partners and other third parties upon whom we rely to produce linaclotide are unable to satisfy FDA quality standards and related regulatory requirements, experience manufacturing difficulties, or are unable to manufacture sufficient quantities of our product candidates, our development and commercialization efforts may be materially harmed.

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 (along with our U.S. collaboration partner, Forest) entered into a commercial supply agreement with PolyPeptide Laboratories, Inc. and Polypeptide Laboratories (SWEDEN) AB for the manufacture of the linaclotide API that will be used to obtain regulatory approval of linaclotide in the U.S., Canada and/or Mexico, and, pending any such approval, that will be incorporated into the finished product for commercialization in those countries. In addition, we have established development

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agreements with multiple peptide manufacturers and continue to pursue commercial supply agreements with these manufacturers for the linaclotide API. We may not be able to enter into agreements with such other manufacturers on commercially reasonable terms, or at all. If we enter into a commercial supply agreement with another manufacturer but then change or add manufacturers, the regulatory authorities in each territory 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 linaclotide. While we believe we will have arrangements to produce a sufficient amount of API, if we lose a manufacturer, it would take us a substantial amount of time to identify and develop a relationship with an alternative manufacturer.

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.

Upon production of our API, each of our collaboration partners, Forest, Almirall and Astellas, is responsible for completing the manufacturing process of linaclotide in its respective territory, which consists of finishing and packaging linaclotide into capsules. In addition, we are pursuing arrangements with additional manufacturers to complete the manufacturing process of linaclotide in the parts of the world outside of our partnered territories, and for the purpose of introducing redundancy into our supply chain in case of a manufacturing shortage or supply interruption. We will be dependent upon the success of our partners, and these other manufacturers, provided that we are successful in developing supply arrangements with the other manufacturers, in producing drug product for commercial sale. No party has experience producing finished drug product for linaclotide at commercial scale, and such efforts may fail. Traditionally, peptide manufacturing is costly and time consuming, resulting in low yields and poor stability. We cannot give any assurances that we will overcome 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, and the challenges associated with complex supply chain management. We, together with our partners Forest and Almirall, are currently evaluating the stability of different batch sizes of 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 or MAA 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 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 quality of linaclotide is compromised due to a

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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.

Because we work with partners to develop, manufacture and promote linaclotide, we are dependent upon third parties in our efforts to obtain regulatory approval for, and to commercialize, linaclotide.

We co-develop and plan to co-promote linaclotide in the U.S. with Forest. Forest plays a significant role in the conduct of the clinical trials for linaclotide and the subsequent collection and analysis of data. Each of Almirall, our European partner, and Astellas, our partner in certain Asian countries, is responsible for obtaining regulatory approval of linaclotide in its respective territory. In addition, each of our partners is responsible for completing the manufacturing process of linaclotide upon production of the API, which consists of finishing and packaging linaclotide into capsules. Employees of our partners are not our employees, and we have limited ability to control the amount or timing of resources that they devote to linaclotide. If any of our partners fails to devote sufficient time and resources to linaclotide, or if its performance is substandard, it will delay the potential approval of regulatory applications for linaclotide as well as the commercialization and manufacturing of linaclotide. A material breach by any of our partners of our collaboration agreement with such partner could also delay regulatory approval and commercialization of linaclotide. In addition, the execution of our clinical development program for linaclotide, and the compilation and analysis of the data produced from the clinical trials, requires coordination among various parties. Further, each of our partners is responsible for reporting adverse event information to us. These functions may not be carried out effectively and efficiently if we fail to communicate and coordinate with our partners, and vice versa. Moreover, although we have non-compete restrictions in place with each of our partners, they may have relationships with other commercial entities, some of which may compete with us. If any of our partners assists our competitors, it could harm our competitive position.

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

We anticipate submitting an NDA for linaclotide with the FDA in the third quarter of 2011. However, 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 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;

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suspend regulatory approval;

suspend any ongoing clinical trials;

refuse to approve pending applications or supplements to applications submitted 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.

We have out-licensed the European rights to develop and commercialize linaclotide to Almirall, and we have out-licensed the same rights in certain Asian countries to Astellas. In the future, we may seek 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. Almirall anticipates submitting an MAA with the EMA in the second half of 2011. The time required to obtain approval in other jurisdictions, including the E.U., 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 linaclotide and have an adverse effect on its commercial potential or require costly post-marketing studies.

Linaclotide may not be widely adopted by patients, payors or healthcare providers, which would adversely impact our potential profitability and future business prospects.

The commercial success of linaclotide depends upon its level of market adoption by patients, payors and healthcare providers. If linaclotide does not achieve an adequate level of market adoption for any reason, our potential profitability and our future business prospects will be severely adversely impacted. The degree of market acceptance of linaclotide depends on a number of factors, including:

our ability to demonstrate to the medical community, particularly general practitioners, internists and gastrointestinal specialists who may purchase or prescribe linaclotide, the clinical efficacy and safety of linaclotide as the prescription product of choice for patients who suffer from IBS-C or CC;

the effectiveness of our sales and marketing organizations and our distribution network;

the ability of physicians and other providers to be adequately reimbursed for linaclotide in a timely manner from government and private payors; and

the actual or perceived safety profile of linaclotide, particularly if unanticipated adverse events related to linaclotide treatment arise and create safety concerns among potential patients or prescribers.

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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 globally with certain prescription therapies and over the counter products for the treatment of IBS-C and CC, or certain associated symptoms. 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 other companies are developing products which could compete with linaclotide, should they be approved by the FDA. Currently, there are a few compounds in late stage development and other potential competitors are in earlier stages of development for the treatment of patients with either IBS-C or CC. 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.

Certain 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.

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.

If any of our partners undergoes a change in control or management, this may adversely affect our collaborative relationship.

We work jointly and collaboratively with Forest, Almirall and Astellas on many decisions related to the development, manufacturing and commercialization of linaclotide. In doing so, we have established relationships with several key members of our partners' management teams in functional areas such as development, quality, regulatory and commercial. The success of our collaboration is highly dependent on the resources, efforts and skills of our partners and their key employees. If a partner undergoes a change of control or a change of management, we will need to reestablish many of these relationships and we will need to regain alignment of our development and commercialization strategy for linaclotide. Further, any change of control or management may result in a reprioritization of linaclotide within such partner's profile, and such a change may adversely affect the timeline and likelihood of achieving regulatory approval and, ultimately, the commercialization of linaclotide, or such partner may

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fail to maintain the financial resources necessary to continue financing its portion of the development, manufacturing or commercialization costs.

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.

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. Further, several European countries have implemented government measures to either freeze or reduce pricing of pharmaceutical products. 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.

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:

- federal healthcare program anti-kickback laws, 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;

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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;

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; and

the recently-enacted federal Physician Payments Sunshine Act, and similar state laws in certain states, that require pharmaceutical and medical device companies to monitor and report payments, gifts and other remuneration made to physicians and other health care professional and health care organizations.

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.

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, as evidenced by the passing of the Patient Protection and Affordable Healthcare Act and the Health Care and Education Reconciliation Act. This healthcare reform law increases the number of individuals who receive health insurance coverage and closes a gap in drug coverage under Medicare Part D as established under the Medicare Prescription Drug Improvement Act of 2003; each of these reforms could potentially increase our future revenue from linaclotide or any other product candidates that are approved for sale. The law, however, also implements cost containment measures that could adversely affect our future revenue. These measures include increased drug rebates under Medicaid for brand name prescription drugs and extension of these rebates to Medicaid managed care. The legislation also extends 340B discounted pricing on outpatient drugs to children's hospitals, critical access hospitals, and rural health centers; this expansion reduces the amount of reimbursement received for drugs purchased by these new 340B-covered entities.

Additional provisions of the health care reform law, which become effective in 2011, may negatively affect our future revenue and prospects for profitability. Along with other pharmaceutical manufacturers and importers of brand name prescription drugs, we would be assessed a fee based on

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our proportionate share of sales of brand name prescription drugs to certain government programs, including Medicare and Medicaid. As part of the health care reform law's provisions closing a funding gap that currently exists in the Medicare Part D prescription drug program (commonly known as the "donut hole"), we will also be required to provide a 50% discount on brand name prescription drugs sold to beneficiaries who fall within the donut hole.

In the aftermath of the healthcare reform law, private health insurers and managed care plans are likely to continue challenging the prices charged for medical products and services. These cost-control initiatives could decrease the price we might establish for linaclotide, which would result in lower product revenue or royalties payable to us.

In addition, in 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. 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.

The Food and Drug Administration Amendments Act of 2007 gives 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.

In pursuing our growth strategy, we will incur a variety of costs and may devote resources to potential opportunities that are never completed or for which we never receive the benefit. 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 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.

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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.

Delays in the completion of clinical testing of any of our product candidates 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

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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. Each protocol amendment requires institutional review board review and approval, which may adversely impact the costs, timing or successful completion of the associated clinical trials. If we experience delays in completion or if we terminate any of our clinical trials, the commercial prospects for our product candidate 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.

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 A. McCourt, our senior vice president, marketing and sales and chief commercial officer. 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 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

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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 currently have product liability insurance coverage for our clinical trials that is 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 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 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.

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

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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.

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;

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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.

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.

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.

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 the issuance of equity, including our initial public offering, 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 $53.0 million, approximately $71.2 million and approximately $53.9 million in the years ended December 31, 2010, 2009 and 2008, respectively. As of December 31, 2010, we had an accumulated deficit of approximately $367.5 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

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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 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 Annual Report on Form 10-K and additional cash milestone payments we may receive from our current and future collaborators give us substantial strategic optionality and will enable us to operate the company in a productive way through at least 2014. However, unforeseen circumstances may arise, our strategic imperatives could change, or opportunities to create or acquire new development programs may emerge, which could require 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 associated with launching and commercializing linaclotide, should it be approved by FDA;
- if linaclotide receives regulatory approval, the level of underlying demand for that product;
- 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 collaboration, 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 and annual operating results may fluctuate significantly.

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

- the achievement and timing of milestone payments under our existing collaboration and license agreements;
- our execution of any collaboration, licensing or similar arrangements, and the timing of payments we may make or receive under these arrangements;
- the costs associated with launching and commercializing linaclotide and any of our product candidates, if we receive regulatory approval of such candidate;

if linaclotide receives regulatory approval, the level of underlying demand for that product and wholesalers' buying patterns;

variations in the level of expenses related to our development programs;

addition or termination of clinical trials;

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regulatory developments affecting our product candidates; and

any intellectual property infringement lawsuit in which we may become involved.

If our 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 or annual fluctuations in our operating results may, in turn, cause the price of our stock to fluctuate substantially.

Risks Relating to Securities Markets and Investment in Our Stock

The concentration of our capital stock ownership with our pre-IPO investors (and their affiliates), founders, directors, executives and employees 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 for the following matters (for which each share of our Class B common stock has ten votes per share and each share of our Class A common stock has one vote 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; and

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 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 pre-IPO investors (and their affiliates), founders, directors, executives and employees, 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. As of March 15, 2011, the holders of our Class A common stock own 48.9% and the holders of our Class B common stock own 51.1% 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 have 8.7% and holders of our Class B common stock have 91.3% of the total votes in each of the matters identified in the list above. This concentrated control with our Class B common stock holders limits the ability of the Class A common stockholders to influence those corporate matters and, as a result, we may take actions that many of our stockholders do not view as beneficial, which could adversely affect the market price 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 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 pre-IPO investors (and each of their affiliates), founders, directors, executives and employees, each of whom hold shares of our Class B common stock, 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 are 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 acquirer from conducting a solicitation of proxies to elect such acquirer'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 are not 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 or a majority of our board of directors. As a result, a holder, or holders, controlling a majority of our capital stock are not 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.

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:

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, including clinical trial results, or intellectual property rights of others;

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

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actual and anticipated fluctuations in our quarterly and annual operating results;

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

sales of additional shares of our common stock;

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.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K, including the sections titled "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 Annual Report on Form 10-K 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:

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 goal to execute on our owner-related business principles;

our expectations regarding federal, state and foreign regulatory requirements;

the therapeutic benefits and effectiveness of our product candidates;

the safety profile and related adverse events of our product candidates;

our ability to manufacture sufficient amounts of linaclotide for commercialization activities with target characteristics;

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;

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the accuracy of our estimates of the size and characteristics of the markets that may be addressed by our product candidates;

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 Annual Report on Form 10-K.

Any or all of our forward-looking statements in this Annual Report on Form 10-K may turn out to be inaccurate. These forward-looking statements may be affected by inaccurate assumptions or by known or unknown risks and uncertainties, including the risks, uncertainties and assumptions identified under the heading "Risk Factors" in this Annual Report on Form 10-K. In light of these risks, uncertainties and assumptions, the forward-looking events and circumstances discussed in this Annual Report on Form 10-K 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 Annual Report on Form 10-K. 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 Annual Report on Form 10-K.

Item 1B. ***Unresolved Staff Comments***

None.

Item 2. ***Properties***

Our corporate headquarters and operations are located in Cambridge, Massachusetts, where, as of December 31, 2010, we lease and occupy approximately 170,679 rentable square feet of office and laboratory space at 301 Binney Street. In February 2011, we amended our lease at 301 Binney Street to lease an additional 23,307 rentable square feet of office space that we do not yet occupy. The term of our lease at 301 Binney Street expires on January 31, 2016, with an option to extend the term of the lease for two additional five year periods. We believe that our facilities are suitable and adequate for our needs for the foreseeable future.

Item 3. ***Legal Proceedings***

None.

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Item 4. ***Reserved***

Executive Officers of the Registrant

The following table sets forth the name, age and position of each of our executive officers as of March 15, 2011:

Name	Age	Position
Peter M. Hecht, Ph.D.	47	Chief Executive Officer, Director
Michael J. Higgins	48	Senior Vice President, Chief Operating Officer and Chief Financial Officer
Mark G. Currie, Ph.D.	56	Senior Vice President, R&D and Chief Scientific Officer
Thomas A. McCourt	53	Senior Vice President, Marketing and Sales and Chief Commercial Officer

Peter M. Hecht has served as our chief executive officer and a director 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 board of directors of Whitehead Institute. He also serves on the Leadership Council for The David H. Koch Institute for Integrative Cancer Research at the Massachusetts Institute of Technology. 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 senior vice president, 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. 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.

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 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 CC 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.

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PART II

Item 5. ***Market For Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities***

Shares of our Class A common stock are traded on the NASDAQ Global Select Market under the symbol "IRWD." Our shares have only been publicly traded since February 3, 2010; therefore, the following table shows the high and low sales price for our Class A common stock as reported by NASDAQ for each quarter in the year ended December 31, 2010.

	Class A Common Stock 2010	
	High	Low
First Quarter	$ 14.91	$ 11.20
Second Quarter	$ 15.03	$ 9.73
Third Quarter	$ 13.14	$ 8.90
Fourth Quarter	$ 11.49	$ 10.00

As of March 15, 2011, there were 42 stockholders of record of our Class A common stock and 199 stockholders of record of our Class B common stock. The number of record holders is based upon the actual number of holders registered on the books of the company at such date and does not include holders of shares in "street names" or persons, partnerships, associations, corporations or other entities identified in security position listings maintained by depositories.

We did not purchase any of our equity securities during the period covered by this report. The following sets forth information regarding all unregistered securities issued during the last fiscal year:

1. From January 1, 2010 through December 31, 2010, we issued options to purchase 1,541,000 shares of our Class A common stock to our employees, consultants and directors with an exercise price of $11.25 per share.

2. From January 1, 2010 through December 31, 2010, we issued 58,551 shares of our Class B common stock upon the exercise of stock options to our employees, consultants and directors.

These issuances of restricted securities were deemed to be exempt from registration under the Securities Act in reliance upon Rule 701 promulgated under Section 3(b) of the Securities Act of 1933, as amended, or the Securities Act, as transactions pursuant to a written compensation benefit plan and contracts relating to compensation as provided under Rule 701.

In February 2010, we completed our IPO of our Class A common stock pursuant to a registration statement on Form S-1, as amended (File No. 333-163275) that was declared effective on February 2, 2010. There has been no material change in our planned use of proceeds from the IPO from that described in the final prospectus filed with the SEC pursuant to Rule 424(b) under the Securities Act on February 4, 2010. As of December 31, 2010, approximately $72.3 million of the net proceeds remained available and were invested in liquid, short-term, interest-bearing funds, pending their use to fund our operations. Since our IPO, we estimate that we have used the proceeds in the following way:

approximately $28.0 million to fund the development and commercialization of linaclotide;

approximately $18.3 million to fund both research and development of early stage product candidates and preclinical research in multiple therapeutic areas, including gastrointestinal disease, pain and inflammation, respiratory disease, and cardiovascular disease; and

approximately $84.6 million for general corporate purposes.

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 are entitled to share equally in any

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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.

The information required to be disclosed by Item 201(d) of Regulation S-K, "Securities Authorized for Issuance Under Equity Compensation Plans," is referenced under Item 12 of Part III of this Annual Report on Form 10-K.

Corporate Performance Graph

The following performance graph and related information shall not be deemed to be "soliciting material" or to be "filed" with the SEC, nor shall such information be incorporated by reference into any future filing under the Securities Act or the Exchange Act, except to the extent that we specifically incorporate it by reference into such filing.

The following graph compares the performance of our Class A common stock to the NASDAQ Stock Market (U.S.) and to the NASDAQ Pharmaceutical Index from February 3, 2010 (the first date that shares of our Class A common stock were publicly traded) through December 31, 2010. The comparison assumes $100 was invested after the market closed on February 3, 2010 in our Class A common stock and in each of the foregoing indices, and it assumes reinvestment of dividends, if any.

COMPARISON OF 10-MONTH CUMULATIVE TOTAL RETURN
Among the NASDAQ Stock Market (U.S.),
the NASDAQ Pharmaceutical Index,
and Ironwood Pharmaceuticals, Inc.

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Item 6. ***Selected Consolidated Financial Data***

You should read the following selected financial data together with our consolidated financial statements and the related notes appearing elsewhere in this Annual Report on Form 10-K. We have derived the consolidated statements of operations data for the years ended December 31, 2010, 2009 and 2008 and the consolidated balance sheet data as of December 31, 2010 and 2009 from our audited financial statements included elsewhere in this Annual Report on Form 10-K. We have derived the consolidated statement of operations data for the years ended December 31, 2007 and 2006 and consolidated balance sheet data as of December 31, 2008, 2007 and 2006 from our audited financial statements not included in this Annual Report on Form 10-K. Our historical results for any prior period are not necessarily indicative of results to be expected in any future period.

	Years Ended December 31,				
	2010	2009	2008	2007	2006
	(in thousands, except share and per share data)				
Consolidated Statement of Operations Data:					
Collaborative arrangements revenue	$ 43,857	$ 34,321	$ 18,383	$ 4,608	$
Operating expenses:					
Research and development[(1)]	77,454	76,100	51,421	50,424	29,559
General and administrative[(1)]	27,169	19,037	15,269	8,872	7,158
Total operating expenses	104,623	95,137	66,690	59,296	36,717
Loss from operations	(60,766)	(60,816)	(48,307)	(54,688)	(36,717)
Other income (expense):					
Interest expense	(196)	(318)	(291)	(232)	(198)
Interest and investment income	614	240	2,088	3,872	2,276
Remeasurement of forward purchase contracts		600	(900)	600	
Other income	993				
Other income (expense), net	1,411	522	897	4,240	2,078
Net loss from continuing operations before income tax benefit	(59,355)	(60,294)	(47,410)	(50,448)	(34,639)
Income tax benefit	(2,944)	(296)			
Net loss from continuing operations	(56,411)	(59,998)	(47,410)	(50,448)	(34,639)
Net income (loss) from discontinued operations[(1)]	4,551	(13,314)	(7,621)	(2,712)	(2,640)
Net loss	(51,860)	(73,312)	(55,031)	(53,160)	(37,279)
Net (income) loss from discontinued operations attributable to noncontrolling interest	(1,121)	2,127	1,157	408	99
Net loss attributable to Ironwood Pharmaceuticals, Inc.	$ (52,981)	$ (71,185)	$ (53,874)	$ (52,752)	$ (37,180)
Net income (loss) per share attributable to Ironwood Pharmaceuticals, Inc. basic and diluted:					
Continuing operations	$ (0.63)	$ (8.43)	$ (6.88)	$ (7.57)	$ (5.40)
Discontinued operations	0.04	(1.57)	(0.94)	(0.34)	(0.39)
Net loss per share	$ (0.59)	$ (10.00)	$ (7.82)	$ (7.91)	$ (5.79)

Weighted average number of common shares used in net income (loss) per share attributable to Ironwood Pharmaceuticals, Inc. basic and diluted	89,653,364	7,116,774	6,889,817	6,666,601	6,417,499

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

Research and development	$ 4,112	$ 2,372	$ 1,627	$ 673	$ 316
General and administrative	3,384	2,723	991	359	633
Discontinued operations	59	149	176	122	

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	December 31,				
	2010	2009	2008	2007	2006
	(in thousands)				
Consolidated Balance Sheet Data:					
Cash, cash equivalents and available-for-sale securities	$ 248,027	$ 122,306	$ 88,375	$ 87,860	$ 47,421
Working capital of continuing operations (excluding deferred revenue)	234,699	107,485	86,022	101,036	36,029
Assets of discontinued operations		2,346	3,817	4,949	7,843
Total assets	301,365	162,451	138,371	135,635	57,520
Deferred revenue, including current portion	102,433	126,002	66,008	74,392	
Long-term debt, including current portion		1,763	1,815	2,752	2,243
Capital lease obligations, including current portion	590	255	306		
Liabilities of discontinued operations		2,301	1,327	786	1,008
Total liabilities	141,814	162,441	95,382	90,207	9,900
Convertible preferred stock		298,350	273,400	223,802	173,851
Noncontrolling interest		3,212	5,339	6,495	6,903
Total stockholders' equity (deficit)	159,551	(298,340)	(230,411)	(178,374)	(126,231)

Item 7. ***Management's Discussion and Analysis of Financial Condition and Results of Operations***

Forward-Looking Information

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 Annual Report on Form 10-K. 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" in Item 1A of this Annual Report on Form 10-K, 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 differentiated medicines that improve patients' lives. To achieve this, we are building a team, a culture and processes centered on creating and marketing important new drugs. We believe that linaclotide, our GC-C agonist being developed for the treatment of patients with IBS-C or CC, could present patients and healthcare practitioners with a unique therapy for a major medical need not yet met by existing therapies. Linaclotide is our only product candidate that has demonstrated clinical proof of concept. In addition to linaclotide, we have a pipeline of early stage, pre-proof of concept development candidates in multiple therapeutic areas, including gastrointestinal disease, pain and inflammation, and respiratory disease. We are also conducting early stage, preclinical research in these therapeutic areas, as well as in the area of cardiovascular disease. 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.

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

Prior to September 2010, we held a majority ownership interest in Microbia, Inc. (formerly known as Microbia Precision Engineering), a subsidiary formed in September 2006. Microbia, Inc., or Microbia, engaged in a specialty biochemicals business based on a proprietary strain-development platform. On September 21, 2010, we sold our interest in Microbia to DSM Holding Company USA, Inc., or DSM, in exchange for cash proceeds of $9.5 million, the payment of approximately

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$1.1 million of Microbia debt and interest by DSM and future contingent consideration based on the sale of products incorporating Microbia's technology.

We currently operate in one reportable business segment human therapeutics. Our human therapeutics segment consists of the development and commercialization of our product candidates, including linaclotide. Prior to the sale of our interest in Microbia, we also operated in the biomanufacturing segment. Our biomanufacturing segment, which comprised a much smaller part of our business, consisted of our majority ownership interest in Microbia. Our human therapeutics segment represented 100% and 99% of our total assets at December 31, 2010 and 2009, respectively, while our biomanufacturing segment represented approximately 1% of our total assets at December 31, 2009. For the years ended December 31, 2010, 2009 and 2008, results of operations of our biomanufacturing segment are included in net income (loss) from discontinued operations in our financial statements.

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 $53.0 million, $71.2 million and $53.9 million in the years ended December 31, 2010, 2009 and 2008, respectively. As of December 31, 2010, we had an accumulated deficit of approximately $367.5 million and we expect to incur losses for the foreseeable future.

Financial Overview

Revenue. Revenue to date from our human therapeutics segment is generated primarily through our collaboration agreement with Forest and our license agreements with Almirall and Astellas. The terms of these agreements 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 was generated by our former subsidiary, Microbia, which had entered into research and development service agreements with various third parties. These agreements generally provided for fees for research and development services rendered. As a result of the sale of our interest in Microbia, revenue from our biomanufacturing segment is included in net income (loss) from discontinued operations. 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.

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, research and development related facility costs and third-party contract costs relating to research, formulation, manufacturing, preclinical study and clinical trial activities. The costs of revenue related to the Microbia services contracts and costs associated with Microbia's research and development activities are included in net income (loss) from discontinued operations. 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.

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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 Phase 3 clinical development for the treatment of IBS-C and CC and is our only product candidate that has demonstrated clinical proof of concept. In September and November 2010, we announced the positive top-line results from each of the two Phase 3 clinical trials assessing the safety and efficacy of linaclotide in patients with IBS-C, and in November 2009, we announced that we achieved positive results in each of our Phase 3 CC trials. We have a pipeline of early stage, pre-proof of concept development candidates in multiple therapeutic areas, including gastrointestinal disease, pain and inflammation, and respiratory disease. We are also conducting early stage, preclinical research in these therapeutic areas, as well as in the area of cardiovascular disease.

The following table sets forth our research and development expenses related to our product pipeline for the years ended December 31, 2010, 2009 and 2008. These expenses relate primarily to external costs associated with manufacturing, preclinical studies and clinical trial costs. Costs related to facilities, depreciation, share-based compensation and research and development support services are not directly charged to programs.

	Years Ended December 31,		
	2010	2009	2008
		(unaudited)	
		(in thousands)	
Demonstrated clinical proof of concept	$ 26,684	$ 41,052	$ 13,588
Early stage	13,067	5,742	10,917
Early stage, preclinical	6,134	5,701	3,724

We began tracking program expenses for linaclotide in 2004, and research and development program expenses from inception to December 31, 2010 were approximately $123.4 million. 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.

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 our other product candidates 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, or any of our other product candidates will generate revenues and cash flows.

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, supportive data. In addition, we are actively engaged in evaluating externally discovered drug candidates at all stages of development. In evaluating potential assets, we apply the same criteria as those used for investments in internally-discovered assets.

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 provided that no other clinical trials are necessary to obtain regulatory approval in the U.S. If our other product candidates are successful in early stage clinical trials, we would expect external costs to increase as the programs progress 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.

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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 may not be favorable.
- The emergence of competing technologies and products and other adverse market developments may negatively impact us.

As a result of the uncertainties discussed above, we are unable to determine the duration and costs to complete current or future preclinical and 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.

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. Additionally, our research and development costs will increase as we will fund full-time equivalents for Protagonist's drug discovery activities under the terms of our collaboration agreement.

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, general and administrative related facility costs and professional fees for accounting and legal services. As a result of our IPO in February 2010, we have experienced and will likely continue to experience increases in general and administrative expense relating to operating as a public company. These increases include legal fees, accounting fees, costs associated with implementing and complying with the requirements of the Sarbanes-Oxley Act of 2002 and the Dodd-Frank Wall Street Reform and Protection Act of 2010 and fees for investor relations services. We also anticipate substantial increases in 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 U.S., or GAAP. The preparation of these financial statements requires us to make certain

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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 estimates and assumptions, including those related to revenue recognition, available-for-sale securities, impairments of long-lived assets, income taxes including the valuation allowance for deferred tax assets, research and development expenses, contingencies, and share-based compensation are monitored and analyzed by us for changes in facts and circumstances, and material changes in these estimates could occur in the future. Prior to our IPO, we also evaluated our estimates and judgments regarding the fair value assigned to our common stock. 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. Actual results may differ from our estimates under different assumptions or conditions.

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 Annual Report on Form 10-K.

As a result of the sale of our interest in Microbia, we have presented the assets, liabilities, operations, and cash flows of Microbia as discontinued operations for all periods presented prior to the sale.

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; the sale of drug substance to our collaborators; and royalties on product sales. In addition, prior to September 2010, we generated services revenue through agreements that generally provided for fees for research and development services rendered.

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.

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.

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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. In the case where we cannot reliably estimate the period of performance due to our continued involvement in research and development, we defer the commencement of revenue recognition of the up-front license fee until the earlier of either (i) the expected performance period of our joint steering committee obligations can be reasonably and reliably estimated or (ii) we are no longer contractually obligated to perform all joint steering committee duties. As a result, at December 31, 2009, we deferred the entire $30.0 million up-front licensing fee received from Astellas in November 2009. We began recognizing revenue from this up-front payment from Astellas in March 2010, when an estimate of the development period could be derived.

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 to date under our Forest collaboration agreement and our Almirall license agreement have been considered substantive. As of December 31, 2010, we had not achieved any milestones under our Astellas 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, we may experience significant fluctuations in our

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collaborative revenues from quarter to quarter and year to year depending on the timing of achieving such substantive milestones.

Services Revenue

Prior to September 2010, services revenue was recognized when there was persuasive evidence that an arrangement existed, services had been rendered or delivery had occurred, the price was fixed or determinable, and collection was reasonably assured. Revenue from research and development services rendered was recognized as services were performed. As a result of the sale of our interest in Microbia in September 2010, services revenue is included in net income (loss) from discontinued operations.

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 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 were 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.

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

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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 weighted average assumptions used in calculating the fair value of share-based awards granted in 2010, 2009 and 2008 are set forth below: