ACCELERON PHARMA INC
Form S-1
January 09, 2014

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As filed with the Securities and Exchange Commission on January 9, 2014

Registration No. 333-

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM S-1

REGISTRATION STATEMENT
UNDER
THE SECURITIES ACT OF 1933

ACCELERON PHARMA INC.

(Exact name of registrant as specified in its charter)

Delaware	**2836**	**27-0072226**
(State or other jurisdiction of incorporation or organization)	(Primary Standard Industrial Classification Code Number)	(I.R.S. Employer Identification Number)

128 Sidney Street
Cambridge, MA 02139
(617) 649-9200

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

John L. Knopf, Ph.D.
Chief Executive Officer and President
128 Sidney Street
Cambridge, MA 02139
(617) 649-9200

(Name, address, including zip code, and telephone number, including area code, of agent for service)

Copies to:

Marc Rubenstein, Esq.
Ropes & Gray LLP
Prudential Tower
800 Boylston Street
Boston, MA 02199
(617) 951-7000

John D. Quisel, Ph.D., Esq.
Vice President,
General Counsel and Secretary
Acceleron Pharma Inc.
128 Sidney Street
Cambridge, MA 02139
(617) 649-9200

Jonathan L. Kravetz, Esq.
Brian P. Keane, Esq.
Mintz, Levin, Cohn, Ferris, Glovsky
and Popeo, P.C.
One Financial Center
Boston, MA 02111
(617) 542-6000

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

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

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

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

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

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

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

CALCULATION OF REGISTRATION FEE

Title of Each Class of Securities to be Registered	**Proposed Maximum Aggregate Offering Price(1)**	**Amount of Registration Fee**
Common Stock, $0.001 par value per share	$115,000,000	$14,812

(1) Estimated solely for the purpose of calculating the registration fee in accordance with Rule 457(o) of the Securities Act of 1933, as amended.

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

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The information in this preliminary prospectus is not complete and may be changed. This preliminary prospectus is not an offer to sell these securities and we are not soliciting offers to buy these securities in any jurisdiction where the offer or sale is not permitted.

SUBJECT TO COMPLETION, DATED JANUARY 9, 2014

PRELIMINARY PROSPECTUS

$100,000,000

Common Stock
$ per share

We are selling shares of our common stock.

We have granted the underwriters an option to purchase up to additional shares of common stock.

Our common stock is listed on the NASDAQ Global Market under the symbol "XLRN". On January 8, 2014, the last sale price our common stock was $41.26 per share.

We are an "emerging growth company" as that term is used in the Jumpstart Our Business Startups Act of 2012 and, as such, have elected to comply with certain reduced public company reporting requirements for this prospectus and future filings.

Investing in our common stock involves risk. See "Risk Factors" beginning on page 11.

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

	Per share	Total
Public Offering Price	$	$
Underwriting Discounts and Commissions(1)	$	$
Proceeds to Acceleron (before expenses)	$	$

(1) We refer you to "Underwriting" beginning on page 154 for additional information regarding underwriting compensation.

The underwriters expect to deliver the shares of common stock to investors on or about January , 2014 through the book-entry facilities of The Depositary Trust Company.

Citigroup **Leerink Partners**

Piper Jaffray

JMP Securities

, 2014

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We are responsible for the information contained in this prospectus and in any free-writing prospectus we prepare or authorize. We have not authorized anyone to provide you with different information, and we take no responsibility for any other information others may give you. We are not, and the underwriters are not, making an offer to sell these securities in any jurisdiction where the offer or sale is not permitted. You should not assume that the information contained in this prospectus is accurate as of any date other than the date on the cover of this prospectus.

Trademarks

We own or have rights to trademarks, service marks and trade names that we use in connection with the operation of our business, including our corporate name, logos and website names. Other trademarks, service marks and trade names appearing in this prospectus are the property of their respective owners. The trademarks that we own include Acceleron Pharma®. Solely for convenience, some of the trademarks, service marks and trade names referred to in this prospectus are listed without the ® and symbols, but we will assert, to the fullest extent under applicable law, our rights to our trademarks, service marks and trade names.

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SUMMARY

This summary highlights information contained in other parts of this prospectus. Because it is only a summary, it does not contain all of the information that you should consider before investing in shares of our common stock and it is qualified in its entirety by, and should be read in conjunction with, the more detailed information appearing elsewhere in this prospectus. You should read the entire prospectus carefully, especially "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations", before deciding to buy shares of our common stock. Unless the context requires otherwise, references in this prospectus to "Acceleron", "we", "us" and "our" refer to Acceleron Pharma Inc.

Overview

We are a clinical stage biopharmaceutical company focused on the discovery, development and commercialization of novel protein therapeutics for cancer and rare diseases. Our research focuses on the biology of the Transforming Growth Factor-Beta (TGF-β) protein superfamily, a large and diverse group of molecules that are key regulators in the growth and repair of tissues throughout the human body. We are leaders in understanding the biology of the TGF-β superfamily and in targeting these pathways to develop important new medicines. By coupling our discovery and development expertise, including our proprietary knowledge of the TGF-β superfamily, with our internal protein engineering and manufacturing capabilities, we have built a highly productive research and development platform that has generated innovative clinical and preclinical protein therapeutic candidates with novel mechanisms of action.

We have three internally discovered protein therapeutic candidates that are currently being studied in numerous ongoing Phase 2 clinical trials, focused on cancer and rare diseases. These differentiated protein therapeutic candidates have the potential to significantly improve clinical outcomes for patients.

The Acceleron Discovery and Development Platform: Novel Approaches to Potent Biology

We focus on discovering and developing protein therapeutics that target a group of approximately 30 secreted proteins, or ligands, that are collectively referred to as the TGF-β superfamily. These ligands bind to subsets of 12 different receptors on the surface of cells, triggering intracellular changes in gene expression that guide cell growth and differentiation. The TGF-β superfamily ligands and their receptors represent a diverse and under-explored set of drug targets with the potential to yield therapeutics that modulate the growth and repair of diseased cells and tissues.

Members of the TGF-β superfamily are now recognized as important regulators of red blood cell formation. We have shown that inhibition of members of the TGF-β superfamily ameliorates anemia in mouse models of β- thalassemia and myelodysplastic syndromes (MDS). These red blood cell disorders are generally unresponsive to currently approved drugs. Based on our findings, we are developing two protein therapeutic candidates, sotatercept and ACE- 536, each of which is currently in Phase 2 clinical trials to treat patients with these diseases.

Members of the TGF-β superfamily also play a significant role in regulating blood vessel formation. We and our academic collaborators have shown that mice with a defect in a particular receptor for members of the TGF-β superfamily are resistant to tumor growth due to reduced blood vessel formation in the tumor. We have used this insight to design our anti-angiogenic agent, dalantercept, which is currently in Phase 2 clinical trials for the treatment of cancer.

Sotatercept and ACE-536: Novel Protein Therapeutic Candidates in Phase 2 Clinical Trials for β-thalassemia and MDS

Together with our collaboration partner, Celgene Corporation, we are developing sotatercept and ACE-536, our lead protein therapeutic candidates, to treat anemia and associated complications in patients with β-thalassemia and MDS. Clinical trials are underway in other diseases as well.

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Sotatercept and ACE-536 have already shown promising biological activity in initial clinical trials. We and Celgene have conducted six clinical trials with sotatercept in over 160 healthy volunteers and cancer patients. We have conducted one clinical trial with ACE-536 in healthy volunteers. In these studies, both sotatercept and ACE-536 caused a dose-dependent increase in the number of red blood cells. Based on these results, we and Celgene have initiated Phase 2 clinical trials with each of these protein therapeutic candidates in β-thalassemia and MDS. We and Celgene plan to initiate Phase 3 clinical trials for one or both of these protein therapeutic candidates in one or both of β-thalassemia and MDS by the end of 2014 or early 2015.

β-thalassemia

β-thalassemia is a hereditary disease arising from defects in genes involved in the production of hemoglobin, the protein responsible for carrying oxygen in red blood cells. During red blood cell formation in the bone marrow, these genetic defects cause most of the cells to die before they mature into fully functional red blood cells. As a consequence, patients with β-thalassemia have anemia, a lower than normal number of red blood cells, and many patients experience a broad array of complications arising from their disease, including an enlarged spleen, skeletal deformities and serious organ damage, such as liver fibrosis and heart failure, resulting from the accumulation of iron. There is no approved drug and no effective drug therapy for the anemia of β-thalassemia. Frequent blood transfusions are used to manage the treatment of anemia in patients with β-thalassemia, but further contribute to the accumulation of iron and associated organ toxicities.

We and Celgene have shown that sotatercept and ACE-536 increase the production of red blood cells by promoting their maturation in the bone marrow. We believe this mechanism of action may be particularly beneficial for patients suffering from diseases, such as β-thalassemia, that are characterized by diminished red blood cell maturation. In a mouse model of β-thalassemia, the mouse version of ACE-536 demonstrated broad disease modifying effects. In this model, the mouse version of ACE-536 increased red blood cell production, reduced spleen size, increased bone density and reduced levels of iron in the kidney and liver.

The Thalassaemia International Federation estimates that there are approximately 300,000 patients worldwide with β-thalassemia, approximately 20,000 of which are in the United States and Europe, who are dependent on frequent blood transfusions. We estimate that there are at least as many β-thalassemia patients who do not receive frequent blood transfusions. Many of these patients have hemoglobin levels that are approximately half that of normal individuals and experience significant complications from the disease.

Myelodysplastic Syndromes (MDS)

MDS are a group of heterogeneous hematologic diseases characterized by abnormal proliferation and differentiation of blood precursor cells, including red blood cell precursors, in the bone marrow. This leads to anemia, which is present in the vast majority of MDS patients at the time of diagnosis. Much like the anemia of β-thalassemia, the anemia of MDS is characterized by an over-abundance of early stage red blood cell precursors, a large proportion of which fails to mature into functional red blood cells during the later phases of the red blood cell formation process. Drugs that stimulate the production of early stage red blood cell precursors, such as recombinant erythropoietin, are often used to treat anemia in MDS patients, yet many do not experience a substantial improvement of their anemia with these drugs. Although not approved by the United States Food and Drug Administration (FDA) for use in patients with MDS, these products generate an estimated $500 to $700 million in annual U.S. sales from use in these patients, according to our market research.

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Additional Opportunities for Sotatercept and ACE-536

Although sotatercept and ACE-536 have similar effects on red blood cells, sotatercept has been shown to increase bone mass and biomarkers of bone growth in humans. Many patients with chronic kidney disease suffer from both anemia and bone loss. Celgene is conducting two Phase 2 clinical trials of sotatercept in patients with chronic kidney disease-mineral and bone disorder. Additionally, we have shown that sotatercept inhibits tumor growth in mouse models of multiple myeloma, a cancer of the bone marrow, and sotatercept is being studied in an investigator-sponsored Phase 2 trial in multiple myeloma patients. Celgene and its collaborators continue to explore sotatercept in additional clinical trials including trials in patients with Diamond-Blackfan anemia and myelofibrosis.

Acceleron and Celgene are exploring the preclinical activity of sotatercept and ACE-536 in other red blood cell disorders including sickle cell disease.

Our Partnership with Celgene

We are developing sotatercept and ACE-536 through our exclusive worldwide collaborations with Celgene. As of January 1, 2013, Celgene became responsible for paying 100% of worldwide development costs for both programs. Additionally, we may receive up to $560.0 million of potential development, regulatory and commercial milestone payments and, if these protein therapeutic candidates are commercialized, we will receive a royalty on net sales in the low-to-mid 20% range. If approved, we also will co-promote sotatercept and ACE-536 in North America, for which our commercialization costs will be entirely funded by Celgene.

Dalantercept: Novel Protein Therapeutic Candidate in Phase 2 Clinical Trials for Cancer

Our third clinical stage protein therapeutic candidate, dalantercept, is designed to inhibit blood vessel formation in tumors through a mechanism that is distinct from, and potentially synergistic with, vascular endothelial growth factor (VEGF) pathway inhibitors, the dominant class of cancer drugs that inhibit blood vessel formation. The VEGF pathway inhibitors collectively generate worldwide sales in excess of $8 billion annually. We are developing dalantercept primarily for use in combination with these successful products to produce better outcomes for cancer patients.

Inhibiting Angiogenesis to Limit Tumor Growth

Angiogenesis is a process by which new blood vessels are formed. Angiogenesis can be simplified to two major stages the proliferative stage followed by the maturation stage. During the proliferative stage, vascular endothelial cells, the cells lining the inside of the blood vessels, increase in number. This proliferative stage is followed by the maturation stage during which the endothelial cells coalesce to form tubes which are then stabilized through the recruitment of perivascular cells that form an outer layer of the blood vessels resulting in fully formed, functional vessels.

Tumors depend on angiogenesis to form new blood vessels that supply nutrients and oxygen to feed the rapidly growing malignant cells. The principal molecule driving the proliferative stage of angiogenesis in tumors is a protein called VEGF. Inhibiting VEGF-driven angiogenesis to control tumor growth has become an important and widely-used approach to cancer treatment. There are several FDA-approved cancer drugs that inhibit the VEGF pathway. Despite the success of these drugs, many patients fail to respond or develop resistance to VEGF pathway inhibitor therapy, resulting in an unmet need for new therapies to inhibit angiogenesis by a different mechanism.

We are using our knowledge of the TGF-β superfamily to develop dalantercept, a novel protein therapeutic candidate targeting the maturation stage of angiogenesis. Recently, the activin receptor-like kinase 1 (ALK1) has been recognized as an important regulator of the maturation stage of angiogenesis. ALK1 is one of the 12 receptors for ligands in the TGF-β superfamily and is found

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primarily on endothelial cells. The importance of the ALK1 pathway in angiogenesis was discovered in part through research into a genetic disease in which patients manifest vascular defects, including a reduced ability to form capillary beds, which are the networks of small blood vessels that connect arteries to veins and are necessary for nutrient and waste exchange in tissues. This research revealed that these patients have only one of two functional copies of the ALK1 gene. The resulting decreased signaling through the ALK1 receptor inhibits blood vessel maturation, leading to the reduced formation of capillary beds.

Opportunities for Dalantercept

We reasoned that leveraging the biology of the ALK1 pathway to inhibit maturation of blood vessels could impair the growth of tumors by limiting the development of capillary beds within the tumor. To test this hypothesis, mice with a predisposition to develop tumors were bred to have only one copy, rather than two copies, of the ALK1 gene that normally occur. In response to the loss of half of the ALK1 genes, tumor growth and size and blood vessel density in the tumor were reduced by half. We have also shown in two mouse cancer models that treatment with dalantercept decreases metastases. This is in contrast to VEGF pathway inhibitors, many of which have been shown to increase metastases in mouse cancer models. These results and additional research in the field have established the ALK1 signaling pathway as a promising target for developing a new class of anti-angiogenesis agents, ALK1 pathway inhibitors. We are developing dalantercept to treat cancer by inhibiting the ligands of the TGF-β superfamily that signal through the ALK1 receptor.

We believe one promising opportunity for dalantercept will be its use in combination with VEGF pathway inhibitors because these agents target distinct sequential steps in tumor angiogenesis. Moreover, we believe that dalantercept sensitizes blood vessels to increase the effects of treatment with VEGF pathway inhibitors. A combination of ALK1 and VEGF pathway inhibitors could have application in a number of different oncology indications where VEGF pathway inhibitors are currently used, such as liver cancer, brain cancer, non-small cell lung cancer, colorectal cancer and renal cell carcinoma.

With respect to our third clinical stage protein therapeutic candidate, dalantercept, we have conducted a single agent Phase 1 clinical trial in patients with advanced solid tumors. Additionally, we have studied the single agent activity of dalantercept in a Phase 2 clinical trial in patients with advanced head and neck cancer. Our ongoing focus is on the use of dalantercept in combination with an approved VEGF pathway inhibitor where we have both a mechanistic rationale and supportive preclinical data demonstrating dalantercept in combination with a VEGF pathway inhibitor provides enhanced anti-tumor effects in mice bearing human renal cell carcinoma xenographs. In an ongoing Phase 2 clinical trial of dalantercept in combination with axitinib, an approved VEGF pathway inhibitor, in patients with advanced renal cell carcinoma we have completed the dose escalation stage. We have now initiated the dose expansion phase of this study and plan to start the randomized controlled part of the study at the end of Q1 or early Q2 2014. We also intend to initiate a Phase 2 clinical trial of dalantercept in combination with the VEGF pathway inhibitor sorafenib in patients with liver cancer in the first half of 2014.

We have not entered into a partnership for dalantercept and retain worldwide rights to this program.

ACE-083: Neuromuscular Disorders

In addition to our clinical stage programs, we are developing a protein therapeutic candidate, ACE-083, for a first-in-human clinical trial that we expect to initiate by the end of 2014. ACE-083 has been designed to promote muscle growth in those muscles in which the drug is injected, with minimal systemic effect. We are focused on the development of ACE-083 for diseases in which increases in the size and function of specific muscles may provide a clinical benefit, including inclusion body myositis, facioscapulohumeral dystrophy (FSHD) and disuse atrophy.

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Our Development Pipeline

The status of our three clinical stage protein therapeutic candidates and our most advanced preclinical candidate is summarized below:

Our Strategy

Our goal is to be a leader in the discovery, development and commercialization of novel protein therapeutics for cancer and rare diseases. Key components of our strategy are:

Advance sotatercept and ACE-536 into Phase 3 trials in collaboration with Celgene. We and Celgene are jointly developing sotatercept and ACE-536. Assuming successful completion of the ongoing Phase 2 clinical trials in β-thalassemia and MDS, we plan to initiate Phase 3 clinical trials with Celgene for one or both protein therapeutic candidates in one or both diseases by the end of 2014 or early 2015.

Explore new indications for sotatercept and ACE-536 with Celgene. We and Celgene are continuing our preclinical research to assess the opportunity for sotatercept and ACE-536 to treat certain red blood cell disorders known as hemoglobinopathies, which include diseases such as thalassemias and sickle cell disease. Based on our encouraging preclinical and clinical data in β-thalassemia and our emerging understanding of the mechanism of action of these protein therapeutic candidates, we believe there is a potential for activity for sotatercept and ACE-536 in sickle cell disease, and we continue to explore development of these protein therapeutic candidates for this disease.

Advance dalantercept into Phase 3-enabling clinical trials. Beyond our ongoing Phase 2 clinical trials, in 2014, we plan to initiate additional clinical trials of dalantercept in combination with either an approved anti-angiogenesis agent or chemotherapy in advanced solid tumors. One of these trials is expected to be in patients with liver cancer and other trials

may be in patients with brain cancer, lung cancer or colon cancer.

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Utilize our discovery and development platform to develop additional protein therapeutic candidates. In addition to sotatercept, ACE-536 and dalantercept, all of which were internally discovered using our research and development platform, we intend to continue to discover and develop other protein therapeutics that target and regulate various pathways in the TGF-β superfamily. We plan to bring an additional protein therapeutic candidate, ACE-083, into the clinic in 2014 targeting diseases involving muscle loss. We are also conducting pre-clinical development of ALK1 pathway inhibitors distinct from dalantercept for the treatment of diseases of the eye including age-related macular degeneration. In addition we are developing new protein therapeutic candidates for the treatment of cancer and diseases involving fibrosis.

Strategically leverage collaborations to advance our protein therapeutic candidates. We have received more than $250.0 million from our collaboration partners, including Celgene. Our two collaborations with Celgene for sotatercept and ACE-536 provide us with significant funding and access to Celgene's considerable scientific, development, regulatory and commercial capabilities. We will continue to strategically evaluate possible collaborations where doing so could enhance the development or commercialization of other protein therapeutic candidates in our pipeline.

Establish commercialization and marketing capabilities in North America and potentially other markets. We have retained co-promotion rights in North America for sotatercept and ACE-536, which will be entirely funded by Celgene. We intend to build hematology, oncology and neuromuscular disorder focused specialty sales forces and marketing capability to commercialize our protein therapeutic candidates that receive regulatory approval.

Risk Factors

An investment in our common stock involves a high degree of risk. Any of the factors set forth under "Risk Factors" may limit our ability to successfully execute our business strategy. You should carefully consider all of the information set forth in this prospectus and, in particular, should evaluate the specific factors set forth under "Risk Factors" in deciding whether to invest in our common stock. Among these important risks are the following:

We have incurred net operating losses since our inception and anticipate that we will continue to incur substantial operating losses for the foreseeable future. We may never achieve or sustain profitability.

We will require substantial additional financing to achieve our goals, and a failure to obtain this necessary capital when needed could force us to delay, limit, reduce or terminate our development or commercialization efforts of our protein therapeutic candidates.

If Celgene does not devote sufficient resources to the development of sotatercept and ACE-536, is unsuccessful in its efforts or chooses to terminate its agreements with us, our business will be materially harmed.

If our protein therapeutic candidates fail to demonstrate safety and efficacy to the satisfaction of regulatory authorities, we may incur additional costs or experience delays in completing, or ultimately be unable to complete the development and commercialization of our protein therapeutic candidates.

Our future commercial success depends upon attaining significant market acceptance of our protein therapeutic candidates, if approved, among physicians, patients and health care payers and, if we fail to do so, our business will be materially harmed.

We expect to rely on third parties in the manufacturing and clinical development of our protein therapeutic candidates. If they fail to meet deadlines or perform in an unsatisfactory manner our business could be harmed.

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If we are unable to obtain or protect intellectual property rights related to our protein therapeutic candidates, we may not be able to prevent competitors with the same or similar protein therapeutics from entering our markets.

Implications of Being an Emerging Growth Company

As a company with less than $1.0 billion in revenue during our most recently completed fiscal year, we qualify as an "emerging growth company" as defined in Section 2(a) of the Securities Act of 1933, as amended, which we refer to as the Securities Act, as modified by the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. As an emerging growth company, we may take advantage of specified reduced disclosure and other requirements that are otherwise applicable, in general, to public companies that are not emerging growth companies. These provisions include:

Reduced disclosure about our executive compensation arrangements;

No non-binding shareholder advisory votes on executive compensation or golden parachute arrangements;

Exemption from the auditor attestation requirement in the assessment of our internal control over financial reporting; and

Reduced disclosure of financial information in this prospectus, including two years of audited financial information and two years of selected financial information.

We may take advantage of these exemptions for up to five years or such earlier time that we are no longer an emerging growth company. We would cease to be an emerging growth company if we have more than $1.0 billion in annual revenues as of the end of a fiscal year, if we are deemed to be a large-accelerated filer under the rules of the Securities and Exchange Commission, or if we issue more than $1.0 billion of non-convertible debt over a three-year-period.

The JOBS Act permits an emerging growth company to take advantage of an extended transition period to comply with new or revised accounting standards applicable to public companies. We are choosing to "opt out" of this provision.

Corporate Information

We were incorporated in the state of Delaware in June 2003 as Phoenix Pharma, Inc., and we subsequently changed our name to Acceleron Pharma Inc. and commenced operations in February 2004. Our principal executive offices are located at 128 Sidney Street, Cambridge, Massachusetts 02139, and our telephone number is (617) 649-9200. Our Internet website is *www.acceleronpharma.com*. The information on, or that can be accessed through, our website is not part of this prospectus, and you should not rely on any such information in making the decision whether to purchase our common stock.

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THE OFFERING

Common stock offered by us	shares
Common stock to be outstanding after this offering	shares
Option to purchase additional shares	The underwriters have an option for a period of 30 days to purchase up to additional shares of our common stock.
Use of proceeds	The net proceeds from this offering will be approximately $93.3 million, or approximately $107.4 million if the underwriters exercise their option to purchase additional shares in full, after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us. We intend to use the net proceeds of this offering (1) to continue development of dalantercept, (2) to conduct clinical trials and associated activities with a new protein therapeutic candidate, ACE-083, (3) to continue to advance and expand our preclinical research pipeline of protein therapeutic candidates and (4) for working capital and other general corporate purposes, including funding the costs of operating as a public company. See "Use of Proceeds".
Risk factors	You should read the "Risk Factors" section of this prospectus for a discussion of factors to consider carefully before deciding to invest in shares of our common stock.
NASDAQ Global Market symbol	XLRN

The number of shares of common stock to be outstanding after this offering is based on 28,348,633 shares of common stock outstanding as of January 1, 2014 and excludes the following:

- 3,942,304 shares of common stock issuable upon exercise of stock options outstanding as of January 1, 2014 at a weighted-average exercise price of $7.05 per share;
- 979,699 shares of common stock issuable upon the exercise of outstanding warrants as of January 1, 2014 at a weighted-average exercise price of $6.53 per share;
- 2,089,945 shares of common stock reserved for future issuance under our 2013 Equity Incentive Plan as of January 1, 2014; and
- 275,000 shares of common stock reserved for future issuance under our Employee Stock Purchase Plan as of January 1, 2014.

Unless otherwise indicated, all information in this prospectus assumes no issuance or exercise of stock options or warrants on or after January 1, 2014 and no exercise of the underwriters' option to purchase up to an additional shares of common stock in this offering.

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SUMMARY FINANCIAL DATA

The following summary financial data for the years ended December 31, 2011 and 2012 are derived from our audited financial statements included elsewhere in this prospectus. The summary financial data as of September 30, 2013 and for the nine months ended September 30, 2012 and 2013 have been derived from our unaudited financial statements included elsewhere in this prospectus. These unaudited financial statements have been prepared on a basis consistent with our audited financial statements and, in our opinion, contain all adjustments, consisting only of normal and recurring adjustments, necessary for a fair presentation of such financial data. You should read this data together with our audited financial statements and related notes included elsewhere in this prospectus and the information under the captions "Selected Financial Data" and "Management's Discussion and Analysis of Financial Condition and Results of Operations". Our historical results are not necessarily indicative of our future results, and our operating results for the nine-month period ended September 30, 2013 are not necessarily indicative of the results that may be expected for the fiscal year ending December 31, 2013 or any other interim periods or any future year or period.

	Year Ended December 31,		Nine Months Ended September 30,	
(in thousands, except per share data)	**2011**	**2012**	**2012**	**2013**
Revenue:				
Collaboration revenue:				
License and milestone	$ 74,406	$ 9,696	$ 7,226	$ 36,044
Cost-sharing, net	4,760	5,558	4,043	9,666
Contract manufacturing	1,745			
Total revenue	80,911	15,254	11,269	45,710
Costs and expenses:				
Research and development	32,713	35,319	25,646	25,834
General and administrative	8,142	8,824	6,318	9,472
Cost of contract manufacturing revenue	1,500			
Total costs and expenses	42,355	44,143	31,964	35,306
Income (loss) from operations	38,556	(28,889)	(20,695)	10,404
Total other expense, net	(2,290)	(3,693)	(1,508)	(14,192)
Net income (loss)	$ 36,266	$ (32,582)	$ (22,203)	$ (3,788)
Comprehensive income (loss)	$ 36,266	$ (32,582)	$ (22,203)	$ (3,788)
Net income (loss) per share applicable to common stockholders(1)				
Basic	$ 0.80	$ (24.84)	$ (17.73)	$ (6.74)
Diluted	$ 0.78	$ (24.84)	$ (17.73)	$ (6.74)
Weighted-average number of common shares used in computing net income (loss) per share applicable to common stockholders				
Basic	2,328	2,401	2,397	3,100
Diluted	2,716	2,401	2,397	3,100

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(in thousands)	September 30, 2013 Actual	As adjusted(2)(3)
Balance Sheet Data:		
Cash and cash equivalents	$ 116,479	$
Total assets	127,260	
Total current liabilities	16,523	
Long-term deferred revenue	6,205	
Long-term notes payable	10,979	
Warrants to purchase common stock	16,526	
Total stockholders' equity	74,564	

(1) See Note 2 within the notes to our financial statements appearing elsewhere in this prospectus for a description of the method used to calculate basic and diluted net income (loss) per common share and pro forma basic and diluted net income (loss) per common share.

(2) As adjusted to reflect the sale of shares of our common stock in this offering at an assumed public offering price of $ per share (the last reported price of our common stock on The NASDAQ Global Market on January , 2014), after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

(3) A $1.00 increase (decrease) in the assumed public offering price of $ per share (the last reported price of our common stock on The NASDAQ Global Market on January , 2014), would increase (decrease) the as adjusted amount of each of cash and cash equivalents and total stockholders' equity by approximately $, assuming that the number of shares offered by us, as set forth on the cover of this prospectus, remains the same and after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

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RISK FACTORS

Investing in our common stock involves a high degree of risk. You should carefully consider the risks and uncertainties described below together with all of the other information contained in this prospectus, including our financial statements and the related notes appearing at the end of this prospectus, before deciding to invest in our common stock. If any of the following risks actually occurs, our business, prospects, operating results and financial condition could suffer materially, the trading price of our common stock could decline and you could lose all or part of your investment. The risks and uncertainties described below are not the only ones we face. Additional risks and uncertainties not presently known to us or that we currently believe to be immaterial may also adversely affect our business.

Risks related to our financial position and need for additional capital

We have incurred net operating losses since our inception and anticipate that we will continue to incur substantial operating losses for the foreseeable future. We may never achieve or sustain profitability.

We have incurred net losses during most fiscal periods since our inception. As of September 30, 2013, we had an accumulated deficit of $174.2 million. We do not know whether or when we will become profitable. To date, we have not commercialized any products or generated any revenues from the sale of products, and we do not expect to generate any product revenues in the foreseeable future. Our losses have resulted principally from costs incurred in our discovery and development activities.

We anticipate that our expenses will increase in the future as we expand our discovery, research, development, manufacturing and commercialization activities. However, we also anticipate that these increased expenses will be partially offset by milestone payments we expect to receive under our agreements with Celgene and potentially by payments we may receive under new collaboration arrangements we may enter into with third parties for dalantercept or other protein therapeutic candidates. If we do not receive the anticipated milestone payments or do not enter into partnerships for dalantercept or other protein therapeutic candidates on acceptable terms, our operating losses will substantially increase over the next several years as we execute our plan to expand our discovery, research, development, manufacturing and commercialization activities. There can be no assurance that we will enter into a new collaboration or achieve milestones and, therefore, no assurance our losses will not increase prohibitively in the future.

To become and remain profitable, we or our partners must succeed in developing our protein therapeutic candidates, obtaining regulatory approval for them, and manufacturing, marketing and selling those products for which we or our partners may obtain regulatory approval. We or they may not succeed in these activities, and we may never generate revenue from product sales that is significant enough to achieve profitability. Even if we achieve profitability in the future, we may not be able to sustain profitability in subsequent periods. Our failure to become or remain profitable would depress our market value and could impair our ability to raise capital, expand our business, discover or develop other protein therapeutic candidates or continue our operations. A decline in the value of our company could cause you to lose all or part of your investment.

We will require substantial additional financing to achieve our goals, and a failure to obtain this necessary capital when needed could force us to delay, limit, reduce or terminate our product development or commercialization efforts.

As of September 30, 2013, our cash and cash equivalents were $116.5 million. We believe that we will continue to expend substantial resources for the foreseeable future developing dalantercept and new protein therapeutic candidates. These expenditures will include costs associated with research and development, potentially acquiring new technologies, conducting preclinical studies and clinical trials, potentially obtaining regulatory approvals and manufacturing products, as well as marketing and selling products approved for sale, if any. In addition, other unanticipated costs may arise. Because the

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outcome of our planned and anticipated clinical trials is highly uncertain, we cannot reasonably estimate the actual amounts necessary to successfully complete the development and commercialization of our protein therapeutic candidates.

Celgene pays development, manufacturing and commercialization and certain patent costs for sotatercept and ACE-536. Other than those costs, our future capital requirements depend on many factors, including:

- the scope, progress, results and costs of researching and developing our other protein therapeutic candidates, and conducting preclinical studies and clinical trials;
- the timing of, and the costs involved in, obtaining regulatory approvals for our other protein therapeutic candidates if clinical trials are successful;
- the cost of commercialization activities for our other protein therapeutics, if any of these protein therapeutics is approved for sale, including marketing, sales and distribution costs;
- the cost of manufacturing our other protein therapeutic candidates for clinical trials in preparation for regulatory approval and in preparation for commercialization;
- our ability to establish and maintain strategic partnerships, licensing or other arrangements and the financial terms of such agreements;
- the costs involved in preparing, filing, prosecuting, maintaining, defending and enforcing patent claims, including litigation costs and the outcome of such litigation; and
- the timing, receipt, and amount of sales of, or royalties on, our future products, if any.

Based on our current operating plan, we believe that the net proceeds we receive from this offering, together with receipt of anticipated milestone payments and our existing cash and cash equivalents will be sufficient to fund our projected operating requirements into the first quarter of 2017. However, our operating plan may change as a result of many factors currently unknown to us, and we may need additional funds sooner than planned. In addition, we may seek additional capital due to favorable market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. Additional funds may not be available when we need them on terms that are acceptable to us, or at all. If adequate funds are not available to us on a timely basis, we may be required to delay, limit, reduce or terminate preclinical studies, clinical trials or other development activities for one or more of our protein therapeutic candidates or delay, limit, reduce or terminate our establishment of sales and marketing capabilities or other activities that may be necessary to commercialize our protein therapeutic candidates.

Raising additional capital may cause dilution to our existing stockholders, restrict our operations or require us to relinquish rights to our technologies or protein therapeutics on unfavorable terms to us.

We may seek additional capital through a variety of means, including through private and public equity offerings and debt financings. To the extent that we raise additional capital through the sale of equity or convertible debt securities, your ownership interest will be diluted, and the terms may include liquidation or other preferences that adversely affect your rights as a stockholder. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take certain actions, such as incurring additional debt, making capital expenditures or declaring dividends. If we raise additional funds through strategic partnerships with third parties, we may have to relinquish valuable rights to our technologies or protein therapeutics, or grant licenses on terms that are not favorable to us. If we are unable to raise additional funds through equity or debt financing when needed, we may be required to delay, limit, reduce or terminate our product development or commercialization efforts for dalantercept or any protein therapeutics other than sotatercept or

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ACE-536, or grant rights to develop and market protein therapeutics that we would otherwise prefer to develop and market ourselves.

Risks Related to Regulatory Review and Approval of Our Protein Therapeutic Candidates

If we or our partners do not obtain regulatory approval for our current and future protein therapeutics, our business will be adversely affected.

Our protein therapeutic candidates will be subject to extensive governmental regulations relating to, among other things, development, clinical trials, manufacturing and commercialization. In order to obtain regulatory approval for the commercial sale of any protein therapeutic candidates, we or our partners must demonstrate through extensive preclinical studies and clinical trials that the protein therapeutic candidate is safe and effective for use in each target indication. Clinical testing is expensive, time-consuming and uncertain as to outcome. We or our partners may gain regulatory approval for sotatercept, ACE-536, dalantercept, or any other protein therapeutic candidate in some but not all of the territories available or some but not all of the target indications, resulting in limited commercial opportunity for the approved protein therapeutics, or we or they may never obtain regulatory approval for these protein therapeutic candidates.

Delays in the commencement, enrollment or completion of clinical trials of our protein therapeutic candidates could result in increased costs to us as well as a delay or failure in obtaining regulatory approval, or prevent us from commercializing our protein therapeutic candidates on a timely basis, or at all.

We cannot guarantee that clinical trials will be conducted as planned or completed on schedule, if at all. A failure of one or more clinical trials can occur at any stage of testing. Events that may prevent successful or timely commencement, enrollment or completion of clinical development include:

- delays by us or our partners in reaching a consensus with regulatory agencies on trial design;
- delays in reaching agreement on acceptable terms with prospective clinical research organizations, or CROs, and clinical trial sites;
- delays in obtaining required Institutional Review Board, or IRB, approval at each clinical trial site;
- delays in recruiting suitable patients to participate in clinical trials;
- imposition of a clinical hold by regulatory agencies for any reason, including safety concerns or after an inspection of clinical operations or trial sites;
- failure by CROs, other third parties or us or our partners to adhere to clinical trial requirements;
- failure to perform in accordance with the FDA's good clinical practices, or GCP, or applicable regulatory guidelines in other countries;
- delays in the testing, validation, manufacturing and delivery of the protein therapeutic candidates to the clinical sites;
- delays caused by patients not completing participation in a trial or not returning for post-treatment follow-up;
- clinical trial sites or patients dropping out of a trial;

occurrence of serious adverse events in clinical trials that are associated with the protein therapeutic candidates that are viewed to outweigh its potential benefits; or

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changes in regulatory requirements and guidance that require amending or submitting new clinical protocols.

Delays, including delays caused by the above factors, can be costly and could negatively affect our or Celgene's ability to complete a clinical trial. If we or Celgene are not able to successfully complete clinical trials, we will not be able to obtain regulatory approval and will not be able to commercialize our protein therapeutic candidates.

Clinical failure may occur at any stage of clinical development, and because our protein therapeutic candidates are in an early stage of development, there is a high risk of failure, and we may never succeed in developing marketable products or generating product revenue.

Our early encouraging preclinical and clinical results for sotatercept, ACE-536 and dalantercept are not necessarily predictive of the results of our ongoing or future clinical trials. Promising results in preclinical studies of a drug candidate may not be predictive of similar results in humans during clinical trials, and successful results from early clinical trials of a drug candidate may not be replicated in later and larger clinical trials or in clinical trials for different indications. If the results of our or our partners' ongoing or future clinical trials are inconclusive with respect to the efficacy of our protein therapeutic candidates or if we or they do not meet the clinical endpoints with statistical significance or if there are safety concerns or adverse events associated with our protein therapeutic candidates, we or our partner may be prevented or delayed in obtaining marketing approval for our protein therapeutic candidates. In addition, data obtained from trials and studies are susceptible to varying interpretations, and regulators may not interpret our data as favorably as we do, which may delay or prevent regulatory approval. Alternatively, even if we or our partners obtain regulatory approval, that approval may be for indications or patient populations that are not as broad as intended or desired or may require labeling that includes significant use or distribution restrictions or safety warnings. We or our partners may also be required to perform additional or unanticipated clinical trials to obtain approval or be subject to additional post-marketing testing requirements to maintain regulatory approval. In addition, regulatory authorities may withdraw their approval of a product or impose restrictions on its distribution, such as in the form of a modified risk evaluation and mitigation strategy.

If we or any of our partners violate the guidelines pertaining to promotion and advertising of any of our protein therapeutics, if approved, we or they may be subject to disciplinary action by the FDA's Office of Prescription Drug Promotion (OPDP) or other regulatory authorities.

The FDA's Office of Prescription Drug Promotion, or OPDP, is responsible for reviewing prescription drug advertising and promotional labeling to ensure that the information contained in these materials is not false or misleading. There are specific disclosure requirements, and the applicable regulations mandate that advertisements cannot be false or misleading or omit material facts about the product. Prescription drug promotional materials must present a fair balance between the drug's effectiveness and the risks associated with its use. Most warning letters from OPDP cite inadequate disclosure of risk information.

OPDP prioritizes its actions based on the degree of risk to the public health, and often focuses on newly introduced drugs and those associated with significant health risks. There are two types of letters that OPDP typically sends to companies that violate its drug advertising and promotional guidelines: notice of violation letters, or untitled letters, and warning letters. In the case of an untitled letter, OPDP typically alerts the drug company of the violation and issues a directive to refrain from future violations, but does not typically demand other corrective action. A warning letter is typically issued in cases that are more serious or where the company is a repeat offender. Although we have not received any such letters from OPDP, we or any partner may inadvertently violate OPDP's guidelines in the future and be subject to a OPDP untitled letter or warning letter, which may have a negative impact on our business.

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If we or our partners fail to obtain regulatory approval in jurisdictions outside the United States, we and they will not be able to market our products in those jurisdictions.

We and our partners intend to market our protein therapeutic candidates, if approved, in international markets. Such marketing will require separate regulatory approvals in each market and compliance with numerous and varying regulatory requirements. The approval procedures vary from country-to-country and may require additional testing. Moreover, the time required to obtain approval may differ from that required to obtain FDA approval. In addition, in many countries outside the United States, a protein therapeutic must be approved for reimbursement before it can be approved for sale in that country. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one foreign regulatory authority does not ensure approval by regulatory authorities in other foreign countries or by the FDA. The foreign regulatory approval process may include all of the risks associated with obtaining FDA approval. We or our partners may not obtain foreign regulatory approvals on a timely basis, if at all. We or our partners may not be able to file for regulatory approvals and may not receive necessary approvals to commercialize our products in any market.

Even if we or our partners receive regulatory approval for our protein therapeutic candidates, such products will be subject to ongoing regulatory review, which may result in significant additional expense. Additionally, our protein therapeutic candidates, if approved, could be subject to labeling and other restrictions, and we or our partners may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our products.

Any regulatory approvals that we or our partners receive for our protein therapeutic candidates may also be subject to limitations on the approved indicated uses for which the product may be marketed or to conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase 4 clinical trials, and surveillance to monitor safety and efficacy. In addition, if the FDA approves any of our protein therapeutic candidates, the manufacturing processes, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion and recordkeeping for the product will be subject to extensive and ongoing regulatory requirements. These requirements include submissions of safety and other post-marketing information and reports, registration, as well as continued compliance with current good manufacturing practice, or cGMP, and GCP, for any clinical trials that we or our partners conduct post-approval.

Later discovery of previously unknown problems with an approved protein therapeutic, including adverse events of unanticipated severity or frequency, or with manufacturing operations or processes, or failure to comply with regulatory requirements, may result in, among other things:

- restrictions on the marketing or manufacturing of the product, withdrawal of the product from the market, or voluntary or mandatory product recalls;
- fines, warning letters, or holds on clinical trials;
- refusal by the FDA to approve pending applications or supplements to approved applications filed by us or our partners, or suspension or revocation of product license approvals;
- product seizure or detention, or refusal to permit the import or export of products; and
- injunctions or the imposition of civil or criminal penalties.

The FDA's policies may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our protein therapeutic candidates. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we or our partners are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or not able

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to maintain regulatory compliance, we or our partners may lose any marketing approval that may have been obtained and we may not achieve or sustain profitability, which would adversely affect our business.

Risks Related to Our Reliance on Third Parties

We are dependent on Celgene for the successful development and commercialization of two of our three clinical stage protein therapeutic candidates, sotatercept and ACE-536. If Celgene does not devote sufficient resources to the development of these candidates, is unsuccessful in its efforts, or chooses to terminate its agreements with us, our business will be materially harmed.

We have entered into collaboration agreements with Celgene to develop and commercialize sotatercept and ACE-536. Pursuant to the sotatercept agreement, responsibility for all clinical and other product development activities and for manufacturing sotatercept has been transferred to Celgene. For ACE-536, we are responsible for conducting the two ongoing Phase 2 clinical trials, and we are also responsible for manufacturing supplies for Phase 1 and Phase 2 studies. Celgene will be responsible for all clinical development and manufacturing activities after such studies are completed. As of January 1, 2013, Celgene became responsible for paying 100% of worldwide development costs for sotatercept and ACE-536. We will co-promote sotatercept and ACE-536, if approved by the FDA and its counterparties, in North America. Celgene will be responsible for all commercialization costs, including the cost of our promotion activities.

Celgene is obligated to use commercially reasonable efforts to develop and commercialize sotatercept and ACE-536. Celgene may determine that it is commercially reasonable to develop and commercialize only sotatercept or ACE-536 and discontinue the development or commercialization of the other protein therapeutic candidate, or Celgene may determine that it is not commercially reasonable to continue development of one or both of sotatercept and ACE-536. In the event of any such decision, we may be unable to progress the discontinued candidate or candidates ourselves. In addition, under our collaboration agreements, once Celgene takes over development activities of a protein therapeutic candidate, it may determine the development plan and activities for that protein therapeutic candidate. We may disagree with Celgene about the development strategy it employs, but we will have no rights to impose our development strategy on Celgene. Similarly, Celgene may decide to seek regulatory approval for, and limit commercialization of, either or both of sotatercept and ACE-536 to narrower indications than we would pursue. We would be prevented from developing or commercializing a candidate in an indication that Celgene has chosen not to pursue.

This partnership may not be scientifically or commercially successful due to a number of important factors, including the following:

- Celgene has wide discretion in determining the efforts and resources that it will apply to its partnership with us. The timing and amount of any development milestones, and downstream commercial milestones and royalties that we may receive under such partnership will depend on, among other things, the efforts, allocation of resources and successful development and commercialization of these protein therapeutic candidates by Celgene.

- Celgene may develop and commercialize, either alone or with others, products that are similar to or competitive with the protein therapeutic candidates that are the subject of its partnerships with us. For example, Celgene is currently commercializing and/or developing certain of its existing products, lenalidomide and azacitidine, for certain MDS patients for which sotatercept and ACE-536 are also being developed.

- Celgene may terminate its partnership with us without cause and for circumstances outside of our control, which could make it difficult for us to attract new strategic partners or adversely affect how we are perceived in scientific and financial communities.

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Celgene may develop or commercialize our protein therapeutic candidates in such a way as to elicit litigation that could jeopardize or invalidate our intellectual property rights or expose us to potential liability.

Celgene may not comply with all applicable regulatory requirements, or fail to report safety data in accordance with all applicable regulatory requirements.

If Celgene were to breach its arrangements with us, we may need to enforce our right to terminate the agreement in legal proceedings, which could be costly and cause delay in our ability to receive rights back to the relevant protein therapeutic candidates. If we were to terminate an agreement with Celgene due to Celgene's breach or Celgene terminated the agreement without cause, the development and commercialization of sotatercept and ACE-536 could be delayed, curtailed or terminated because we may not have sufficient financial resources or capabilities to continue development and commercialization of these candidates on our own.

Celgene may enter into one or more transactions with third parties, including a merger, consolidation, reorganization, sale of substantial assets, sale of substantial stock or other change in control, which could divert the attention of its management and adversely affect Celgene's ability to retain and motivate key personnel who are important to the continued development of the programs under the strategic partnership with us. In addition, the third-party to any such transaction could determine to reprioritize Celgene's development programs such that Celgene ceases to diligently pursue the development of our programs and/or cause the respective partnership with us to terminate.

We and Celgene rely on third parties to conduct preclinical studies and clinical trials for our protein therapeutic candidates, and if they do not properly and successfully perform their obligations to us, we may not be able to obtain regulatory approvals for our protein therapeutic candidates.

We design the clinical trials for dalantercept and will do so for any future unpartnered protein therapeutic candidates, and we will continue to work with Celgene on trials for sotatercept and ACE-536. However, we and Celgene rely on CROs and other third parties to assist in managing, monitoring and otherwise carrying out many of these trials. We and Celgene compete with many other companies for the resources of these third parties. The third parties on whom we and Celgene rely generally may terminate their engagements at any time, and having to enter into alternative arrangements would delay development and commercialization of our protein therapeutic candidates.

The FDA and foreign regulatory authorities require compliance with regulations and standards, including GCP, for designing, conducting, monitoring, recording, analyzing, and reporting the results of clinical trials to assure that the data and results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. Although we and Celgene rely on third parties to conduct many of our and their clinical trials, we and Celgene are responsible for ensuring that each of these clinical trials is conducted in accordance with its general investigational plan, protocol and other requirements.

If these third parties do not successfully carry out their duties under their agreements, if the quality or accuracy of the data they obtain is compromised due to their failure to adhere to clinical trial protocols or to regulatory requirements, or if they otherwise fail to comply with clinical trial protocols or meet expected deadlines, the clinical trials of our protein therapeutic candidates may not meet regulatory requirements. If clinical trials do not meet regulatory requirements or if these third parties need to be replaced, preclinical development activities or clinical trials may be extended, delayed, suspended or terminated. If any of these events occur, we or Celgene may not be able to obtain regulatory approval of our protein therapeutic candidates on a timely basis or at all.

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We and Celgene intend to rely on third-party manufacturers to make our protein therapeutics, and any failure by a third-party manufacturer may delay or impair our and Celgene's ability to complete clinical trials or commercialize our protein therapeutic candidates.

Manufacturing biologic drugs is complicated and is tightly regulated by the FDA, the European Medicines Agency, or EMA, and comparable regulatory authorities around the world. We currently manufacture drug substance for our preclinical studies, Phase 1 clinical trials and Phase 2 clinical trials of ACE-536 and dalantercept. For Phase 3 and commercial supply of our products that we have not partnered, we expect to use contract manufacturing organizations. Successfully transferring complicated manufacturing techniques to contract manufacturing organizations and scaling up these techniques for commercial quantities will be time consuming and we may not be able to achieve such transfer. Moreover, the market for contract manufacturing services for protein therapeutics is highly cyclical, with periods of relatively abundant capacity alternating with periods in which there is little available capacity. If any need we or Celgene have for contract manufacturing services increases during a period of industry-wide tight capacity, we or Celgene may not be able to access the required capacity on a timely basis or on commercially viable terms.

In addition, we contract with fill & finishing providers with the appropriate expertise, facilities and scale to meet our needs. Failure to maintain cGMP can result in a contractor receiving FDA sanctions, which can impact our and Celgene's contractors' ability to operate or lead to delays in our clinical development programs. We believe that our current fill & finish contractors are operating in accordance with cGMP, but we can give no assurance that FDA or other regulatory agencies will not conclude that a lack of compliance exists. In addition, any delay in contracting for fill & finish services, or failure of the contract manufacturer to perform the services as needed, may delay clinical trials, registration and launches. Any such issues may have a substantial negative effect on our business.

For our two lead products, sotatercept and ACE-536, we rely on our collaboration partner Celgene to produce, or contract for the production of, bulk drug substance and finished drug product for late stage clinical trials and for commercial supplies of any approved candidates. Any failure by Celgene or by third-parties with which Celgene contracts may delay or impair the ability to complete late stage clinical trials or commercialize either or both of sotatercept and ACE-536, if approved.

We produced drug substance for preclinical and Phase 1 and 2 clinical trials for sotatercept and ACE-536. Celgene is now responsible for manufacturing sotatercept and will be responsible for manufacturing ACE-536 for future late-stage clinical trials. Celgene generally does not perform the manufacture of the drug substance or drug product for either sotatercept or ACE-536 itself. Celgene has used and may continue to use contract manufacturers for the manufacture of drug substance and drug product for sotatercept and we have no expectation that Celgene plans to perform the manufacture of bulk drug substance or drug product for either sotatercept or ACE-536 in the future. However, Celgene would have the right to manufacture sotatercept or ACE-536, itself or through the use of contract manufacturers. We understand that they have entered into a manufacturing arrangement for Phase 2 supplies of sotatercept bulk drug substance with contract manufacturers with considerable biotherapeutics manufacturing experience, including manufacturing monoclonal antibodies through processes similar to those used for sotatercept. To date Celgene has not entered into an arrangement with a third party to manufacture supplies of sotatercept or ACE-536 for Phase 3 trials or commercial sales. If they are unable to contract at the appropriate time with a manufacturer willing and able to manufacture sufficient quantities of sotatercept and ACE-536 to meet Phase 3 and commercial demand, either for technical or business reasons, the development and commercialization of sotatercept and ACE-536 may be delayed.

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We may not be successful in establishing and maintaining additional strategic partnerships, which could adversely affect our ability to develop and commercialize products, negatively impacting our operating results.

In addition to our current collaborations with Celgene, a part of our strategy is to strategically evaluate and, as deemed appropriate, enter into additional partnerships in the future when strategically attractive, including potentially with major biotechnology or pharmaceutical companies. We face significant competition in seeking appropriate partners for our protein therapeutic candidates, and the negotiation process is time-consuming and complex. In order for us to successfully partner our protein therapeutic candidates, potential partners must view these protein therapeutic candidates as economically valuable in markets they determine to be attractive in light of the terms that we are seeking and other available products for licensing by other companies. Even if we are successful in our efforts to establish new strategic partnerships, the terms that we agree upon may not be favorable to us, and we may not be able to maintain such strategic partnerships if, for example, development or approval of a protein therapeutic is delayed or sales of an approved product are disappointing. Any delay in entering into new strategic partnership agreements related to our protein therapeutic candidates could delay the development and commercialization of our protein therapeutic candidates and reduce their competitiveness even if they reach the market.

If we fail to establish and maintain additional strategic partnerships related to our protein therapeutic candidates, we will bear all of the risk and costs related to the development of any such protein therapeutic candidate, and we may need to seek additional financing, hire additional employees and otherwise develop expertise for which we have not budgeted. This could negatively affect the development of any unpartnered protein therapeutic candidate.

Risks Related to Our Intellectual Property

If we are unable to obtain or protect intellectual property rights related to our protein therapeutic candidates, we may not be able to compete effectively.

We rely upon a combination of patents, trade secret protection and confidentiality agreements to protect the intellectual property related to our platform technology and protein therapeutic candidates. The patent position of biotechnology companies is generally uncertain because it involves complex legal and factual considerations. The standards applied by the United States Patent and Trademark Office, or USPTO, and foreign patent offices in granting patents are not always applied uniformly or predictably. For example, there is no uniform worldwide policy regarding patentable subject matter or the scope of claims allowable in biotechnology patents. The patent applications that we own or in-license may fail to result in issued patents with claims that cover our protein therapeutic candidates in the United States or in other countries. There is no assurance that all potentially relevant prior art relating to our patents and patent applications has been found. We may be unaware of prior art that could be used to invalidate an issued patent or prevent our pending patent applications from issuing as patents. Even if patents do successfully issue and even if such patents cover our protein therapeutic candidates, third parties may challenge their validity, enforceability or scope, which may result in such patents being narrowed or invalidated. Furthermore, even if they are unchallenged, our patents and patent applications may not adequately protect our intellectual property, provide exclusivity for our protein therapeutic candidates or prevent others from designing around our claims. Any of these outcomes could impair our ability to prevent competition from third parties, which may have an adverse impact on our business.

If patent applications we hold or have in-licensed with respect to our platform or protein therapeutic candidates fail to issue, if their breadth or strength of protection is threatened, or if they fail to provide meaningful exclusivity for our protein therapeutic candidates, it could dissuade companies from collaborating with us. Several patent applications covering our protein therapeutic candidates have been filed recently. We cannot offer any assurances about which, if any, patents will issue, the breadth of any such patents or whether any issued patents will be found invalid and unenforceable or will be threatened

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by third parties. Any successful challenge to these patents or any other patents owned by or licensed to us could deprive us of rights necessary for the successful commercialization of any protein therapeutic candidate that we or our partners may develop. Since patent applications in the United States and most other countries are confidential for a period of time after filing, and some remain so until issued, we cannot be certain that we were the first to file any patent application related to a protein therapeutic candidate. Furthermore, if third parties have filed such patent applications, an interference proceeding in the United States can be initiated by the USPTO or a third party to determine who was the first to invent any of the subject matter covered by the patent claims of our applications. In addition, patents have a limited lifespan. In the United States, the natural expiration of a patent is generally 20 years after it is filed. Various extensions may be available; however, the life of a patent and the protection it affords is limited. If we encounter delays in obtaining regulatory approvals, the period of time during which we could market a protein therapeutic under patent protection could be reduced. Even if patents covering our protein therapeutic candidates are obtained, once the patent life has expired for a product, we may be open to competition from biosimilar products.

Any loss of patent protection could have a material adverse impact on our business. We and our partner may be unable to prevent competitors from entering the market with a product that is similar to or the same as our protein therapeutics. In addition, the royalty we would receive under our collaboration agreements with Celgene for sotatercept and ACE-536 would be reduced by 50% if such product ceases to be covered by a valid claim of our patents even if no competitor with a similar product has entered the market.

Third-party claims of intellectual property infringement or misappropriation may prevent or delay our development and commercialization efforts.

Our commercial success depends in part on us and our partners not infringing the patents and proprietary rights of third parties. There is a substantial amount of litigation, both within and outside the United States, involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries, including patent infringement lawsuits, interferences, oppositions and inter partes reexamination proceedings before the USPTO and corresponding foreign patent offices. Numerous U.S. and foreign issued patents and pending patent applications owned by third parties exist in the fields in which we and our partners are developing and may develop our protein therapeutic candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our protein therapeutic candidates may be subject to claims of infringement of the patent rights of third parties.

Third parties may assert that we are employing their proprietary technology without authorization. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of our protein therapeutic candidates, that we failed to identify. For example, applications filed before November 29, 2000 and certain applications filed after that date that will not be filed outside the United States remain confidential until issued as patents. Except for the preceding exceptions, patent applications in the United States and elsewhere are generally published only after a waiting period of approximately 18 months after the earliest filing. Therefore, patent applications covering our platform technology or our protein therapeutic candidates could have been filed by others without our knowledge. Additionally, pending patent applications which have been published can, subject to certain limitations, be later amended in a manner that could cover our platform technologies, our protein therapeutic candidates or the use or manufacture of our protein therapeutic candidates.

If any third-party patents were held by a court of competent jurisdiction to cover aspects of our materials, formulations, methods of manufacture or methods for treatment, the holders of any such patents would be able to block our ability to develop and commercialize the applicable protein therapeutic candidate until such patent expired or unless we or our partners obtain a license. These

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licenses may not be available on acceptable terms, if at all. Even if we or our partners were able to obtain a license, the rights may be nonexclusive, which could result in our competitors gaining access to the same intellectual property. Ultimately, we or our partners could be prevented from commercializing a product, or be forced to cease some aspect of our business operations, if, as a result of actual or threatened patent infringement claims, we or our partners are unable to enter into licenses on acceptable terms. If Celgene is required to enter a license agreement with a third party in order to import, develop, manufacture or commercialize sotatercept or ACE-536, the royalty rate and sales milestone payments that we could receive may be reduced by up to 50%. This could harm our business significantly.

Parties making claims against us or our partners may obtain injunctive or other equitable relief, which could effectively block our or our partners' ability to further develop and commercialize one or more of our protein therapeutic candidates. Defending against claims of patent infringement or misappropriation of trade secrets could be costly and time consuming, regardless of the outcome. Thus, even if we were to ultimately prevail, or to settle at an early stage, such litigation could burden us with substantial unanticipated costs. In addition, litigation or threatened litigation could result in significant demands on the time and attention of our management team, distracting them from the pursuit of other company business. In the event of a successful claim of infringement against us or our partners, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, pay royalties, redesign our infringing products or obtain one or more licenses from third parties, which may be impossible or require substantial time and monetary expenditure.

We may face a claim of misappropriation if a third party believes that we inappropriately obtained and used trade secrets of such third party. If we are found to have misappropriated a third party's trade secrets, we may be prevented from further using such trade secrets, limiting our ability to develop our protein therapeutic candidates, and we may be required to pay damages.

During the course of any patent or other intellectual property litigation, there could be public announcements of the results of hearings, rulings on motions, and other interim proceedings in the litigation. If securities analysts or investors regard these announcements as negative, the perceived value of our protein therapeutics, programs, or intellectual property could be diminished. Accordingly, the market price of our common stock may decline.

We have in-licensed a portion of our intellectual property, and, if we fail to comply with our obligations under these arrangements, we could lose such intellectual property rights or owe damages to the licensor of such intellectual property.

We are a party to a number of license agreements that are important to our business, and we may enter into additional license agreements in the future. Our discovery and development platform is built, in part, around patents exclusively in-licensed from academic or research institutions. Certain of our in-licensed intellectual property also covers sotatercept and dalantercept. See "Business Intellectual Property In-Licenses" for a description of our license agreements with the Beth Israel Deaconess Medical Center, the Ludwig Institute for Cancer Research and the Salk Institute for Biological Studies.

Our existing license agreements impose, and we expect that future license agreements will impose, various diligence, milestone payment, royalty and other obligations on us. If there is any conflict, dispute, disagreement or issue of non-performance between us and our licensing partners regarding our rights or obligations under the license agreements, including any such conflict, dispute or disagreement arising from our failure to satisfy payment obligations under any such agreement, we may owe damages, our licensor may have a right to terminate the affected license, and our and our partners' ability to utilize the affected intellectual property in our drug discovery and development efforts, and our ability to enter into collaboration or marketing agreements for an affected protein therapeutic candidate, may be adversely affected.

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For example, the Salk Institute for Biological Studies recently filed a lawsuit against us alleging under one of our license agreements with them, which pertains to ActRIIB, its entitlement to a further share of certain payments received by us under our now-terminated agreement with Shire AG and a share of certain payments received by us under our on-going collaboration agreement with Celgene in connection with ACE-536. Although we and Salk have agreed that ACE-536 is not covered by any patent rights licensed from Salk, an unfavorable outcome in this litigation may lead to us owing significant damages to Salk and higher-than-anticipated future payments under this license in connection with development milestone payments that we may receive from Celgene. It is possible that Salk may seek to terminate the license covering the receptor. We do not believe that such a termination would have a material impact on our business or the development of any of our products. The patents under this license covered only one of our protein therapeutic candidates, ACE-031, the development of which has been discontinued. See "Business Legal Proceedings" for a description of this proceeding.

Confidentiality agreements with employees and third parties may not prevent unauthorized disclosure of trade secrets and other proprietary information.

In addition to the protection afforded by patents, we rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable or that we elect not to patent, processes for which patents are difficult to enforce and any other elements of our platform technology and discovery and development processes that involve proprietary know-how, information or technology that is not covered by patents. However, trade secrets can be difficult to protect. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, and outside scientific advisors, contractors and collaborators. Although we use reasonable efforts to protect our trade secrets, our employees, consultants, contractors, or outside scientific advisors might intentionally or inadvertently disclose our trade secret information to competitors. In addition, competitors may otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques.

Enforcing a claim that a third party illegally obtained and is using any of our trade secrets is expensive and time consuming, and the outcome is unpredictable. In addition, courts outside the United States sometimes are less willing than U.S. courts to protect trade secrets. Misappropriation or unauthorized disclosure of our trade secrets could impair our competitive position and may have a material adverse effect on our business

Risks Related to Commercialization of Our Protein Therapeutic Candidates

Our future commercial success depends upon attaining significant market acceptance of our protein therapeutic candidates, if approved, among physicians, patients, health care payers and, in cancer markets, acceptance by the operators of major cancer clinics.

Even if we or our partners obtain regulatory approval for sotatercept, ACE-536, dalantercept or any other protein therapeutics that we may develop or acquire in the future, the product may not gain market acceptance among physicians, health care payors, patients and the medical community. Market acceptance of any approved products depends on a number of factors, including:

- the efficacy and safety of the product, as demonstrated in clinical trials;
- the clinical indications for which the product is approved and the label approved by regulatory authorities for use with the product, including any warnings that may be required on the label;
- acceptance by physicians and patients of the product as a safe and effective treatment;
- the cost, safety and efficacy of treatment in relation to alternative treatments;
- the availability of adequate reimbursement and pricing by third party payers and government authorities;
- the continued projected growth of drug markets in our various indications;

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relative convenience and ease of administration;

the prevalence and severity of adverse side effects; and

the effectiveness of our, and our partners' sales and marketing efforts.

Market acceptance is critical to our ability to generate significant revenue. Any protein therapeutic candidate, if approved and commercialized, may be accepted in only limited capacities or not at all. If any approved products are not accepted by the market to the extent that we expect, we may not be able to generate significant revenue and our business would suffer.

Reimbursement may be limited or unavailable in certain market segments for our protein therapeutic candidates, which could make it difficult for us to sell our products profitably.

Market acceptance and sales of any approved protein therapeutics will depend significantly on the availability of adequate coverage and reimbursement from third-party payers and may be affected by existing and future health care reform measures. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which drugs they will pay for and establish reimbursement levels. Reimbursement by a third-party payer may depend upon a number of factors, including the third-party payor's determination that use of a product is:

a covered benefit under its health plan;

safe, effective and medically necessary;

appropriate for the specific patient;

cost-effective; and

neither experimental nor investigational.

Obtaining coverage and reimbursement approval for a product from a government or other third party payer is a time consuming and costly process that could require us to provide supporting scientific, clinical and cost-effectiveness data for the use of our products to the payer. We or our partners may not be able to provide data sufficient to gain acceptance with respect to coverage and reimbursement. We cannot be sure that coverage or adequate reimbursement will be available for any of our protein therapeutic candidates. Also, we cannot be sure that reimbursement amounts will not reduce the demand for, or the price of, our products. If reimbursement is not available or is available only to limited levels, we may not be able to commercialize certain of our products. In addition in the United States, third-party payers are increasingly attempting to contain health care costs by limiting both coverage and the level of reimbursement of new drugs. As a result, significant uncertainty exists as to whether and how much third-party payers will reimburse patients for their use of newly approved drugs, which in turn will put pressure on the pricing of drugs.

Price controls may be imposed in foreign markets, which may adversely affect our future profitability.

In some countries, particularly member states of the European Union, the pricing of prescription drugs is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after receipt of marketing approval for a product. In addition, there can be considerable pressure by governments and other stakeholders on prices and reimbursement levels, including as part of cost containment measures. Political, economic and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various European Union member states and parallel distribution, or arbitrage between low-priced and high-priced member states, can further reduce prices. In some countries, we or our partners may be required to conduct a clinical trial or other studies that compare the cost-effectiveness of our protein therapeutic candidates

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to other available therapies in order to obtain or maintain reimbursement or pricing approval. Publication of discounts by third-party payers or authorities may lead to further pressure on the prices or reimbursement levels within the country of publication and other countries. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be adversely affected.

The impact of recent healthcare reform legislation and other changes in the healthcare industry and in healthcare spending on us is currently unknown, and may adversely affect our business model.

Our revenue prospects could be affected by changes in healthcare spending and policy in the United States and abroad. We operate in a highly regulated industry and new laws, regulations or judicial decisions, or new interpretations of existing laws, regulations or decisions, related to health care availability, the method of delivery or payment for health care products and services could negatively impact our business, operations and financial condition. There is significant interest in promoting health care reform, as evidenced by the enactment in the United States of the Patient Protection and Affordable Care Act and the Health Care and Education Reconciliation Act in 2010. It is likely that federal and state legislatures within the United States and foreign governments will continue to consider changes to existing health care legislation. We cannot predict the reform initiatives that may be adopted in the future or whether initiatives that have been adopted will be repealed or modified. The continuing efforts of the government, insurance companies, managed care organizations and other payers of healthcare services to contain or reduce costs of healthcare may adversely affect:

- the demand for any drug products for which we may obtain regulatory approval;
- our ability to set a price that we believe is fair for our products;
- our ability to obtain coverage and reimbursement approval for a product;
- our ability to generate revenues and achieve or maintain profitability; and
- the level of taxes that we are required to pay.

We face substantial competition, which may result in others discovering, developing or commercializing products before, or more successfully, than we do.

Our future success depends on our or our partners' ability to demonstrate and maintain a competitive advantage with respect to the design, development and commercialization of our protein therapeutic candidates. Our objective is to design, develop and commercialize new products with superior efficacy, convenience, tolerability and safety. In many cases, the protein therapeutics that we commercialize with our strategic partners or on our own will compete with existing, market-leading products.

There are products currently approved to treat patients with MDS, including iron chelation therapy, immunomodulators and various chemotherapeutic agents. In addition, erythropoiesis stimulating agents and red blood cell transfusions are extensively used to treat anemia in MDS. ACE-536 or sotatercept, if approved, will compete with these therapies. In addition, one or more products not currently approved for the treatment of anemia in MDS may in the future be granted marketing approval for the treatment of anemia in MDS or other conditions for which ACE-536 or sotatercept might be approved, including Aranesp®, being developed by Amgen, which is in Phase 3 trials. While there are currently no drug products approved for the treatment of anemia in β-thalassemia, red blood cell transfusions are extensively used and sotatercept or ACE-536, if approved, would compete with this therapy. In addition, HQK-1001, a fetal hemoglobin stimulating agent being developed by HemaQuest Pharmaceuticals, has completed a Phase 1/2 clinical trial and an investigator sponsored Phase 2 clinical trial in patients with β-thalassemia. Further, the future approval, in one or

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more regions, of a biosimilar product to one of our products could create substantial competition and have a material impact on our business.

Sotatercept or ACE-536, if approved for the treatment of chemotherapy-induced anemia or anemia of chronic kidney disease, would compete with erythropoiesis-stimulating agents, such as Epogen® and Aranesp®, marketed by Amgen, and Procrit®, marketed by Johnson & Johnson, that are currently approved for the treatment of chemotherapy-induced anemia or anemia of chronic kidney disease and other therapies in development including oral, small molecule treatments being developed by Astellas Pharma and Fibrogen designed to increase the body's production of erythropoietin.

While we anticipate that dalantercept, if approved for the treatment of cancer, would likely be approved in combination with certain VEGF pathway inhibitors that are currently approved for the treatment of various cancer types, dalantercept would compete with other products, including other angiogenesis inhibitors, approved for the treatment of these cancers.

Many of our potential competitors have significantly greater financial, manufacturing, marketing, drug development, technical and human resources than we do. Large pharmaceutical companies, in particular, have extensive experience in clinical testing, obtaining regulatory approvals, recruiting patients and in manufacturing pharmaceutical products. These companies also have significantly greater research and marketing capabilities than we do and may also have products that have been approved or are in late stages of development, and have collaborative arrangements in our target markets with leading companies and research institutions. Established pharmaceutical companies may also invest heavily to accelerate discovery and development of novel compounds or to in-license novel compounds that could make the protein therapeutics that we develop obsolete. As a result of all of these factors, our competitors may succeed in obtaining patent protection and/or FDA approval or discovering, developing and commercializing protein therapeutics before we do. In addition, any new product that competes with an approved product must demonstrate compelling advantages in efficacy, convenience, tolerability and safety in order to overcome price competition and to be commercially successful. If we are not able to compete effectively against potential competitors, our business will not grow and our financial condition and operations will suffer.

Our protein therapeutics may cause undesirable side effects or have other properties that delay or prevent their regulatory approval or limit their commercial potential.

Undesirable side effects caused by our protein therapeutics could cause us, Celgene or regulatory authorities to interrupt, delay or halt clinical trials and could result in the denial of regulatory approval by the FDA or other regulatory authorities and potential products liability claims. We and Celgene are currently conducting a number of Phase 2 trials for our clinical stage protein therapeutic candidates. Serious adverse events deemed to be caused by our protein therapeutics could have a material adverse effect on the development of our protein therapeutic candidates and our business as a whole. The most common adverse event to date in the clinical trials evaluating the safety and efficacy of our protein therapeutic candidates has been hypertension in our clinical trials for sotatercept and fluid retention in our clinical trials for dalantercept. Our understanding of the relationship between our protein therapeutic candidates and these events may change as we gather more information, and additional unexpected adverse events may occur. There can be no assurance that additional adverse events associated with our protein therapeutic candidates will not be observed. Recently, we discontinued the development of ACE-031, another of our clinical stage protein therapeutics that binds to ligands of the TGF-β superfamily. Clinical development of ACE-031 was put on clinical hold in 2011 due to preliminary safety observations in patients. After gathering further information from animal toxicology studies, we and our ACE-031 partner, Shire AG, determined that the risk-benefit profile of ACE-031 was not appropriate for the intended patient population, boys aged four and older with a genetic muscle wasting disease, and we discontinued development of this protein therapeutic candidate. As is typical in drug development, we have a program of ongoing toxicology studies in animals for our other clinical stage protein therapeutics and cannot provide assurance that the findings from such studies or any ongoing or future clinical trials will not adversely affect our clinical development activities.

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If we or others identify undesirable side effects caused by our protein therapeutic candidates either before or after receipt of marketing approval, a number of potentially significant negative consequences could result, including:

- our clinical trials may be put on hold;
- we or our partners may be unable to obtain regulatory approval for our protein therapeutic candidates;
- regulatory authorities may withdraw approvals of our protein therapeutic candidates;
- regulatory authorities may require additional warnings on the label;
- a medication guide outlining the risks of such side effects for distribution to patients may be required;
- 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 our protein therapeutics and could substantially increase commercialization costs.

Risks Related to Our Business and Industry

If we fail to attract and keep senior management and key scientific personnel, we may be unable to successfully develop our protein therapeutics, conduct our clinical trials and commercialize our protein therapeutic candidates.

We are highly dependent on members of our senior management, including John L. Knopf, Ph.D., our Chief Executive Officer and President and one of our founders. The loss of the services of any of these persons could impede the achievement of our research, development and commercialization objectives. We do not maintain "key person" insurance for any of our executives or other employees.

Recruiting and retaining qualified scientific, clinical, manufacturing, sales and marketing personnel will also be critical to our success. We may not be able to attract and retain these personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors, including our scientific co-founders, may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us.

Our employees may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements and insider trading.

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with FDA regulations, to provide accurate information to the FDA, to comply with manufacturing standards we have established, to comply with federal and state healthcare fraud and abuse laws and regulations, to report financial information or data accurately or to disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Employee misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and

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serious harm to our reputation. It is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions.

We may encounter difficulties in managing our growth and expanding our operations successfully.

As we seek to advance our protein therapeutic candidates through clinical trials and commercialization, we will need to expand our development, regulatory, manufacturing, marketing and sales capabilities or contract with third parties to provide these capabilities for us. As our operations expand, we expect that we will need to manage additional relationships with various strategic partners, suppliers and other third parties. Future growth will impose significant added responsibilities on members of management. Our future financial performance and our ability to commercialize our protein therapeutic candidates and to compete effectively will depend, in part, on our ability to manage any future growth effectively. To that end, we must be able to manage our development efforts and clinical trials effectively and hire, train and integrate additional management, administrative and, if necessary, sales and marketing personnel. We may not be able to accomplish these tasks, and our failure to accomplish any of them could prevent us from successfully growing our company.

If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of our protein therapeutics.

We face an inherent risk of product liability as a result of the clinical testing of our protein therapeutic candidates and will face an even greater risk if we commercialize any products. For example, we may be sued if any product we develop allegedly causes injury or is found to be otherwise unsuitable during product testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability, and a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our protein therapeutic candidates. Even a successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in:

injury to our reputation;

withdrawal of clinical trial participants;

costs to defend the related litigations;

a diversion of management's time and our resources;

substantial monetary awards to trial participants or patients;

product recalls, withdrawals, or labeling, marketing or promotional restrictions;

loss of revenue;

the inability to commercialize our protein therapeutic candidates; and

a decline in our stock price.

Failure to obtain and retain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims could prevent or inhibit the commercialization of products we develop. We currently carry product liability insurance covering our clinical trials in the amount of

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$10 million in the aggregate. Although we maintain such insurance, any claim that may be brought against us could result in a court judgment or settlement in an amount that is not covered, in whole or in part, by our insurance or that is in excess of the limits of our insurance coverage. Our insurance policies also have various exclusions, and we may be subject to a product liability claim for which we have no coverage. We will have to pay any amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts.

We must comply with environmental laws and regulations, and failure to comply with these laws and regulations could expose us to significant liabilities.

We use hazardous chemicals and radioactive and biological materials in certain aspects of our business and are subject to a variety of federal, state and local laws and regulations governing the use, generation, manufacture, distribution, storage, handling, treatment and disposal of these materials. Although we believe our safety procedures for handling and disposing of these materials and waste products comply with these laws and regulations, we cannot eliminate the risk of accidental injury or contamination from the use, manufacture, distribution, storage, handling, treatment or disposal of hazardous materials. In the event of contamination or injury, or failure to comply with environmental, occupational health and safety and export control laws and regulations, we could be held liable for any resulting damages and any such liability could exceed our assets and resources. We are uninsured for third-party contamination injury.

Risks Related to Our Common Stock and This Offering

We are eligible to be treated as an "emerging growth company" as defined in the Jumpstart Our Business Startups Act of 2012, and we cannot be certain if the reduced disclosure requirements applicable to emerging growth companies will make our common stock less attractive to investors.

We are an "emerging growth company", as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. For as long as we continue to be an emerging growth company, we may take advantage of exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies, including (1) not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, which we refer to as the Sarbanes-Oxley Act, (2) reduced disclosure obligations regarding executive compensation in this prospectus and our periodic reports and proxy statements and (3) exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved. In addition, as an emerging growth company, we are only required to provide two years of audited financial statements and two years of selected financial data in this prospectus. We could be an emerging growth company for up to five years, although circumstances could cause us to lose that status earlier, including if the market value of our common stock held by non-affiliates exceeds $700.0 million as of any June 30 before that time or if we have total annual gross revenue of $1.0 billion or more during any fiscal year before that time, in which cases we would no longer be an emerging growth company as of the following December 31 or, if we issue more than $1.0 billion in non-convertible debt during any three-year period before that time, we would cease to be an emerging growth company immediately. We cannot predict if investors will find our common stock less attractive because we may rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

Under the JOBS Act, emerging growth companies can also delay adopting new or revised accounting standards until such time as those standards apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

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Our stock price could be highly volatile, and, as a result you may not be able to resell your shares at or above the public offering price.

Since our initial public offering in September 2013, the price of our common stock as reported on The NASDAQ Global Market has ranged from a low of $16.78 on November 6 and 8, 2013 to a high of $43.70 on January 7, 2014. The market price of shares of our common stock could be subject to wide fluctuations in response to many risk factors listed in this section, and others beyond our control, including:

- results of clinical trials of our protein therapeutic candidates, including sotatercept, ACE-536 and dalantercept;
- the timing of the release of results of our clinical trials that are being conducted by Celgene;
- results of clinical trials of our competitors' products;
- regulatory actions with respect to our products or our competitors' products;
- actual or anticipated fluctuations in our financial condition and operating results;
- publication of research reports by securities analysts about us or our competitors or our industry;
- our failure or the failure of our competitors to meet analysts' projections or guidance that we or our competitors may give to the market;
- additions and departures of key personnel;
- strategic decisions by us or our competitors, such as acquisitions, divestitures, spin-offs, joint ventures, strategic investments or changes in business strategy;
- the passage of legislation or other regulatory developments affecting us or our industry;
- fluctuations in the valuation of companies perceived by investors to be comparable to us;
- sales of our common stock by us, our insiders or our other stockholders;
- speculation in the press or investment community;
- announcement or expectation of additional financing efforts;
- changes in accounting principles;
- terrorist acts, acts of war or periods of widespread civil unrest;

natural disasters and other calamities;

changes in market conditions for biopharmaceutical stocks; and

changes in general market and economic conditions.

In addition, the stock market has recently experienced significant volatility, particularly with respect to pharmaceutical, biotechnology and other life sciences company stocks. The volatility of pharmaceutical, biotechnology and other life sciences company stocks often does not relate to the operating performance of the companies represented by the stock. As we operate in a single industry, we are especially vulnerable to these factors to the extent that they affect our industry or our products, or to a lesser extent our markets. In the past, securities class action litigation has often been initiated against companies following periods of volatility in their stock price. This type of litigation could result in substantial costs and divert our management's attention and resources, and could also require us to make substantial payments to satisfy judgments or to settle litigation.

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Our principal stockholders and management own a significant percentage of our stock and will be able to exercise significant influence over matters subject to stockholder approval.

As of January 1, 2014, our executive officers, directors and principal stockholders, together with their respective affiliates, beneficially owned approximately 43.7% of our common stock, including shares subject to outstanding options and warrants that are exercisable within 60 days after such date, and we expect that upon completion of this offering, that same group will continue to beneficially hold at least % of our outstanding common stock. Accordingly, even after this offering, these stockholders will be able to exert a significant degree of influence over our management and affairs and over matters requiring stockholder approval, including the election of our board of directors and approval of significant corporate transactions. This concentration of ownership could have the effect of entrenching our management and/or the board of directors, delaying or preventing a change in our control or otherwise discouraging a potential acquirer from attempting to obtain control of us, which in turn could have a material and adverse effect on the fair market value of our common stock.

A significant portion of our total outstanding shares may be sold into the public market in the near future, which could cause the market price of our common stock to drop significantly, even if our business is doing well.

Sales of a substantial number of shares of our common stock in the public market, or the market perception that the holders of a large number of shares intend to sell shares, could reduce the market price of our common stock. As of January 1, 2014, based on the number of shares of our common stock then outstanding, assuming (1) the closing of this offering, (2) no exercise of the underwriters' option to purchase additional shares of common stock, and (3) no exercise of outstanding options or warrants, we would have had outstanding an aggregate of approximately shares of common stock. Of these shares, 7,482,723 shares of common stock, including the 6,417,000 shares sold in our initial public offering, and all of the shares of common stock to be sold in this offering, will be freely tradable in the public market without restriction or further registration under the Securities Act of 1933, as amended, or the Securities Act, unless the shares are held by any of our "affiliates" as such term is defined in Rule 144 of the Securities Act. The remaining shares of common stock are "restricted securities" as such term is defined in Rule 144 or are subject to lock up agreements in effect in connection with the initial public offering or entered into in connection with this offering and will be available for sale in the public market are as follows:

Number of Shares and % of Total Outstanding	Date Available for Sale into Public Market
5,896,337 shares, or 21%	March 17, 2014 due to lock up agreements in effect in connection with our initial public offering. However, the representatives of the underwriters can waive the provisions of these lock-up agreements and allow these stockholders to sell their shares at any time.
14,969,573 shares, or 53%	90 days after the date of this prospectus, due to lock-up agreements between the holders of these shares and the underwriters. However, the representatives of the underwriters can waive the provisions of these lock-up agreements and allow these stockholders to sell their shares at any time.

In addition, as of January 1, 2014, there were 979,699 shares subject to outstanding warrants, 3,942,304 shares subject to outstanding options and an additional 2,089,945 shares reserved for future issuance under our employee benefit plans that will become eligible for sale in the public market to the extent permitted by any applicable vesting requirements, the lock-up agreements and Rules 144 and 701 under the Securities Act of 1933, as amended. Moreover, after this offering, holders of an aggregate of approximately 14.8 million shares of our common stock and holders of warrants to purchase 540,097

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shares of our common stock will have rights, subject to some conditions, to require us to file registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders. If such holders, by exercising their registration rights, cause a large number of securities to be registered and sold into the public market, these sales could have an adverse effect on the market price for our common stock. These rights have been waived in connection with this offering pursuant to the terms of the registration rights agreement. We have also registered all shares of common stock that we may issue under our 2013 Equity Incentive Plan, and intend to register annual increases pursuant to this plan on a post effective amendment to the registration statement. Once these shares are issued in accordance with the terms of the plans, they can be freely sold in the public market upon issuance, subject to the lock-up agreements and the restrictions imposed on our affiliates under Rule 144. For more information, see "Shares Eligible for Future Sale Rule 144".