ACCELERON PHARMA INC
Form 424B5
January 04, 2016

Use these links to rapidly review the document
TABLE OF CONTENTS
TABLE OF CONTENTS

Table of Contents

Subject to completion, dated January 4, 2016

The information in this preliminary prospectus supplement is not complete and may be changed. A registration statement relating to our common stock has become effective under the Securities Act of 1933, as amended. This preliminary prospectus supplement and the accompanying prospectus are not an offer to sell these securities, and we are not soliciting an offer to buy these securities in any jurisdiction where the offer or sale is not permitted.

Filed Pursuant to Rule 424(b)(5)
Registration No. 333-208845

PRELIMINARY PROSPECTUS SUPPLEMENT
(To prospectus dated January 4, 2016)

$150,000,000

Acceleron Pharma Inc.

COMMON STOCK

We are offering shares of our common stock with an aggregate public offering price of approximately $150,000,000.

Our common stock trades on the Nasdaq Global Market under the symbol "XLRN". On December 31, 2015, the last reported sale price of our common stock was $48.76 per share.

Our collaboration partner and one of our principal stockholders, Celgene, has indicated to us an intent to purchase our common stock in this offering at the public offering price, as described under "Underwriting" beginning on page S-43 of this prospectus supplement, in an amount that will result in Celgene increasing its holding to no more than 15% of our total outstanding common stock subsequent to the offering. However, because indications of interest are not binding agreements or commitments to purchase, the underwriters could determine to sell more, less or no shares to this stockholder, and this stockholder could determine to purchase more, less or no shares in this offering.

Investing in our common stock involves risks. See "Risk Factors" beginning on page S-8 of this prospectus supplement, the accompanying prospectus and the other documents that are incorporated by reference herein.

	Per Share	***Total***
Public offering price	*$*	*$*

Underwriting discounts and commissions[(1)]	*$*	*$*
Proceeds, before expenses, to us	*$*	*$*

(1) *We have agreed to reimburse the underwriters for certain expenses incurred in connection with this offering. See "Underwriting."*

The underwriters also have the right to purchase up to an additional $22,500,000 in shares of common stock from us at the public offering price, less the underwriting discounts and commissions, at their option, within 30 days of the date of this prospectus supplement. If the underwriters exercise their option to purchase additional shares in full, the total underwriting discounts and commissions payable by us will be $10,350,000 and the total proceeds, before expenses, to us will be $162,150,000.

You should carefully read this prospectus supplement and the accompanying prospectus, together with the documents we incorporated by reference, before you invest in our stock.

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

The shares of common stock will be ready for delivery on or about January , 2016.

MORGAN STANLEY *LEERINK PARTNERS* *UBS INVESTMENT BANK*

JMP SECURITIES

The date of this prospectus supplement is January , 2016.

Table of Contents

TABLE OF CONTENTS

Prospectus Supplement

Presentation of Information	S-ii
Note Regarding Forward Looking Statements	S-iii
Incorporation of Certain Information by Reference	S-iv
Where You Can Find More Information	S-v
Summary	S-1
Risk Factors	S-8
Use of Proceeds	S-34
Price Range of Our Common Stock	S-35
Dividend Policy	S-36
Capitalization	S-37
Dilution	S-38
Material United States Federal Income Tax Considerations for Non-U.S. Holders	S-39
Underwriting	S-43
Legal Matters	S-47
Experts	S-47

Prospectus

About This Prospectus	1
Our Business	2
Risk Factors	3
Cautionary Note Regarding Forward-Looking Statements	3
Use of Proceeds	5
Plan of Distribution	6
Where You Can Find More Information	7
Incorporation of Certain Documents by Reference	7

Legal Matters 8

Experts 8

Table of Contents

PRESENTATION OF INFORMATION

These offering materials consist of two documents: (1) this prospectus supplement, which describes the terms of the common stock that we are currently offering, and (2) the accompanying prospectus, which provides general information about us. The information in this prospectus supplement supersedes any inconsistent information included or incorporated by reference in the accompanying prospectus.

You should rely only on the information contained or incorporated by reference in this prospectus supplement and the accompanying prospectus and any relevant free writing prospectus. Neither we nor the underwriters have authorized anyone to provide you with information different from that contained in this prospectus supplement and the accompanying prospectus and any relevant free writing prospectus. If you receive any information not authorized by us or the underwriters, you should not rely on it. You should not assume that the information contained or incorporated by reference in this prospectus supplement or the accompanying prospectus or any relevant free writing prospectus is accurate as of any date other than its respective date.

We and the underwriters are offering to sell, and seeking offers to buy, shares of our common stock only in jurisdictions where offers and sales are permitted. The distribution of this prospectus supplement, the accompanying prospectus or any free writing prospectus and the offering of the common stock in certain jurisdictions may be restricted by law. Persons outside the United States who come into possession of this prospectus supplement, the accompanying prospectus or any free writing prospectus must inform themselves about, and observe any restrictions relating to, the offering of the common stock and the distribution of this prospectus supplement, the accompanying prospectus and any free writing prospectus outside the United States. This prospectus supplement, the accompanying prospectus and any free writing prospectus do not constitute, and may not be used in connection with, an offer to sell, or a solicitation of an offer to buy, any securities offered by this prospectus supplement, the accompanying prospectus or any free writing prospectus by any person in any jurisdiction in which it is unlawful for such person to make such an offer or solicitation.

It is important for you to read and consider all of the information contained in this prospectus supplement, the accompanying prospectus and the documents incorporated by reference in these documents in making your investment decision. We include cross-references in this prospectus supplement and the accompanying prospectus to captions in these materials where you can find additional related discussions. The table of contents in this prospectus supplement provides the pages on which these captions are located.

Unless the context otherwise requires, "Acceleron", the "Company", "we", "us", "our" and similar names refer to Acceleron Pharma Inc. and its wholly-owned subsidiary. When we refer to "you" we mean the holders of common stock offered hereby.

Table of Contents

NOTE REGARDING FORWARD LOOKING STATEMENTS

This prospectus supplement contains various "forward-looking statements" within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act, which represent our expectations or beliefs concerning future events. Words such as "anticipate", "believe", "contemplate", "continue", "could", "estimate", "expect", "forecast", "goal", "intend", "may", "plan", "potential", "predict", "project", "should", "strategy", "target", "will", "would", "vision", or, in each case, the negative or other variations thereon or other similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

The forward-looking statements in this prospectus supplement include, among other things, statements regarding our intentions, beliefs, projections, outlook, analyses or current expectations concerning, among other things:

- our ongoing and planned preclinical studies and clinical trials;
- clinical trial data and the timing of results of our ongoing clinical trials;
- our plans to develop and commercialize dalantercept and ACE-083, and our and Celgene's plans to develop and commercialize luspatercept and sotatercept;
- the timing of, and our and Celgene's ability to, obtain and maintain regulatory approvals for our therapeutic candidates;
- our commercialization, marketing and manufacturing capabilities and strategy; and
- our estimates regarding our results of operations, financial condition, liquidity, capital requirements, prospects, growth and strategies.

By their nature, forward-looking statements involve risks and uncertainties because they relate to events, competitive dynamics, and industry change and depend on the economic circumstances that may or may not occur in the future or may occur on longer or shorter timelines than anticipated. We caution you that forward-looking statements are not guarantees of future performance and that our actual results of operations, financial condition and liquidity, and events in the industry in which we operate may differ materially from the forward-looking statements contained herein.

Any forward-looking statements that we make in this prospectus supplement speak only as of the date of such statement. You should read carefully the risk factors described in the section "Risk Factors" beginning on page S-8 of this prospectus supplement to better understand the risks and uncertainties inherent in our business and underlying any forward-looking statements.

Table of Contents

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

We incorporate by reference in this prospectus supplement and the accompanying prospectus the documents listed below and any future filings we make with the Securities and Exchange Commission, or the SEC, under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act (in each case, other than those documents or the portions of those documents not deemed to be filed) until we have sold all of the securities to which this prospectus supplement relates. Any statement in a document incorporated by reference is an important part of this prospectus supplement and the accompanying prospectus. Any statement in a document incorporated by reference in this prospectus supplement and the accompanying prospectus will be deemed to be modified or superseded to the extent a statement contained in this prospectus supplement, the accompanying prospectus or any subsequently filed document that is incorporated by reference in this prospectus supplement and the accompanying prospectus modifies or supersedes such statement.

We incorporate by reference in this prospectus only the documents set forth below that have been previously filed with the SEC:

Our Annual Report on Form 10-K for the year ended December 31, 2014, filed March 2, 2015;

Our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2015, June 30, 2015 and September 30, 2015, filed with the SEC on May 7, 2015, August 6, 2015 and November 4, 2015, respectively;

Our Definitive Proxy Statement on Schedule 14A, filed with the SEC on April 17, 2015;

Our Current Reports on Form 8-K filed with the SEC on March 6, 2015, May 5, 2015 (as amended on May 6, 2015), June 9, 2015, June 15, 2015, September 11, 2015, October 23, 2015, December 10, 2015 and December 17, 2015; and

The description of our common stock contained in our Registration Statement on Form 8-A, filed September 9, 2013, including any amendments or reports filed for the purpose of updating such description.

We will provide without charge to each person to whom a copy of this prospectus supplement is delivered, upon the written or oral request of such person, a copy of any or all of the documents incorporated by reference (other than exhibits to those documents, unless the exhibits are specifically incorporated by reference into those documents). Requests should be directed to:

Acceleron Pharma Inc.
128 Sidney Street
Cambridge, Massachusetts 02139
(617) 649-9200

Copies of these filings are also available, without charge, through the "Investors & Media" section of our website (www.acceleronpharma.com) as soon as reasonably practicable after they are filed electronically with the SEC. The information contained on our website is not a part of this prospectus.

Table of Contents

WHERE YOU CAN FIND MORE INFORMATION

We file annual and quarterly reports, current reports, proxy statements, and other information with the SEC. We make these documents publicly available, free of charge, on our website at www.acceleronpharma.com as soon as reasonably practicable after filing such documents with the SEC.

You may read and copy any materials that we file with the SEC at its Public Reference Room, 100 F Street, N.E., Washington, D.C. 20549. You may obtain information on the operation of the Public Reference Room by calling the SEC at (800) 732-0330. Our filings are also available to the public from the website maintained by the SEC at http://www.sec.gov.

We have filed a Registration Statement on Form S-3 under the Securities Act with the SEC with respect to the securities being offered pursuant to this prospectus supplement. This prospectus supplement and the accompanying prospectus omit certain information contained in the Registration Statement on Form S-3, as permitted by the SEC. Refer to the Registration Statement on Form S-3, including the exhibits, for further information about us and the securities being offered pursuant to this prospectus supplement. Statements in this prospectus supplement and the accompanying prospectus regarding the provisions of documents filed with, or incorporated by reference in, the registration statement are not necessarily complete and each statement is qualified in all respects by that reference. Copies of all or any part of the registration statement, including the documents incorporated by reference or the exhibits, may be obtained upon payment of the prescribed rates at the offices of the SEC listed above and through the SEC's website.

Table of Contents

SUMMARY

This summary highlights selected information included or incorporated by reference in this prospectus supplement and the accompanying prospectus and does not contain all of the information that may be important to you. You should carefully review this entire prospectus supplement and the accompanying prospectus, including the risk factors and financial statements included and incorporated by reference in this prospectus supplement and the accompanying prospectus.

Our Business

Overview

We are a clinical stage biopharmaceutical company focused on the discovery, development and commercialization of novel therapeutic candidates that are based on the mechanisms that the human body uses to regulate the growth and repair of its cells and tissues. Our research focuses on key natural regulators of cellular growth and repair, particularly the Transforming Growth Factor-Beta, or TGF-ß protein superfamily. We believe that we are a leading company in discovering and developing therapeutic candidates that regulate cellular growth and repair. By combining our discovery and development expertise, including our proprietary knowledge of the TGF-ß superfamily, and our internal protein engineering and manufacturing capabilities, we have built a highly productive discovery and development platform that has generated innovative therapeutic candidates with novel mechanisms of action. These differentiated therapeutic candidates have the potential to significantly improve clinical outcomes for patients across many fields of medicine, and we have focused our discovery and development efforts on treatments for cancer and rare diseases.

We have four internally discovered therapeutic candidates that are currently in clinical trials. Luspatercept, our lead program, and sotatercept, are partnered with Celgene Corporation, or Celgene. Celgene is conducting the Phase 3 clinical trials for luspatercept and is responsible for paying 100% of the development costs for all other clinical trials for luspatercept and sotatercept, including our ongoing earlier stage clinical trials for these therapeutic candidates. We may receive up to an additional $560 million of potential development, regulatory and commercial milestone payments and, if these therapeutic candidates are commercialized, we will receive a royalty on net sales in the low-to-mid 20% range. We will co-promote luspatercept and sotatercept, if approved, in North America for which our commercialization costs will be entirely funded by Celgene. We wholly own and are independently developing dalantercept, ACE-083 and our preclinical programs.

Table of Contents

Product Pipeline

Luspatercept

Luspatercept is designed to promote red blood cell production through a novel mechanism, and we are developing luspatercept to treat anemia and associated complications in patients with myelodysplastic syndromes, or MDS, and ß-thalassemia. In December 2015, Celgene initiated two Phase 3 clinical trials with luspatercept: one trial in patients with very low, low and intermediate risk MDS per the Revised International Prognostic Scoring System, the "MEDALIST" trial, and a second trial in regularly transfused patients with ß-thalassemia, the "BELIEVE" trial. We are also conducting two Phase 2 clinical trials of luspatercept for each of MDS and ß-thalassemia.

MDS

With respect to MDS, both our and Celgene's objective is to develop luspatercept as a treatment to increase hemoglobin levels and decrease red blood cell transfusion burden, with patients ultimately becoming transfusion independent. In addition to the Phase 3 clinical trial, we are currently conducting two Phase 2 clinical trials of luspatercept in patients with MDS. The first clinical trial is designed as a two-part trial, with an ascending dose part to evaluate the safety and efficacy in patients with low or intermediate risk MDS per the International Prognostic Scoring System, and an expansion part in which additional patients are enrolled at a selected dose level (3-month base study). We have currently completed enrollment in all of the dose escalation cohorts and we have completed enrollment of patients in the initial expansion cohort of the trial for a total of 58 patients. We have expanded the trial to include two additional cohorts of patients to further evaluate the effects of luspatercept in selected MDS patient populations. All patients enrolled in the base study are eligible to enroll in a second Phase 2 trial (extension study) that permits dosing with luspatercept for up to an additional two years. These trials are being conducted at sites in Germany.

Table of Contents

We believe that preliminary results from the long-term Phase 2 MDS extension study are encouraging. We presented these results, using a data cut-off date of August 31, 2015, at the 57th American Society of Hematology (ASH) Annual Meeting and Exposition in December 2015. As of the cut-off date, a total of 32 patients were treated in the extension study in which luspatercept was administered subcutaneously once every 3 weeks. Of these 32 patients, 13 had a low red blood cell (RBC) transfusion burden (LTB; < 4 units RBC/8 weeks) and 19 had a high transfusion burden (HTB; ≥4 units RBC/8 weeks). 59% of patients had been treated previously with erythropoiesis stimulating agents (ESA) and 19% of patients had previously been treated with lenalidomide. With regard to LTB patients, 9 of 13 (69%) LTB patients achieved the International Working Group (IWG) Hematologic Improvement Erythroid (HI-E) response criterion of a hemoglobin increase ≥1.5 g/dL for ≥8 weeks. With regard to HTB patients, 13 of 19 (68%) HTB patients achieved the IWG HI-E criterion of a reduction of ≥4 units RBC over 8 weeks, and 8 of 19 (42%) HTB patients treated with luspatercept achieved RBC transfusion independence for ≥8 weeks. An additional 3 of 3 (100%) LTB patients with 2 units/8 weeks at baseline achieved RBC transfusion independence for ≥8 weeks. A substantial majority of the patients in the Phase 2 trial had a bone marrow cell morphology referred to as ring sideroblasts and given the encouraging response rates in these patients, the Phase 3 trial has been designed to focus on patients with this particular cellular morphology. The most common adverse events observed in this extension study, which may be related to luspatercept, were bone pain, headache, hypotonia, myalgia and nausea. There were no drug-related serious adverse events.

The Phase 3 MDS MEDALIST trial targets patients with very low, low or intermediate risk MDS with ring sideroblasts who require RBC transfusions. The trial is double-blinded, placebo-controlled and will enroll an estimated 210 patients randomized 2:1, luspatercept versus placebo. In order to enroll in the trial, patients must be: refractory / intolerant to prior erythropoiesis stimulating agents (ESA) or ESA ineligible, ring sideroblast positive, receive a transfusion of at least 2 units of RBCs every 8 weeks confirmed for a minimum of 16 weeks with no consecutive 8-week period free from transfusion, and no prior lenalidomide, hypomethylating agents or immunosuppressive therapy. Patients are excluded from the study if they have del(5q) or secondary MDS. The primary endpoint for efficacy analysis will be the proportion of patients who become RBC-transfusion independent for a period of at least 8 weeks during the first 24 weeks of treatment.

ß-thalassemia

With respect to ß-thalassemia, both our and Celgene's objective is to develop luspatercept as a treatment to increase hemoglobin levels, decrease transfusion burden, decrease iron overload, improve symptoms associated with anemia, and alleviate other disease complications, such as leg ulcers. In addition to the Phase 3 clinical trial, we are currently conducting two Phase 2 clinical trials of luspatercept in patients with ß-thalassemia. The first clinical trial is designed as a two-part trial, with an ascending dose part to evaluate the safety and efficacy of luspatercept in patients with ß-thalassemia, and an expansion part in which additional patients are enrolled at a selected dose level (3-month base study). We have currently completed enrollment and treatment of all of the dose escalation cohorts as well as the expansion cohort of the trial. Patients enrolled in the initial 3-month trial are eligible to enroll in a second Phase 2 trial (extension study) that permits dosing with luspatercept for up to an additional two years. This trial is currently being conducted at sites in Italy and Greece.

We believe the preliminary results from the Phase 2 clinical trials are encouraging. We presented these results, using a data cut-off date of September 25, 2015, at the 57th ASH Annual Meeting and Exposition in December 2015. As of the cut-off date, a total of 64 patients were treated in the dose escalation and expansion cohorts of this study, in which luspatercept was administered subcutaneously, once every 3 weeks. A total of 59 patients were evaluable for efficacy (5 patients were ongoing with <12 weeks treatment). Of these 59 patients, 31 were non-transfusion dependent and 28 were transfusion dependent. Specifically, 22 of 28 (79%) transfusion dependent patients had a ≥20% reduction in transfusion burden, 21 of 28 (75%) had a ≥33% reduction, and 16 of 28 (57%) had a ≥50% reduction over a 12-week period.

Table of Contents

A trend of reduction in liver iron concentration, or LIC, was observed in the majority of non-transfusion dependent patients with or without iron chelation therapy, and in the majority of transfusion dependent patients receiving iron chelation therapy. Improvement in quality of life in non-transfusion dependent patients correlated with increase in hemoglobin. Rapid healing of leg ulcers, a serious complication of ß-thalassemia, was observed in 3 patients, with 2 additional patients experiencing partial healing. The most common related adverse events were bone pain, myalgia, headache, arthralgia, musculoskeletal pain, asthenia, injection site pain, back pain and pain in jaw. There were no drug-related serious adverse events. 6 of 59 (10%) patients discontinued early with an associated adverse event: bone pain (2 patients) and arthralgia, asthenia, cerebrovascular accident and headache (1 patient each).

The Phase 3 ß-thalassemia BELIEVE trial targets adult ß-thalassemia patients who are regularly transfused. The trial is double-blinded and placebo-controlled and will enroll an estimated 300 patients randomized 2:1, luspatercept versus placebo. In order to enroll in the trial, patients must receive 6-20 units RBC transfused over the prior 24 weeks and have no transfusion-free period ≥ 35 days. Patients will be monitored for a 12-week prospective pre-treatment period to calculate baseline transfusion burden. The primary endpoint for efficacy analysis will be the proportion of patients with at least a 33% reduction in transfusion burden during weeks 13 to 24 of the trial compared to the 12 weeks preceding treatment.

Sotatercept

Sotatercept is designed to promote increases in red blood cells as well as bone mineral density. We and Celgene are developing sotatercept for the treatment of chronic kidney disease, or CKD, a disorder characterized by anemia and a mineral and bone disorder that leads to bone loss and cardiovascular disease. The mineral and bone disorder in these patients is not well-managed with current therapies. Studies in mice show that sotatercept may have beneficial effects on fibrotic damage to the kidney and on the development of calcified deposits that may contribute to the elevated risk of heart disease in CKD patients. Data from our ongoing Phase 2 clinical trial in patients with end-stage kidney disease shows that sotatercept may have positive effects on the mineral and bone disorder in these patients and may decrease the accumulation of vascular calcifications. We and Celgene are considering refocusing the sotatercept program on the treatment of patients with earlier, pre-dialysis kidney disease. We expect to meet with the FDA in the first half of 2016 to discuss the initiation of a clinical trial in pre-dialysis patients.

Dalantercept

Our third clinical stage therapeutic candidate, dalantercept, is designed to treat cancers by inhibiting blood vessel formation through a mechanism that is distinct from, and potentially synergistic with, the dominant class of cancer drugs that inhibit blood vessel formation, the vascular endothelial growth factor, or VEGF, pathway inhibitors. We are developing dalantercept primarily for use in combination with VEGF pathway inhibitors to produce better outcomes for cancer patients. Dalantercept in combination with axitinib, a tyrosine kinase inhibitor of the VEGF pathway, in Part 1 of the ongoing Phase 2 clinical trial, or the "DART" trial in patients with renal cell carcinoma, or RCC, produced clinical outcomes that exceed historical results with axitinib alone. We are currently conducting Part 2 of the DART trial, which is a double-blind, placebo-controlled trial, in which an estimated 130 patients are randomized to dalantercept plus axitinib or placebo plus axitinib. We expect to report on progression free survival from Part 2 of the DART trial by the end of 2016. In the open-label Part 1 and blinded Part 2 of the DART trial, the following serious adverse events have been reported as related to dalantercept, dalantercept or placebo (blinded Part 2), or both dalantercept and axitinib: fluid overload, dyspnea, epistaxis, renal injury, acute renal failure and hyponatremia. Non-serious adverse events associated with axitinib did not generally occur with higher than expected frequency or severity. In addition to the DART trial, we are conducting a clinical trial to evaluate the treatment of patients with advanced hepatocellular cancer (HCC) with a combination of dalantercept plus sorafenib, another tyrosine kinase inhibitor of the VEGF pathway. A total of 21 patients have been enrolled as of December 30, 2015. Five patients were initially treated with dalantercept

Table of Contents

0.6 mg/kg and sorafenib 400 mg; 4 of these patients discontinued within 6 weeks of treatment. Sixteen patients were treated with dalantercept 0.4 mg/kg and sorafenib 400 mg; 8 of these patients discontinued within 6 weeks of treatment and 1 within 12 weeks of treatment. Seven of the 16 patients dosed with 0.4 mg/kg dalantercept and sorafenib 400 mg remain in the trial after receiving between 1 and 18 weeks of treatment. In the first quarter of 2016, a safety review team will review the cumulative safety and efficacy data from this trial to determine whether additional patients should be enrolled. The preliminary data indicate a general lack of efficacy for the dalantercept plus sorafenib combination in the treatment of advanced HCC, and therefore we believe that it is unlikely that additional patients will be enrolled in the HCC trial.

ACE-083

Our fourth clinical stage therapeutic candidate, ACE-083, is designed to promote muscle growth and function in specific, targeted muscles. In 2014, we initiated a Phase 1 clinical trial with ACE-083 in healthy volunteers. ACE-083 has been well tolerated and no serious adverse events have been reported. Initial data from the Phase 1 trial showed that, at the highest dose level tested, ACE-083 generated a mean increase in muscle volume of approximately 14.5% in the treated muscle. We have completed enrollment for the ACE-083 Phase 1 clinical trial, and we expect to initiate a Phase 2 clinical trial with ACE-083 in patients with facioscapulohumeral dystrophy, or FSHD, in the second half of 2016.

Preclinical Programs

In addition to our clinical development activities, we are expanding our research capabilities in order to increase the rate at which our highly productive research group can identify and advance new, internally discovered, therapeutic candidates for clinical development. Our discovery efforts are primarily focused on identifying new protein therapeutic candidates from our IntelliTrap™ platform and identifying novel antibodies. We have selected our first IntelliTrap™ therapeutic candidate, ACE-2494, for pre-clinical evaluation and advancement to clinical trials by the end of 2016.

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" beginning on page S-8 of this prospectus supplement and in our Annual Report on Form 10-K for the year ended December 31, 2014 in deciding whether to invest in our common stock.

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.

Table of Contents

THE OFFERING

Issuer	Acceleron Pharma Inc.
Securities	3,076,292 shares of common stock based on assumed public offering price of $48.76 per share, the last reported sale price of our common stock on the NASDAQ Global Market on December 31, 2015 (or 3,537,735 shares if the underwriters exercise their option to purchase additional shares of common stock in full).
Common stock outstanding after this offering	36,273,941 shares of common stock based on assumed public offering price of $48.76 per share, the last reported sale price of our common stock on the NASDAQ Global Market on December 31, 2015 (assuming no exercise of the underwriters' option to purchase additional shares).
Public offering price per share	$
Use of proceeds	The net proceeds from this offering are estimated to be approximately $140.4 million (or approximately $161.6 million if the underwriters exercise their option to purchase additional shares in full), after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us. We intend to use the net proceeds from this offering to conduct clinical trials and associated activities with ACE-083 and potential therapeutic candidates from our existing research pipeline, to further expand our research and development efforts to expand and advance our pipeline of earlier-stage programs, and for general and administrative expenses (including personnel-related costs), capital expenditures and working capital and other general corporate purposes. See "Use of Proceeds".
U.S. federal income tax consequences	For certain material U.S. federal income tax and estate tax consequences of the holding and disposition of shares of our common stock, see "Material U.S. Tax Considerations for Non-U.S. Holders".
NASDAQ Global Market symbol for our common stock	Our common stock is listed on the NASDAQ Global Market under the symbol "XLRN".

The number of shares of our common stock to be outstanding after the offering is based on 33,197,649 shares of our common stock outstanding as of September 30, 2015, and excludes:

- 3,327,582 shares of common stock issuable upon the exercise of stock options outstanding as of September 30, 2015, at a weighted-average exercise price of $18.57 per share;
- 398,015 shares of common stock issuable upon the exercise of warrants to purchase shares of common stock outstanding as of September 30, 2015, at a weighted-average exercise price of $5.87 per share;
- 524,150 shares of common stock issuable upon vesting of outstanding restricted stock units as of September 30, 2015;

Table of Contents

1,866,889 shares of common stock reserved for future issuance under our 2013 Equity Incentive Plan as of September 30, 2015; and

251,213 shares of common stock reserved for future issuance under our Employee Stock Purchase Plan as of September 30, 2015.

Except as otherwise indicated, all information in this prospectus supplement assumes:

no exercise by the underwriters of their option to purchase up to $22.5 million of additional shares of common stock in this offering; and

no exercise of stock options or warrants and no vesting of restricted stock units after September 30, 2015.

Table of Contents

RISK FACTORS

Investing in our common stock involves a high degree of risk. You should carefully consider the risks and uncertainties described below in addition to the other information included or incorporated by reference in this prospectus supplement before purchasing our common stock. If any of the following risks actually occurs, our business, financial condition or results of operations would likely suffer, possibly materially. In that case, the trading price of our common stock could fall, and you may lose all or part of the money you paid to buy our common stock. 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 this Offering

Our stock price could be extremely volatile and, as a result, you may not be able to resell your shares at or above the price you paid for them.

Since our initial public offering in September 2013, the price of our common stock, as reported on the NASDAQ Global Market, or NASDAQ, has ranged from a low of $16.78 on November 8, 2013 to a high of $57.89 on January 22, 2014. In addition, the stock market in general has been highly volatile. As a result, the market price of our common stock is likely to be similarly volatile, and investors in our common stock may experience a decrease, which could be substantial, in the value of their stock, including decreases unrelated to our operating performance or prospects, and could lose part or all of their investment. The price of our common stock could be subject to wide fluctuations in response to a number of factors, including those described elsewhere in this prospectus and others such as:

- variations in our operating performance and the performance of our competitors;
- actual or anticipated fluctuations in our quarterly or annual 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;
- speculation in the press or investment community;
- changes in accounting principles;
- terrorist acts, acts of war or periods of widespread civil unrest;

natural disasters and other calamities; and

changes in general market and economic conditions.

As we operate in a single industry, we are especially vulnerable to these factors to the extent that they affect our industry, 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.

Table of Contents

Your percentage ownership in us may be diluted by future issuances of capital stock, which could reduce your influence over matters on which stockholders vote.

Pursuant to the terms of our certificate of incorporation and amended and restated bylaws, our board of directors has the authority, without action or vote of our stockholders, to issue all or any part of our authorized but unissued shares of capital stock, including shares of our authorized but unissued preferred stock. Issuances of common stock or voting preferred stock would reduce your influence over matters on which our stockholders vote, and, in the case of issuances of preferred stock, would likely result in your interest in us being subject to the prior rights of holders of that preferred stock.

If you purchase shares in this offering, you will suffer immediate and substantial dilution.

If you purchase shares of our common stock in this offering, you will incur immediate and substantial dilution in the as adjusted net tangible book value of your stock of $41.26 per share as of September 30, 2015, based on assumed public offering price of $48.76 per share, the last reported sale price of our common stock on the NASDAQ Global Market on December 31, 2015, because the price that you pay will be substantially greater than the net tangible book value per share of the shares you acquire. You will experience additional dilution upon the exercise of options and warrants to purchase our common stock, as well as upon the vesting of outstanding restricted stock units, including those options currently outstanding and those granted in the future, and the issuance of restricted stock or other equity awards under our stock incentive plans. To the extent we raise additional capital by issuing equity securities, our stockholders will experience substantial additional dilution.

We have broad discretion to determine how to use the funds raised in this offering, and may use them in ways that may not enhance our operating results or the market price of our common stock.

Our management will have broad discretion over the use of proceeds from this offering, and we could spend the proceeds from this offering in ways our stockholders may not agree with or that do not yield a favorable return, if at all. We intend to use the net proceeds from this offering for the development of our product candidates and for other general corporate and working capital purposes. However, our use of these proceeds may differ substantially from our current plans. If we do not invest or apply the proceeds of this offering in ways that improve our operating results, we may fail to achieve expected financial results, which could cause the market price of our common stock to decline.

Our ability to use net operating loss and tax credit carryforwards and certain built-in losses to reduce future tax payments is limited by provisions of the Internal Revenue Code, and it is possible that certain transactions or a combination of certain transactions may result in material additional limitations on our ability to use our net operating loss and tax credit carryforwards.

As of December 31, 2014, we had U.S. federal and state net operating loss carryforwards, or NOL carryforwards, of $211.2 million and $165.0 million, respectively, available to reduce future taxable income, if any. These federal NOL carryforwards expire at various times through 2034 and the state NOL carryforwards expire at various times through 2034. These net operating losses have been fully offset by a valuation allowance due to uncertainties surrounding our ability to realize these tax benefits. In general, if we experience or have experienced a greater than 50 percent aggregate change in ownership of certain significant stockholders over a three-year period, or a Section 382 ownership change, utilization of our pre-change NOL carryforwards will be subject to an annual limitation under Section 382 of the Internal Revenue Code of 1986, as amended (the "Internal Revenue Code"), and similar state laws. Such limitations may result in expiration of a portion of the NOL carryforwards before utilization and may be substantial. If we experience a Section 382 ownership change in connection with this offering or as a result of future changes in our stock ownership, some of which changes are outside our control, the tax benefits related to the NOL carryforwards may be limited or lost.

Table of Contents

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, 2015, we had an accumulated deficit of $280.4 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, ACE-083 or other therapeutic candidates. If we do not receive the anticipated milestone payments or do not enter into partnerships for dalantercept, ACE-083 or other 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 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 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, 2015, our cash, cash equivalents and investments were $148.2 million. We believe that we will continue to expend substantial resources for the foreseeable future developing dalantercept, ACE-083 and new 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 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 therapeutic candidates.

Celgene pays development, manufacturing and commercialization and certain patent costs for sotatercept and luspatercept. Other than those costs, our future capital requirements depend on many factors, particularly in connection with the development of our other therapeutic candidates including dalantercept and ACE-083:

- the scope, progress, results and costs of researching and developing our other therapeutic candidates, and conducting preclinical studies and clinical trials;

Table of Contents

- the timing of, and the costs involved in, obtaining regulatory approvals for our other therapeutic candidates if clinical trials are successful;

- the cost of commercialization activities for our other therapeutic candidates, if any of these therapeutic candidates is approved for sale, including marketing, sales and distribution costs;

- the cost of manufacturing our other 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 our current cash, cash equivalents and investments, together with the net proceeds from this offering and receipt of anticipated milestone payments will be sufficient to fund our projected operating requirements into the second half of 2019. 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 that 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 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 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 therapeutic candidates 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 therapeutic candidates, 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, ACE-083 or any therapeutic candidates other than luspatercept or sotatercept, or grant rights to develop and market therapeutic candidates that we would otherwise prefer to develop and market ourselves.

Risks Related to Regulatory Review and Approval of Our Therapeutic Candidates

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

Our 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 therapeutic candidates, we or our partners must demonstrate through extensive preclinical studies and clinical trials that the therapeutic candidate is safe

Table of Contents

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, luspatercept, dalantercept, ACE-083 or any other therapeutic candidate in some but not all of the territories available or some but not all of the target indications or may receive approval with limited labeling or boxed warnings, resulting in limited commercial opportunity for the approved therapeutic candidates, or we or they may never obtain regulatory approval for these therapeutic candidates.

Delays in the commencement, enrollment or completion of clinical trials of our 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 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 current or future 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 or manufacturing concerns or after an inspection of clinical operations or trial sites;
- failure by CROs, other third parties or us or our current or future 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 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 therapeutic candidates that are viewed to outweigh its potential benefits; or
- 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 therapeutic candidates.

There is a high risk of clinical failure at any stage of clinical development, and we may never succeed in developing marketable products or generating product revenue.

Our encouraging preclinical and clinical results to date for sotatercept, luspatercept, dalantercept and ACE-083 are not necessarily predictive of the results of our ongoing or future clinical trials. Promising

Table of Contents

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 current or future partners' ongoing or future clinical trials are inconclusive with respect to the efficacy of our 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 therapeutic candidates, we or our partner may be prevented or delayed in obtaining marketing approval for our 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 risk evaluation and mitigation strategy.

If we or our current or future 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 current or future partners intend to market our 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 therapeutic candidate 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 current or future 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.

We and Celgene regularly request and receive guidance from the FDA and foreign regulators regarding the design or conduct of clinical trials with our therapeutic candidates. This guidance is not binding on these agencies and could change substantially and unpredictably, potentially in a way that makes our clinical trials or our path to regulatory approval longer, more expensive or otherwise more difficult.

Any guidance that we or Celgene receive from the FDA or foreign regulators regarding the design or conduct of our clinical trials is not necessarily indicative of what these regulators will eventually require from us or Celgene to obtain regulatory approval of our therapeutic candidates. These regulators typically caution that any guidance received from them represents their then-current thinking, does not create or confer any rights to us or Celgene, and does not operate to bind the regulator. If later guidance that we or Celgene receive from the FDA or foreign regulators regarding our clinical trial design or conduct is materially different than the current guidance we have received from these regulators, we may need to change our clinical development plans and it may take longer, be more expensive or otherwise be more difficult to obtain FDA or foreign regulatory approval of our therapeutic candidates and our business may be materially harmed.

We undertake no obligation to disclose guidance that we or Celgene may receive from the FDA or foreign regulators. Any guidance from the FDA or foreign regulators that we may disclose publicly speaks

Table of Contents

only as of the date of such disclosure. We undertake no obligation to update any disclosure we make regarding regulator guidance to reflect additional regulatory guidance received after the date of such disclosure or to reflect the occurrence of unanticipated events that may affect the guidance.

Even if we or our current or future partners receive regulatory approval for our therapeutic candidates, such products will be subject to ongoing regulatory review, which may result in significant additional expense. Additionally, our therapeutic candidates, if approved, could be subject to labeling and other restrictions, and we or our current or future 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 current or future partners receive for our 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 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 therapeutic candidate, 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 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 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.

A Fast Track designation by the FDA may not actually lead to a faster development or regulatory review or approval process.

In the United States, luspatercept received Fast Track designation for the treatment of anemia in patients with lower-risk myelodysplastic syndromes, or MDS, for the treatment of patients with transfusion-dependent ß-thalassemia, and for the treatment of patients with non-transfusion-dependent ß-thalassemia. The FDA grants Fast Track designation to therapies that are considered capable of addressing unmet medical needs and possess the potential to treat serious or life-threatening disease conditions in order to facilitate its development and expedite the review procedure. The FDA has broad discretion in granting Fast Track designation, so even if we believe that a particular product candidate is

Table of Contents

eligible for such designation, the FDA could decide not to grant it. Even though luspatercept has received Fast Track designation for multiple indications, we may not experience a faster development process, review or approval compared to conventional FDA procedures. The FDA may also withdraw Fast Track designation if it believes that the designation is no longer supported by data from our clinical development program.

The Phase 3 MEDALIST and BELIEVE clinical trials may be delayed, suspended or terminated, or may not lead to marketing approval.

In December 2015, Celgene initiated two Phase 3 clinical trials with luspatercept for the treatment of patients with lower risk MDS, the "MEDALIST" trial, or ß-thalassemia, the "BELIEVE" trial. These trials may not be successful and the delay or failure of either one of these clinical trials will materially harm our business. Celgene may experience delays in the conduct of these clinical trials, including delays related to clinical trial site initiation, patient enrollment, patients withdrawing from the trial, or drug supply. If patients experience adverse events while in these or other clinical trials with luspatercept, then one or both of the MEDALIST or BELIEVE trials may be delayed, suspended or terminated. Celgene may not achieve the primary endpoint for one or both trials, or may not achieve one or more secondary endpoints. Data from our luspatercept Phase 2 trials may not be predictive of results obtained in the MEDALIST or BELIEVE trials. Even if the primary endpoint is achieved, one or more health authorities may not approve luspatercept for the desired indication. The MEDALIST and BELIEVE trials were designed with input from health authorities in many different countries, but this guidance is not binding on these regulators, and it may be necessary to conduct one or more additional clinical trials in order to achieve marketing authorization in one or more regulatory jurisdictions. Guidance that we or Celgene receive from the FDA or foreign regulators regarding the design or conduct of the MEDALIST or BELIEVE clinical trials is not necessarily indicative of what these regulators will eventually require from us or Celgene to obtain regulatory approval of luspatercept in these indications. Any regulatory approvals that we or Celgene receive for luspatercept 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.

If we or any of our current or future partners violate the guidelines pertaining to promotion and advertising of any of our therapeutic candidates, 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.

Table of Contents

Risks Related to Our Reliance on Third Parties

We are dependent on Celgene for the successful development and commercialization of sotatercept and our most advanced therapeutic candidate, luspatercept. If Celgene does not devote sufficient resources to the development of these candidates, discontinues 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, one of our principal stockholders that as of September 30, 2015 owned approximately 14% of our common stock, to develop and commercialize sotatercept and luspatercept. Pursuant to the sotatercept agreement, responsibility for all clinical and other product development activities and for manufacturing sotatercept has been transferred to Celgene. For luspatercept, we are responsible for conducting ongoing Phase 2 clinical trials in MDS, 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 luspatercept. We will co-promote sotatercept and luspatercept, 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 luspatercept. Celgene may determine that it is commercially reasonable to develop and commercialize only luspatercept or sotatercept and discontinue the development or commercialization of the other therapeutic candidate, or Celgene may determine that it is not commercially reasonable to continue development of one or both of sotatercept and luspatercept. For example, Celgene may elect not to undertake the development of sotatercept for the treatment of pre-dialysis patients. This may occur for many reasons, including internal business reasons or because of unfavorable regulatory feedback. For example, on review of the safety and efficacy data available to date, the FDA may impose requirements on the clinical trial program that render such a program commercially nonviable. In the event of any such decision, we would be unable to progress sotatercept for this or other indications ourselves. In addition, under our collaboration agreements, once Celgene takes over development activities of a therapeutic candidate, it may determine the development plan and activities for that 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 luspatercept 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. More broadly, if Celgene elects to discontinue the development of both sotatercept and luspatercept, we may be unable to advance the products ourselves.

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 therapeutic candidates by Celgene.

- Celgene may develop and commercialize, either alone or with others, products that are similar to or competitive with the 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 luspatercept is also being developed.

Table of Contents

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.

Celgene may develop or commercialize our 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 may 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 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 luspatercept 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 if we choose not to, or are unable to, enter into a new collaboration for these candidates.

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 currently have limited marketing, sales and distribution experience and capabilities and will be dependent upon Celgene to commercialize luspatercept and sotatercept outside the United States.

We and Celgene share the obligations to commercialize luspatercept and sotatercept in the United States and we are solely dependent on Celgene to commercialize luspatercept and sotatercept outside of the United States. As a company without any commercial products, we have very limited marketing, sales and distribution experience and capabilities in the United States. To successfully commercialize luspatercept and sotatercept in the United States, we will need to establish adequate marketing, sales and distribution capabilities. Failure to establish these capabilities, whether due to insufficient resources or some other cause, will limit or potentially halt our ability to successfully commercialize any therapeutic candidates, and will adversely affect our financial results. Even if we do develop such capabilities, we will compete with other companies that have more experienced and well-funded marketing, sales and distribution operations.

We and Celgene rely on third parties to conduct preclinical studies and clinical trials for our 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 therapeutic candidates.

We design the clinical trials for dalantercept and ACE-083 and will do so for any future unpartnered therapeutic candidates, and we will continue to work with Celgene on trials for sotatercept and luspatercept. 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 therapeutic candidates.

Table of Contents

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 therapeutic candidates may not meet regulatory requirements or may be delayed. 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 therapeutic candidates on a timely basis or at all.

We intend to rely on third-party manufacturers to make our therapeutic candidates, and any failure by a third-party manufacturer may delay or impair our ability to complete clinical trials or commercialize our 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 luspatercept, dalantercept, ACE-083 and ACE-2494. 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 therapeutic candidates is highly cyclical, with periods of relatively abundant capacity alternating with periods in which there is little available capacity. If any need we have for contract manufacturing services increases during a period of industry-wide tight capacity, we 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 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 sotatercept and our most advanced therapeutic candidate, luspatercept, 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 luspatercept, if approved.

We produced drug substance for preclinical and Phase 1 and 2 clinical trials for sotatercept and luspatercept. Celgene is now responsible for manufacturing sotatercept and luspatercept for future late-stage clinical trials. Celgene generally does not perform the manufacture of the drug substance or drug product for either sotatercept or luspatercept 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

Table of Contents

expectation that Celgene plans to perform the manufacture of bulk drug substance or drug product for either sotatercept or luspatercept in the future. However, Celgene would have the right to manufacture sotatercept or luspatercept, itself or through the use of contract manufacturers. We understand that they have entered into manufacturing arrangements for clinical and commercial supplies of sotatercept and luspatercept bulk drug substance with contract manufacturers with considerable biotherapeutics manufacturing experience, including manufacturing monoclonal antibodies through processes similar to those used for sotatercept. If any of these manufacturers is unwilling or unable to manufacture sufficient quantities of sotatercept and/or luspatercept to meet clinical or commercial demand, either for technical or business reasons, the development and commercialization of sotatercept and/or luspatercept may be delayed.

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, part of our strategy is to evaluate and, as deemed appropriate, enter into additional partnerships in the future for our other product candidates when strategically attractive, including potentially with major biotechnology or pharmaceutical companies. We face significant competition in seeking appropriate partners for our therapeutic candidates, and the negotiation process is time-consuming and complex. In order for us to successfully partner our therapeutic candidates, potential partners must view these 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 therapeutic candidate is delayed or sales of an approved product are disappointing. Any delay in entering into new strategic partnership agreements related to our other therapeutic candidates could delay the development and commercialization of these therapeutic candidates and reduce their competitiveness even if they reach the market.

If we fail to establish and maintain additional strategic partnerships related to dalantercept, ACE-083 or other therapeutic candidates, we will bear all of the risk and costs related to the development of any such 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 therapeutic candidate.

Risks Related to Our Intellectual Property

If we are unable to obtain or protect intellectual property rights related to our 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 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 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 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

Table of Contents

unchallenged, our patents and patent applications may not adequately protect our intellectual property, provide exclusivity for our 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 therapeutic candidates fail to issue, if their breadth or strength of protection is threatened, or if they fail to provide meaningful exclusivity for our therapeutic candidates, it could dissuade companies from collaborating with us. Several patent applications covering our 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 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 therapeutic candidate that we or our current or future 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 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 therapeutic candidate under patent protection could be reduced. Even if patents covering our 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 current or future partners may be unable to prevent competitors from entering the market with a product that is similar to or the same as our therapeutic candidates. In addition, the royalty we would receive under our collaboration agreements with Celgene for sotatercept and luspatercept 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 current or future 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 current or future partners are developing and may develop our therapeutic candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our 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 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

Table of Contents

filing. Therefore, patent applications covering our platform technology or our 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 therapeutic candidates or the use or manufacture of our 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 therapeutic candidate until such patent expired or unless we or our partners obtain a license. These 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 luspatercept, 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 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 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 therapeutic candidates, programs, or intellectual property could be diminished. Accordingly, the market price of our common stock could 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.

Table of Contents

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 therapeutic candidate, may be adversely affected.

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 Development and Commercialization of Our Therapeutic Candidates

Our future commercial success depends upon attaining significant market acceptance of our therapeutic candidates, if approved, among physicians, patients, healthcare payers and acceptance by the operators of major medical providers.

Even if we or our current or future partners obtain regulatory approval for sotatercept, luspatercept, dalantercept, ACE-083 or any other therapeutic candidates that we may develop or acquire in the future, the product may not gain market acceptance among physicians, healthcare payers, 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;
- decisions by healthcare organizations to utilize the product;
- 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;

Table of Contents

relative convenience and ease of administration;

the prevalence and severity of adverse side effects; and

the effectiveness of our and our current or future partners' sales and marketing efforts.

Market acceptance is critical to our ability to generate significant revenue. Any 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 therapeutic candidates, which could make it difficult for us to sell our products profitably.

Market acceptance and sales of any approved therapeutic candidates will depend significantly on the availability of adequate coverage and reimbursement from third-party payers and may be affected by existing and future healthcare reform measures. Government authorities and third-party payers, 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 payer'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 current or future 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 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 healthcare 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 and price pressure may be imposed in foreign and U.S. 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 current or future partners may be required to conduct a clinical trial or other

Table of Contents

studies that compare the cost-effectiveness of our therapeutic candidates 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.

Recent and future healthcare reform legislation and other changes in the healthcare industry and in healthcare spending 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 healthcare availability, the method of delivery or payment for healthcare products and services could negatively impact our business, operations and financial condition. There is significant interest in promoting healthcare 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 healthcare 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 therapeutic candidates. Our objective is to design, develop and commercialize new products with superior efficacy, convenience, tolerability and safety. In many cases, the therapeutic candidates 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. Luspatercept 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 luspatercept 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 ß-thalassemia, red blood cell transfusions are extensively used and luspatercept, if approved, would compete with this therapy. Further, the future approval, in one or more regions, of a biosimilar product to one of our products could create substantial competition and have a material impact on our business. In addition, the success of gene and/or cell therapy in ß-thalassemia patients could materially reduce the potential patient population for luspatercept, especially in transfusion dependent patients.

Table of Contents

Sotatercept or luspatercept, 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 as well as immuno-oncology agents, approved for the treatment of these cancers.

If ACE-083 is approved for the treatment of neuromuscular disorders or other diseases characterized by a loss of muscle function, it could compete with a variety of other approaches to treating neuromuscular disorders or muscle loss that are currently in clinical trials, including, among others, a monoclonal antibody targeting the activin receptor type IIB, bimagrumab, being studied by Novartis to treat pathological muscle loss and weakness, and various myostatin monoclonal antibodies being studied to treat disuse muscle atrophy, cancer-related cachexia, and sarcopenia. We intend to conduct our first phase 2 trial of ACE-083 in patients with facioscapulohumeral muscular dystrophy, or FSHD. We are aware of competitors also developing products to treat this disease, including aTyr Pharma. If competitive products prove to be superior to ACE-083, our business may be harmed.

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 therapeutic candidates that we develop obsolete. As a result of all of these factors, our competitors may succeed in obtaining patent protection and/or FDA approval or discovering, developing and commercializing therapeutic candidates 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.

If our clinical trials fail to demonstrate the safety and efficacy of our therapeutic candidates to the satisfaction of regulatory authorities or do not otherwise produce positive results, we may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our therapeutic candidates.

Undesirable side effects caused by our therapeutic candidates 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 clinical trials for our clinical stage therapeutic candidates. Serious adverse events deemed to be caused by our therapeutic candidates could have a material adverse effect on the development of our therapeutic candidates and our business as a whole. For a more complete description of the safety profile for our therapeutic candidates, see the description of each of our therapeutic candidates in the "Our Business" section of this registration statement and in the ""Business"" section of our Annual Report on Form 10-K for the year ended December 31, 2014.

Table of Contents

Our understanding of the relationship between our 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 therapeutic candidates will not be observed. As is typical in drug development, we have a program of ongoing toxicology studies in animals for our clinical stage therapeutic candidates 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.

Before obtaining marketing approval from regulatory authorities for the sale of our therapeutic candidates, we must complete preclinical development and then conduct extensive clinical trials to demonstrate the safety and efficacy of our therapeutic candidates in humans. Clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. A failure of one or more clinical trials can occur at any stage of testing. The outcome of preclinical testing and early clinical trials may not be predictive of the success of later clinical trials, and interim results of a clinical trial do not necessarily predict final results. In addition, preclinical and clinical data are often susceptible to varying interpretations and analyses. Many companies that have believed their therapeutic candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval of their products.

We or our current or future partners may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent our ability to receive marketing approval or commercialize our therapeutic candidates, including:

- regulators or institutional review boards may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- we may have delays in reaching or fail to reach agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites;
- clinical trials of our therapeutic candidates may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional clinical trials or abandon product development programs;
- the number of patients required for clinical trials of our therapeutic candidates may be larger than we anticipate; enrollment in these clinical trials may be slower than we anticipate; or participants may drop out of these clinical trials at a higher rate than we anticipate;
- third-party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;
- we might have to suspend or terminate clinical trials of our therapeutic candidates for various reasons, including a finding that the participants are being exposed to unacceptable health risks;
- regulators, institutional review boards, or the data safety monitoring board for such trials may require that we or our investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks;
- the cost of clinical trials of our therapeutic candidates may be greater than we anticipate;
- the supply or quality of our therapeutic candidates or other materials necessary to conduct clinical trials of our therapeutic candidates may be insufficient or inadequate; and
- our therapeutic candidates may have undesirable side effects or other unexpected characteristics, causing us or our investigators, regulators or institutional review boards to suspend or terminate the trials.

Table of Contents

If we or our current or future partners are required to conduct additional clinical trials or other testing of our therapeutic candidates beyond those that we currently contemplate, if we or our current or future partners are unable to successfully complete clinical trials of our therapeutic candidates or other testing, if the results of these trials or tests are not positive or are only modestly positive or if we or others identify undesirable side effects caused by our therapeutic candidates either before or after receipt of marketing approval, then a number of potentially significant negative consequences could result, including that we or our current or future partners may:

- be delayed in obtaining or be unable to obtain marketing approval for our therapeutic candidates;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- be required to provide a medication guide outlining the risks of such side effects for distribution to patients;
- obtain approval with labeling that includes significant use or distribution restrictions or safety warnings, including boxed warnings;
- suffer reputational harm;
- be sued and held liable for harm caused to patients;
- be subject to additional post-marketing testing requirements; or
- have the product removed from the market after obtaining marketing approval.

Product development costs will also increase if we or our current or future partners experience delays in testing or marketing approvals. We do not know whether any clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. Significant clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our therapeutic candidates, could allow our competitors to bring products to market before we do, and could impair our ability to successfully commercialize our therapeutic candidates, any of which may harm our business and results of operations.

Our results to date do not guarantee that any of our therapeutic candidates will be safe or effective, or receive regulatory approval.

The risk of failure of our current therapeutic candidates is high. To date, the data supporting our clinical development strategy for our therapeutic candidates are derived solely from laboratory and preclinical studies and limited early-to-mid-stage clinical trials. Later clinical trials may not yield data consistent with earlier clinical trials. Similarly, clinical responses seen in patients enrolled at early stages of a clinical trial may not be replicated in patients enrolled in that trial at a later time. In addition, adverse events not observed in early clinical trials may be seen for the first time in later studies, or adverse events observed in a small number of patients in early trials may be seen in a greater number of patients in later studies and have greater statistical significance than previously anticipated. In the event that our clinical trials do not yield data consistent with earlier experience, it may be necessary for us to change our development strategy or abandon development of that therapeutic candidate, either of which could result in delays, additional costs and a decrease in our stock price.

Our Phase 2 clinical trial results for luspatercept are not necessarily indicative or predictive of the results of Celgene's Phase 3 clinical trials. It is impossible to predict when or if any of our therapeutic candidates will prove safe or effective in humans or receive regulatory approval. These therapeutic candidates may not demonstrate in patients the chemical and pharmacological properties ascribed to them in laboratory studies or early-to-mid-stage clinical trials, and they may interact with human biological systems or other drugs in unforeseen, ineffective or harmful ways. If we are unable to discover or successfully develop drugs that are safe and effective in humans, we will not have a viable business.

Table of Contents

We manufacture ACE-083, ACE-2494 and earlier stage luspatercept at our manufacturing facility. If our manufacturing facility is damaged or destroyed or production at this facility is otherwise interrupted, our business and prospects would be negatively affected.

If the manufacturing facility at our corporate headquarters or the equipment in it is damaged or destroyed, we may not be able to quickly or economically replace our manufacturing capacity or replace it at all. In the event of a temporary or protracted loss of this facility or equipment, we might not be able to transfer manufacturing to a third party. Even if we could transfer manufacturing to a third party, the shift would likely be expensive and time-consuming, particularly since the new facility would need to comply with the necessary regulatory requirements and we would need approval from the FDA and foreign regulators before administering any products manufactured at that facility to patients. Such an event could delay our clinical trials or, if our therapeutic candidates are approved by the FDA or foreign regulators, reduce our product sales.

Our expanded research activities may not identify new therapeutic candidates, and we may not be successful in developing any new therapeutic candidates that are identified.

Discovery and development of new therapeutic candidates is an unpredictable activity. We may not succeed in identifying new therapeutic candidates, and if we are unable to do so, our pipeline of clinical stage therapeutic candidates will be reduced in size, potentially harming our business. Our discovery efforts are primarily focused on IntelliTrap™ therapeutic candidates and antibodies. We have not previously manufactured or developed antibodies or IntelliTrap™ proteins, and we may not be successful at doing so. We may be unable to manufacture these candidate therapeutics, these candidate therapeutics may show unacceptable toxicity or pharmacokinetic properties, or these therapeutic candidates may not be safe or effective in clinical trials.

Risks Related to Our Business and Industry

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

We may encounter difficulties in managing our organizational changes and successfully adjusting our operations.

As we seek to advance our 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 therapeutic candidates and to compete

Table of Contents

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 therapeutic candidates.

We face an inherent risk of product liability as a result of the clinical testing of our 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 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 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 $10.0 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 could be subject to securities class action litigation.

In the past, securities class action litigation has often been brought against companies following a decline in the market price of their securities. This risk is especially relevant for us because biopharmaceutical companies have experienced significant stock price volatility in recent years. If we face such litigation, it could result in substantial costs and a diversion of management's attention and resources, which could harm our business.

Table of Contents

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

We 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 materials that we use in our manufacturing process. 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.

Unfavorable global economic conditions could adversely affect our business, financial condition or results of operations.

Our results of operations could be adversely affected by general conditions in the global economy and in the global financial markets. The recent global financial crisis caused extreme volatility and disruptions in the capital and credit markets. A severe or prolonged economic downturn could result in a variety of risks to our business, including, weakened demand for our therapeutic candidates and our ability to raise additional capital when needed on acceptable terms, if at all. Weak global economic conditions, especially in Europe, could decrease the number of clinical trial sites available to us and hinder our ability to conduct clinical trials, which would have a material adverse effect on our business and the development of our therapeutic candidates. A weak or declining economy could also strain our suppliers, possibly resulting in supply disruption, or cause our customers to delay making payments for our services. Any of the foregoing could harm our business and we cannot anticipate all of the ways in which the current economic climate and financial market conditions could adversely impact our business.

Our internal computer systems, or those of our partners, third-party CROs or other contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our therapeutic candidate development programs.

Despite the implementation of security measures, our internal computer systems and those of our current and any future CROs and other contractors, consultants and collaborators are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. While we have not experienced any such material system failure, accident or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our development programs and our business operations. For example, the loss of clinical trial data from completed or future clinical trials could result in delays in our or our partners' regulatory approval efforts and significantly increase our costs to recover or reproduce the data. Likewise, we rely on third parties to manufacture our therapeutic candidates and conduct clinical trials, and similar events relating to their computer systems could also have a material adverse effect on our business. To the extent that any disruption or security breach were to result in a loss of, or damage to, our or any of our partners' data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the further development and commercialization of our therapeutic candidate could be delayed.

Table of Contents

Risks Related to Our Common Stock

We continue to incur significant costs as a result of operating as a public company and complying with the Sarbanes-Oxley Act, especially now that we are a large accelerated filer and are no longer an ""emerging growth company,"" and our management continues to be required to devote substantial time to compliance initiatives.

As a public company, we incur significant legal, accounting and other expenses that we did not incur as a private company. In addition, the Sarbanes-Oxley Act, and rules of the SEC and those of NASDAQ, have imposed various requirements on public companies including requiring establishment and maintenance of effective disclosure and financial controls. Our management and other personnel devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations have increased and will continue to increase our legal and financial compliance costs and will make some activities more time-consuming and costly.

The Sarbanes-Oxley Act requires, among other things, that we maintain effective internal control over financial reporting and disclosure controls and procedures. In particular, we must perform system and process evaluation and testing of our internal control over financial reporting to allow management to report on the effectiveness of our internal control over financial reporting, as required by Section 404 of the Sarbanes-Oxley Act. In addition, because we are no longer an emerging growth company status under the JOBS Act, we are required to have our independent registered public accounting firm attest to the effectiveness of our internal control over financial reporting. Our compliance with Section 404 of the Sarbanes-Oxley Act requires that we incur substantial accounting expense and expend significant management efforts. We currently do not have an internal audit group, and we may need to hire additional accounting and financial staff with appropriate public company experience and technical accounting knowledge. If we are not able to comply with the requirements of Section 404 in a timely manner, or if we or our independent registered public accounting firm identify deficiencies in our internal control over financial reporting that are deemed to be material weaknesses, the market price of our stock could decline and we could be subject to sanctions or investigations by NASDAQ, the SEC or other regulatory authorities, which would require additional financial and management resources.

Our ability to successfully implement our business plan and comply with Section 404 requires us to be able to prepare timely and accurate financial statements. We expect that we will need to continue to improve existing, and implement new operational and financial systems, procedures and controls to manage our business effectively. Any delay in the implementation of, or disruption in the transition to, new or enhanced systems, procedures or controls, may cause our operations to suffer and we may be unable to conclude that our internal control over financial reporting is effective and to obtain an unqualified report on internal controls from our auditors as required under Section 404 of the Sarbanes-Oxley Act. This, in turn, could have an adverse impact on trading prices for our common stock, and could adversely affect our ability to access the capital markets.

If we fail to maintain an effective system of internal control over financial reporting in the future, we may not be able to accurately report our financial condition, results of operations or cash flows, which may adversely affect investor confidence in us and, as a result, the value of our common stock.

The Sarbanes-Oxley Act requires, among other things, that we maintain effective internal controls for financial reporting and disclosure controls and procedures. As of our Annual Report on Form 10-K for the year ended December 31, 2014, we are required, under Section 404 of the Sarbanes-Oxley Act, to furnish a report by management on, among other things, the effectiveness of our internal control over financial reporting. This assessment must include disclosure of any material weaknesses identified by our management in our internal control over financial reporting. A material weakness is a control deficiency, or combination of control deficiencies, in internal control over financial reporting that results in more than a reasonable possibility that a material misstatement of annual or interim financial statements will not be prevented or detected on a timely basis. Section 404 of the Sarbanes-Oxley Act also generally requires an

Table of Contents

attestation from our independent registered public accounting firm on the effectiveness of our internal control over financial reporting. Now that we no longer qualify as an emerging growth company as defined in the JOBS Act, we are no longer exempted from certain requirements, such as the independent registered public accounting firm attestation.

During the evaluation and testing process, if we identify one or more material weaknesses in our internal control over financial reporting, we will be unable to assert that our internal control over financial reporting is effective. We cannot assure you that there will not be material weaknesses or significant deficiencies in our internal control over financial reporting in the future. Any failure to maintain internal control over financial reporting could severely inhibit our ability to accurately report our financial condition, results of operations or cash flows. If we are unable to conclude that our internal control over financial reporting is effective, or if we or our independent registered public accounting firm determines we have a material weakness or significant deficiency in our internal control over financial reporting, we could lose investor confidence in the accuracy and completeness of our financial reports, the market price of our common stock could decline, and we could be subject to sanctions or investigations by the NASDAQ, the SEC or other regulatory authorities. Failure to remedy any material weakness in our internal control over financial reporting, or to implement or maintain other effective control systems required of public companies, could also restrict our future access to the capital markets.

Provisions in our restated certificate of incorporation, our amended and restated by-laws and Delaware law may have anti-takeover effects that could discourage an acquisition of us by others, even if an acquisition would be beneficial to our stockholders, and may prevent attempts by our stockholders to replace or remove our current management.

Our restated certificate of incorporation, amended and restated by-laws and Delaware law contain provisions that may have the effect of delaying or preventing a change in control of us or changes in our management. Our restated certificate of incorporation and by-laws include provisions that:

- authorize "blank check" preferred stock, which could be issued by our board of directors without stockholder approval and may contain voting, liquidation, dividend and other rights superior to our common stock;
- create a classified board of directors whose members serve staggered three-year terms;
- specify that special meetings of our stockholders can be called only by our board of directors;
- prohibit stockholder action by written consent;
- establish an advance notice procedure for stockholder approvals to be brought before an annual meeting of our stockholders, including proposed nominations of persons for election to our board of directors;
- provide that our directors may be removed only for cause;
- provide that vacancies on our board of directors may be filled only by a majority of directors then in office, even though less than a quorum;
- specify that no stockholder is permitted to cumulate votes at any election of directors;
- expressly authorize our board of directors to modify, alter or repeal our amended and restated by-laws; and
- require supermajority votes of the holders of our common stock to amend specified provisions of our restated certificate of incorporation and amended and restated by-laws.

These provisions, alone or together, could delay or prevent hostile takeovers and changes in control or changes in our management.

Table of Contents

In addition, we are subject to the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a publicly-held Delaware corporation from engaging in a "business combination" with an "interested stockholder" for a three-year period following the time that this stockholder becomes an interested stockholder, unless the business combination is approved in a prescribed manner. As a result, you may lose your ability to sell your stock for a price in excess of the prevailing market price due to these protective measures and efforts by stockholders to change the direction or management of the company may be unsuccessful.

Any provision of our restated certificate of incorporation or amended and restated by-laws or Delaware law that has the effect of delaying or deterring a change in control could limit the opportunity for our stockholders to receive a premium for their shares of our common stock, and could also affect the price that some investors are willing to pay for our common stock.

Our restated certificate of incorporation designates the Court of Chancery of the State of Delaware and federal court within the State of Delaware as the exclusive forum for certain types of actions and proceedings that may be initiated by our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our restated certificate of incorporation provides that, subject to limited exceptions, the Court of Chancery of the State of Delaware and federal court within the State of Delaware will be exclusive forums for (1) any derivative action or proceeding brought on our behalf, (2) any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers or other employees to us or our stockholders, (3) any action asserting a claim against us arising pursuant to any provision of the Delaware General Corporation Law, our restated certificate of incorporation or our amended and restated by-laws, or (4) any other action asserting a claim against us that is governed by the internal affairs doctrine. Any person or entity purchasing or otherwise acquiring any interest in shares of our capital stock shall be deemed to have notice of and to have consented to the provisions of our restated certificate of incorporation described above. This choice of forum provision may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage such lawsuits against us and our directors, officers and employees. Alternatively, if a court were to find these provisions of our restated certificate of incorporation inapplicable to, or unenforceable in respect of, one or more of the specified types of actions or proceedings, we may incur additional costs associated with resolving such matters in other jurisdictions, which could adversely affect our business and financial condition.

Sales of our common stock by our employees, including our executive officers, could cause our stock price to fall or prevent it from increasing for numerous reasons, and sales by such persons could be viewed negatively by other investors.

In accordance with the guidelines specified under Rule 10b5-1 of the Securities Exchange Act of 1934, as amended, and our policies regarding stock transactions, a number of our employees, including executive officers, have adopted and may continue to adopt stock trading plans pursuant to which they have arranged to sell shares of our common stock from time to time in the future. Generally, sales under such plans by our executive officers and directors require public filings. Sales of our common stock by such persons could cause the price of our common stock to fall or prevent it from increasing. If sales by employees, executive officers or directors cause a substantial number of shares of our common stock to become available for purchase in the public market, the price of our common stock could fall or may not increase. Also, sales by such persons could be viewed negatively by holders and potential purchasers of our common stock. If securities or industry analysts do not continue to publish research or publish inaccurate or unfavorable research about our business, our share price and trading volume could decline.

The trading market for our common stock may be impacted, in part, by the research and reports that securities or industry analysts publish about us or our business. There can be no assurance that analysts will cover us, continue to cover us or provide favorable coverage. If one or more analysts downgrade our stock or change their opinion of our stock, our share price may decline. In addition, if one or more analysts cease coverage of our company or fail to regularly publish reports on us, we could lose visibility in the financial markets, which could cause our share price or trading volume to decline.

Table of Contents

USE OF PROCEEDS

We estimate that the net proceeds from this offering will be approximately $140.4 million (or approximately $161.6 million if the underwriters exercise their option to purchase additional shares of common stock in full), after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us.

We intend to use the net proceeds from this offering as follows:

- approximately $50.0 million to conduct clinical trials and associated activities with ACE-083;
- approximately $40.0 million to conduct clinical trials and associated activities for potential therapeutic candidates from our existing research pipeline, including antibodies and therapeutic candidates from our IntelliTrap™ platform, such as ACE-2494;
- approximately $20.0 million to further expand our research and development efforts to expand and advance our pipeline of earlier-stage programs; and
- the remainder for general and administrative expenses (including personnel-related costs), potential future development programs, capital expenditures and working capital and other general corporate purposes.

The expected use of the net proceeds from this offering represents our intentions based upon our current plans and business conditions, which could change in the future as our plans and business conditions evolve. The amounts and timing of our actual expenditures depend on numerous factors, including the ongoing status of and results from our clinical trials and other studies, the progress of our preclinical development efforts and any unforeseen cash needs. As a result, our management will have broad discretion in applying the net proceeds of this offering. Although we may use a portion of the net proceeds of this offering for the acquisition or licensing, as the case may be, of product candidates, technologies, compounds, other assets or complementary businesses, we have no current understandings, agreements or commitments to do so.

Pending the use of the proceeds from this offering, we intend to invest the net proceeds in short-term, interest-bearing, investment-grade securities, certificates of deposit or government securities.

Table of Contents

PRICE RANGE OF OUR COMMON STOCK

Our common stock is traded on the NASDAQ Global Market under the symbol "XLRN". The following table summarizes the high and low sale prices for our common stock for the fiscal periods indicated as reported on the NASDAQ Global Market.

	High	Low
2014		
First Quarter	$ 57.89	$ 33.81
Second Quarter	$ 42.24	$ 28.53
Third Quarter	$ 35.00	$ 23.61
Fourth Quarter	$ 48.50	$ 27.64
2015		
First Quarter	$ 43.00	$ 35.11
Second Quarter	$ 37.90	$ 26.94
Third Quarter	$ 36.31	$ 20.00
Fourth Quarter	$ 50.86	$ 21.93

Table of Contents

DIVIDEND POLICY

We have never declared or paid cash dividends on our common stock. We currently intend to retain all available funds and any future earnings, if any, to fund the development and expansion of our business and we do not anticipate paying any cash dividends in the foreseeable future. In addition, any future debt financing arrangement may contain terms prohibiting or limiting the amount of dividends that may be declared or paid on our common stock. Any future determination to pay dividends will be made at the discretion of our board of directors.

Table of Contents

CAPITALIZATION

The following table sets forth our cash and cash equivalents and investments and capitalization as of September 30, 2015:

On an actual basis; and

On an as adjusted basis to reflect the receipt of the estimated net proceeds from the sale of shares of our common stock offered in this offering at an assumed public offering price of $48.76 per share, the last reported price of our common stock on the NASDAQ Global Market on December 31, 2015), after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us.

You should read the following table along with our financial statements and the accompanying notes to those statements and other financial information included or incorporated by reference in this prospectus supplement and the accompanying prospectus.

	As of September 30, 2015	
	Actual	As adjusted
	(in thousands, except share and per share data)	
Cash, cash equivalents and short-term and long-term investments	$ 148,150	$ 288,590
Warrants to purchase common stock	$ 8,064	$ 8,064
Stockholders' equity:		
Undesignated preferred stock, $0.001 par value; 25,000,000 shares authorized and no shares issued or outstanding		
Common stock, $0.001 par value; 175,000,000 share authorized actual and as adjusted; 33,197,649 shares issued and outstanding, actual, and 36,273,941 shares issued and outstanding, as adjusted[(1)]	34	37
Additional paid-in capital	412,710	552,607
Accumulated deficit	(280,395)	(280,395)
Accumulated other comprehensive loss	(21)	(21)
Total stockholders' equity	131,788	272,228
Total capitalization	$ 139,852	$ 280,292

(1) The actual and as adjusted common stock information excludes (i) 3,327,582 shares of common stock issuable upon the exercise of stock options outstanding as of September 30, 2015 at a weighted-average exercise price of $18.57 per share, (ii) 398,015 shares of common stock issuable upon the exercise of warrants to purchase shares of common stock outstanding as of September 30, 2015 at a weighted-average exercise price of $5.87 per share, (iii) 524,150 shares of common stock issuable upon vesting of outstanding restricted stock units as of September 30, 2015, (iv) 1,866,889 shares of common stock reserved for future issuance under our 2013 Equity Incentive Plan as of September 30, 2015, and (v) 251,213 shares of common stock reserved for future issuance under our Employee Stock Purchase Plan as of September 30, 2015.

Table of Contents

DILUTION

If you invest in our common stock, your interest will be diluted to the extent of the difference between the price per share you pay in this offering and the net tangible book value per share of our common stock immediately after this offering. Our net tangible book value of our common stock as of September 30, 2015 was approximately $131.8 million, or approximately $3.97 per share of common stock based upon 33,197,649 shares outstanding as of September 30, 2015. Net tangible book value per share is equal to our total tangible assets, less our total liabilities, divided by the total number of shares outstanding.

After giving effect to the sale by us of 3,076,292 shares of common stock at an assumed offering price of $48.76 per share, the last reported price of our common stock on the NASDAQ Global Market on December 31, 2015, and after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us, our as adjusted net tangible book value as of September 30, 2015 would have been approximately $272.2 million, or $7.50 per share. This would represent an immediate increase in net tangible book value of $3.53 per share to our existing stockholders and an immediate dilution in net tangible book value of $41.26 per share to new investors purchasing our common stock in this offering at the assumed public offering price. The following table illustrates this calculation on a per share basis:

Assumed offering price per share		$ 48.76
Net tangible book value per share as of September 30, 2015	$ 3.97	
Increase in net tangible book value per share attributable to the offering	3.53	
As adjusted net tangible book value per share after giving effect to the offering		$ 7.50
Dilution in net tangible book value per share to new investors in the offering		$ 41.26

This discussion of dilution, and the table quantifying it, assumes no exercise of any outstanding options to purchase shares of our common stock or warrants and no vesting of restricted stock units as of September 30, 2015 and no issuance of up to 461,443 shares of common stock that we may sell to the underwriters upon exercise of their option to purchase additional shares, based on the assumed public offering price of $48.76 per share, the last reported sale price of our common stock on the NASDAQ Global Market on December 31, 2015. The exercise of outstanding options or warrants to purchase shares of our common stock having an exercise price less than the public offering price, or the vesting of restricted stock units, would increase the dilutive effect to new investors.

If the underwriters exercise in full their option to purchase additional shares at the assumed public offering price of $48.76 per share, the last reported sale price of our common stock on the NASDAQ Global Market on December 31, 2015, the pro forma as adjusted net tangible book value after this offering would be approximately $7.99 per share, representing an increase in net tangible book value of approximately $4.02 per share to existing stockholders and immediate dilution in net tangible book value of approximately $40.77 per share to investors purchasing our common stock in this offering at the public offering price.

Table of Contents

MATERIAL UNITED STATES FEDERAL INCOME TAX CONSIDERATIONS FOR NON-U.S. HOLDERS

The following is a summary of the material U.S. federal income and estate tax considerations relating to the purchase, ownership and disposition of our common stock by Non-U.S. Holders (defined below). This summary does not purport to be a complete analysis of all the potential tax considerations relevant to Non-U.S. Holders of our common stock. This summary is based upon the Internal Revenue Code, the Treasury regulations promulgated or proposed thereunder and administrative and judicial interpretations thereof, all as of the date hereof and all of which are subject to change at any time, possibly on a retroactive basis.

This summary assumes that shares of our common stock are held as "capital assets" within the meaning of Section 1221 of the Internal Revenue Code (generally, property held for investment). This summary does not purport to deal with all aspects of U.S. federal income and estate taxation that might be relevant to particular Non-U.S. Holders in light of their particular investment circumstances or status, nor does it address specific tax considerations that may be relevant to particular persons (including, for example, financial institutions, broker-dealers, insurance companies, partnerships or other pass-through entities, certain U.S. expatriates, tax-exempt organizations, pension plans, "controlled foreign corporations", "passive foreign investment companies", corporations that accumulate earnings to avoid U.S. federal income tax, persons in special situations, such as those who have elected to mark securities to market or those who hold common stock as part of a straddle, hedge, conversion transaction, synthetic security or other integrated investment, or holders subject to the alternative minimum or the newly effective 3.8% Medicare tax on net investment income). In addition, except as explicitly addressed herein with respect to estate tax, this summary does not address estate and gift tax considerations or considerations under the tax laws of any state, local or non-U.S. jurisdiction.

For purposes of this summary, a "Non-U.S. Holder" means a beneficial owner of common stock that for U.S. federal income tax purposes is not classified as a partnership and is not:

- an individual who is a citizen or resident of the United States;
- a corporation or any other organization taxable as a corporation for U.S. federal income tax purposes, created or organized in or under the laws of the United States, any state thereof or the District of Columbia;
- an estate, the income of which is included in gross income for U.S. federal income tax purposes regardless of its source; or
- a trust if (1) a U.S. court is able to exercise primary supervision over the trust's administration and one or more U.S. persons have the authority to control all of the trust's substantial decisions or (2) the trust has a valid election in effect under applicable U.S. Treasury regulations to be treated as a U.S. person.

If an entity that is classified as a partnership for U.S. federal income tax purposes holds our common stock, the tax treatment of persons treated as its partners for U.S. federal income tax purposes will generally depend upon the status of the partner and the activities of the partnership. Partnerships and other entities that are classified as partnerships for U.S. federal income tax purposes and persons holding our common stock through a partnership or other entity classified as a partnership for U.S. federal income tax purposes are urged to consult their own tax advisors.

There can be no assurance that the Internal Revenue Service (IRS) will not challenge one or more of the tax consequences described herein, and we have not obtained, nor do we intend to obtain a ruling from the IRS with respect to the U.S. federal income or estate tax consequences to a Non-U.S. Holder of the purchase, ownership or disposition of our common stock.

Table of Contents

THIS SUMMARY IS FOR GENERAL INFORMATION ONLY AND IS NOT INTENDED TO BE TAX ADVICE. NON-U.S. HOLDERS ARE URGED TO CONSULT THEIR TAX ADVISORS CONCERNING THE U.S. FEDERAL INCOME AND ESTATE TAXATION, STATE, LOCAL AND NON-U.S. TAXATION AND OTHER TAX CONSEQUENCES TO THEM OF THE PURCHASE, OWNERSHIP AND DISPOSITION OF OUR COMMON STOCK.

Distributions on Our Common Stock

As discussed under "Dividend Policy" above, we do not currently expect to pay dividends. In the event that we do make a distribution of cash or property with respect to our common stock, any such distributions generally will constitute dividends for U.S. federal income tax purposes to the extent of our current and accumulated earnings and profits, if any, as determined under U.S. federal income tax principles. If a distribution exceeds our current and accumulated earnings and profits, the excess will constitute a return of capital and will first reduce the holder's adjusted tax basis in our common stock, but not below zero. Any remaining excess will be treated as capital gain, subject to the tax treatment described below in " Gain on Sale, Exchange or Other Taxable Disposition of Our Common Stock". Any such distribution would also be subject to the discussion below under the section titled " Additional Withholding and Reporting Requirements".

Dividends paid to a Non-U.S. Holder generally will be subject to a 30% U.S. federal withholding tax unless such Non-U.S. Holder provides us or our agent, as the case may be, with the appropriate IRS Form W-8, such as:

IRS Form W-8BEN or W-8BEN-E (or successor form) certifying, under penalties of perjury, a reduction in withholding under an applicable income tax treaty, or

IRS Form W-8ECI (or successor form) certifying that a dividend paid on common stock is not subject to withholding tax because it is effectively connected with a trade or business in the United States of the Non-U.S. Holder (in which case such dividend generally will be subject to regular graduated U.S. tax rates as described below).

The certification requirement described above must be provided to us or our agent prior to the payment of dividends and must be updated periodically. The certification also may require a Non-U.S. Holder that provides an IRS form or that claims treaty benefits to provide its U.S. taxpayer identification number. Special certification and other requirements apply in the case of certain Non-U.S. Holders that hold shares of our common stock through intermediaries or are pass-through entities for U.S. federal income tax purposes.

Each Non-U.S. Holder is urged to consult its own tax advisor about the specific methods for satisfying these requirements. A claim for exemption will not be valid if the person receiving the applicable form has actual knowledge or reason to know that the statements on the form are false.

If dividends are effectively connected with a trade or business in the United States of a Non-U.S. Holder (and, if required by an applicable income tax treaty, attributable to a U.S. permanent establishment), the Non-U.S. Holder, although exempt from the withholding tax described above (provided that the certifications described above are satisfied), generally will be subject to U.S. federal income tax on such dividends on a net income basis in the same manner as if it were a resident of the United States. In addition, if a Non-U.S. Holder is treated as a corporation for U.S. federal income tax purposes, the Non-U.S. Holder may be subject to an additional "branch profits tax" equal to 30% (unless reduced by an applicable income treaty) of its earnings and profits in respect of such effectively connected dividend income.

Non-U.S. Holders that do not timely provide us or our agent with the required certification, but which are eligible for a reduced rate of U.S. federal withholding tax pursuant to an income tax treaty, may obtain

Table of Contents

a refund or credit of any excess amount withheld by timely filing an appropriate claim for refund with the IRS.

Gain on Sale, Exchange or Other Taxable Disposition of Our Common Stock

Subject to the discussion below under the section titled " Additional Withholding and Reporting Requirements", in general, a Non-U.S. Holder will not be subject to U.S. federal income tax or withholding tax on gain realized upon such holder's sale, exchange or other taxable disposition of shares of our common stock unless (1) such Non-U.S. Holder is an individual who is present in the United States for 183 days or more in the taxable year of disposition, and certain other conditions are met, (2) we are or have been a "United States real property holding corporation", as defined in the Internal Revenue Code (a USRPHC), at any time within the shorter of the five-year period preceding the disposition and the Non-U.S. Holder's holding period in the shares of our common stock, and certain other requirements are met, or (3) such gain is effectively connected with the conduct by such Non-U.S. Holder of a trade or business in the United States (and, if required by an applicable income tax treaty, is attributable to a permanent establishment maintained by such Non-U.S. Holder in the United States).

If the first exception applies, the Non-U.S. Holder generally will be subject to U.S. federal income tax at a rate of 30% (or at a reduced rate under an applicable income tax treaty) on the amount by which such Non-U.S. Holder's capital gains allocable to U.S. sources exceed capital losses allocable to U.S. sources during the taxable year of the disposition. If the third exception applies, the Non-U.S. Holder generally will be subject to U.S. federal income tax with respect to such gain on a net income basis in the same manner as if it were a resident of the United States and a Non-U.S. Holder that is a corporation for U.S. federal income tax purposes may also be subject to a branch profits tax with respect to any earnings and profits attributable to such gain at a rate of 30% (or at a reduced rate under an applicable income tax treaty).

Generally, a corporation is a USRPHC only if the fair market value of its U.S. real property interests (as defined in the Internal Revenue Code) equals or exceeds 50% of the sum of the fair market value of its worldwide real property interests plus its other assets used or held for use in a trade or business. Although there can be no assurance in this regard, we believe that we are not, and do not anticipate becoming, a USRPHC. However, because the determination of whether we are a USRPHC depends on the fair market value of our U.S. real property interests relative to the fair market value of other business assets, there can be no assurance that we will not become a USRPHC in the future. Even if we became a USRPHC, a Non-U.S. Holder would not be subject to U.S. federal income tax on a sale, exchange or other taxable disposition of our common stock by reason of our status as USRPHC so long as our common stock is regularly traded on an established securities market at any time during the calendar year in which the disposition occurs and such Non-U.S. Holder does not own and is not deemed to own (directly, indirectly or constructively) more than 5% of our common stock at any time during the shorter of the five year period ending on the date of disposition and the holder's holding period. However, no assurance can be provided that our common stock will be regularly traded on an established securities market for purposes of the rules described above. Prospective investors are encouraged to consult their own tax advisors regarding the possible consequences to them if we are, or were to become, a USRPHC.

Additional Withholding and Reporting Requirements

Sections 1471 through 1474 of the Internal Revenue Code and related Treasury Regulations, together with other Treasury Department or IRS guidance issued thereunder, and intergovernmental agreements, legislation, rules and other official guidance adopted pursuant to such intergovernmental agreements (commonly referred to as "FATCA") generally will impose a U.S. federal withholding tax of 30% on payments to certain non-U.S. entities (including certain intermediaries), including dividends on our common stock and, on or after January 1, 2017 (which, under recent Treasury guidance, is expected to be delayed until on or after January 1, 2019), the gross proceeds from a sale or other disposition of shares of our common stock, unless such persons comply with a complicated U.S. information reporting, disclosure

Table of Contents

and certification regime. This regime requires, among other things, a broad class of persons to enter into agreements with the IRS to obtain, disclose and report information about their investors and account holders. An intergovernmental agreement between the United States and an applicable foreign country may, however, modify these requirements. The FATCA withholding rules currently apply to dividend payments on our common stock and will apply to payments of gross proceeds from the sale or other disposition of shares of our common stock occurring on or after January 1, 2017 (which, under recent Treasury guidance, is expected to be delayed until on or after January 1, 2019).

Prospective investors should consult their own tax advisors regarding the possible impact of these rules on their investment in our common stock, and the possible impact of these rules on the entities through which they hold our common stock, including, without limitation, the process and deadlines for meeting the applicable requirements to prevent the imposition of this 30% withholding tax under FATCA.

Backup Withholding and Information Reporting

We must report annually to the IRS and to each Non-U.S. Holder the gross amount of the distributions on our common stock paid to the holder and the tax withheld, if any, with respect to the distributions. Non-U.S. Holders may have to comply with specific certification procedures to establish that the holder is not a United States person (as defined in the Internal Revenue Code) in order to avoid backup withholding at the applicable rate, currently 28%, with respect to dividends on our common stock. Dividends paid to Non-U.S. Holders subject to the U.S. withholding tax, as described above under the section titled " Distributions on Our Common Stock", generally will be exempt from U.S. backup withholding.

Information reporting and backup withholding will generally apply to the proceeds of a disposition of our common stock by a Non-U.S. Holder effected by or through the U.S. office of any broker, U.S. or foreign, unless the holder certifies its status as a Non-U.S. Holder and satisfies certain other requirements, or otherwise establishes an exemption. Generally, information reporting and backup withholding will not apply to a payment of disposition proceeds to a Non-U.S. Holder where the transaction is effected outside the United States through a non-U.S. office of a broker. However, for information reporting purposes, dispositions effected through a non-U.S. office of a broker with substantial U.S. ownership or operations generally will be treated in a manner similar to dispositions effected through a U.S. office of a broker. Prospective investors should consult their own tax advisors regarding the application of the information reporting and backup withholding rules to them, including the availability of and procedure for obtaining an exemption from backup withholding.

Copies of information returns may be made available to the tax authorities of the country in which the Non-U.S. Holder resides or, in which the Non-U.S. Holder is incorporated, under the provisions of a specific treaty or agreement.

Backup withholding is not an additional tax. Any amounts withheld under the backup withholding rules from a payment to a Non-U.S. Holder can be refunded or credited against the Non-U.S. Holder's U.S. federal income tax liability, if any, provided that an appropriate claim is timely filed with the IRS.

U.S. Federal Estate Tax

Common stock owned (or treated as owned) by an individual who is not a citizen or a resident of the United States (as defined for U.S. federal estate tax purposes) at the time of death will be included in the individual's gross estate for U.S. federal estate tax purposes unless an applicable estate or other tax treaty provides otherwise, and therefore, may be subject to U.S. federal estate tax.

Table of Contents

UNDERWRITING

Under the terms and subject to the conditions in an underwriting agreement dated the date of this prospectus supplement, the underwriters named below, for whom Morgan Stanley & Co. LLC, Leerink Partners LLC and UBS Securities LLC are acting as representatives, have severally agreed to purchase, and we have agreed to sell to them, severally, the number of shares indicated below:

Name	Number of Shares
Morgan Stanley & Co. LLC	
Leerink Partners LLC	
UBS Securities LLC	
JMP Securities LLC	
Total:	

The underwriters and the representatives are collectively referred to as the "underwriters" and the "representatives," respectively. The underwriters are offering the shares of common stock subject to their acceptance of the shares from us and subject to prior sale. The underwriting agreement provides that the obligations of the several underwriters to pay for and accept delivery of the shares of common stock offered by this prospectus supplement are subject to the approval of certain legal matters by their counsel and to certain other conditions. The underwriters are obligated to take and pay for all of the shares of common stock offered by this prospectus supplement if any such shares are taken. However, the underwriters are not required to take or pay for the shares covered by the underwriters' option to purchase additional shares described below.

The underwriters initially propose to offer part of the shares of common stock directly to the public at the offering price listed on the cover page of this prospectus supplement and part to certain dealers. After the initial offering of the shares of common stock, the offering price and other selling terms may from time to time be varied by the representatives.

We have granted to the underwriters an option, exercisable for 30 days from the date of this prospectus supplement, to purchase up to additional shares of common stock at the public offering price listed on the cover page of this prospectus supplement, less underwriting discounts and commissions. To the extent the option is exercised, each underwriter will become obligated, subject to certain conditions, to purchase about the same percentage of the additional shares of common stock as the number listed next to the underwriter's name in the preceding table bears to the total number of shares of common stock listed next to the names of all underwriters in the preceding table.

The following table shows the per share and total public offering price, underwriting discounts and commissions, and proceeds before expenses to us. These amounts are shown assuming both no exercise and full exercise of the underwriters' option to purchase up to an additional shares of common stock.

		Total	
	Per Share	No Exercise	Full Exercise
Public offering price	$	$	$
Underwriting discounts and commissions:	$	$	$
Proceeds, before expenses, to us	$	$	$

The estimated offering expenses payable by us, exclusive of the underwriting discounts and commissions, are approximately $560,000. We have agreed to reimburse the underwriters for expenses relating to clearance of this offering with the Financial Industry Regulatory Authority up to $.

Our common stock is listed on the NASDAQ Global Market under the trading symbol "XLRN."

We and all directors and officers and certain holders of our outstanding stock and stock options have agreed that, without the prior written consent of Morgan Stanley & Co. LLC and Leerink Partners LLC on

Table of Contents

behalf of the underwriters, we will not and they will not, during the period ending 90 and 60 days, respectively, after the date of this prospectus supplement (collectively, the "restricted period"):

- offer, sell, contract to sell, pledge or otherwise dispose of, or enter into any transaction which is designed to, or might reasonably be expected to, result in the disposition (whether by actual disposition or effective economic disposition due to cash settlement or otherwise), directly or indirectly, any shares of our common stock or any securities convertible into, or exercisable or exchangeable for, such common stock;

- file any registration statement with the Securities and Exchange Commission relating to the offering of any shares of our common stock or any securities convertible into, or exercisable or exchangeable for, such common stock; or

- establish or increase a put equivalent position or liquidate or decrease a call equivalent position within the meaning of Section 16 of the Exchange and the rules and regulations of the Securities and Exchange Commission promulgated thereunder with respect to, any shares of our common stock or any securities convertible into, or exercisable or exchangeable for, such common stock, or publicly announce an intention to effect any such transaction,

whether any such transaction described above is to be settled by delivery of common stock or such other securities, in cash or otherwise. In addition, we and each such person agrees that, without the prior written consent of Morgan Stanley & Co. LLC and Leerink Partners LLC on behalf of the underwriters, we or such other person will not, during the restricted period, make any demand for, or exercise any right with respect to, the registration of any shares of common stock or any security convertible into or exercisable or exchangeable for common stock.

The restrictions described in the immediately preceding paragraph do not apply to:

- shares of common stock disposed of as bona fide gifts where (x) each recipient of a gift of shares agrees in writing to be bound by the same restrictions in place for the transferor for the duration of the restricted period and (y) no filing under Section 13 or Section 16(a) of the Exchange Act reporting a reduction in beneficial ownership of the common stock shall be required or shall be voluntarily made by the transferor during the restricted period;

- the exercise of options to purchase shares or common stock or the receipt of shares of common stock upon the vesting of restricted stock awards disclosed in this prospectus supplement or any related transfer of shares of common stock to us (x) deemed to occur upon the cashless exercise of such options or (y) for the purpose of paying the exercise price of such options or for paying taxes due as a result of the exercise of such options or as a result of the vesting of such shares of common stock, it being understood that all shares of common stock received upon such exercise or transfer will remain subject to the restrictions described above during the restricted period;

- transfers of any shares of our common stock or any securities convertible into, or exercisable or exchangeable for, such common stock to any affiliate (as such term is defined in Rule 405 of the Securities Act), limited partners, general partners, limited liability company members of stockholders of the transferor, or if the transferor is a corporation to any wholly-owned subsidiary of such corporation, provided that in each case (x) the recipient agrees in writing to be bound by the same restrictions in place for the transferor for the duration of the restricted period, and (y) no filing under Section 13 or Section 16(a) of the Exchange Act reporting a reduction in beneficial ownership of the common stock shall be required or shall be voluntarily made by the transferor or the transferee during the restricted period;

- the establishment of a trading plan pursuant to Rule 10b5-1 under the Exchange Act for the transfer of shares of common stock, provided that such plan does not provide for the transfer of

Table of Contents

common stock during the restricted period and no filing or other public announcement shall be required or shall be voluntarily made during the restricted period;

transfers pursuant to a trading plan established prior to the date hereof pursuant to Rule 10b5-1 under the Exchange Act for the transfer of shares of common stock, provided that (x) any filing under Section 13 or Section 16(a) of the Exchange Act made during the restricted period shall clearly indicate in the footnotes thereto that the filing relates to the circumstances described above and (y) we will not otherwise voluntarily effect any public filing or report during the restricted period; or

transfers of any shares of our common stock or any securities convertible into, or exercisable or exchangeable for, such common stock pursuant to a sale of, or an offer to purchase, 100% of our outstanding shares of common stock that is after the date of the underwriting agreement and is approved by our board of directors, whether pursuant to a merger, tender offer or otherwise, to a third party or group of third parties, provided that in the event that such merger, tender offer or other transaction is not completed, such shares of our common stock or any securities convertible into, or exercisable or exchangeable for, such common stock shall remain subject to the restrictions described above during the restricted period.

Morgan Stanley & Co. LLC and Leerink Partners LLC, in their sole discretion, may release the common stock and other securities subject to the lock-up agreements described above in whole or in part at any time.

In order to facilitate the offering of the common stock, the underwriters may engage in transactions that stabilize, maintain or otherwise affect the price of the common stock. Specifically, the underwriters may sell more shares than they are obligated to purchase under the underwriting agreement, creating a short position. A short sale is covered if the short position is no greater than the number of shares available for purchase by the underwriters under the option. The underwriters can close out a covered short sale by exercising the option or purchasing shares in the open market. In determining the source of shares to close out a covered short sale, the underwriters will consider, among other things, the open market price of shares compared to the price available under the option. The underwriters may also sell shares in excess of the option, creating a naked short position.

The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the common stock in the open market after pricing that could adversely affect investors who purchase in this offering. As an additional means of facilitating this offering, the underwriters may bid for, and purchase, shares of common stock in the open market to stabilize the price of the common stock. These activities may raise or maintain the market price of the common stock above independent market levels or prevent or retard a decline in the market price of the common stock. The underwriters are not required to engage in these activities and may end any of these activities at any time.

We and the underwriters have agreed to indemnify each other against certain liabilities, including liabilities under the Securities Act.

A prospectus supplement in electronic format may be made available on websites maintained by one or more underwriters, or selling group members, if any, participating in this offering. The representatives may agree to allocate a number of shares of common stock to underwriters for sale to their online brokerage account holders. Internet distributions will be allocated by the representatives to underwriters that may make Internet distributions on the same basis as other allocations.

The underwriters and their respective affiliates are full service financial institutions engaged in various activities, which may include securities trading, commercial and investment banking, financial advisory, investment management, investment research, principal investment, hedging, financing and brokerage activities. Certain of the underwriters and their respective affiliates have, from time to time, performed,

Table of Contents

and may in the future perform, various financial advisory and investment banking services for us, for which they received or will receive customary fees and expenses.

In addition, in the ordinary course of their various business activities, the underwriters and their respective affiliates may make or hold a broad array of investments and actively trade debt and equity securities (or related derivative securities) and financial instruments (including bank loans) for their own account and for the accounts of their customers and may at any time hold long and short positions in such securities and instruments. Such investment and securities activities may involve our securities and instruments. The underwriters and their respective affiliates may also make investment recommendations or publish or express independent research views in respect of such securities or instruments and may at any time hold, or recommend to clients that they acquire, long or short positions in such securities and instruments.

Selling Restrictions

Canada

The securities may be sold in Canada only to purchasers purchasing, or deemed to be purchasing, as principal that are accredited investors, as defined in National Instrument 45-106 Prospectus Exemptions or subsection 73.3(1) of the Securities Act (Ontario), and are permitted clients, as defined in National Instrument 31-103 Registration Requirements, Exemptions and Ongoing Registrant Obligations. Any resale of the securities must be made in accordance with an exemption from, or in a transaction not subject to, the prospectus requirements of applicable securities laws.

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if this prospectus (including any amendment thereto) contains a misrepresentation, provided that the remedies for rescission or damages are exercised by the purchaser within the time limit prescribed by the securities legislation of the purchaser's province or territory. The purchaser should refer to any applicable provisions of the securities legislation of the purchaser's province or territory for particulars of these rights or consult with a legal advisor.

Pursuant to section 3A.3 of National Instrument 33-105 Underwriting Conflicts (NI 33-105), the underwriters are not required to comply with the disclosure requirements of NI 33-105 regarding underwriter conflicts of interest in connection with this offering.

European Economic Area

In relation to each Member State of the European Economic Area which has implemented the Prospectus Directive (each, a "Relevant Member State") an offer to the public of any shares of our common stock may not be made in that Relevant Member State, except that an offer to the public in that Relevant Member State of any shares of our common stock may be made at any time under the following exemptions under the Prospectus Directive, if they have been implemented in that Relevant Member State:

(a) to any legal entity which is a qualified investor as defined in the Prospectus Directive;

(b) to fewer than 100 or, if the Relevant Member State has implemented the relevant provision of the 2010 PD Amending Directive, 150, natural or legal persons (other than qualified investors as defined in the Prospectus Directive), as permitted under the Prospectus Directive, subject to obtaining the prior consent of the representatives for any such offer; or

(c) in any other circumstances falling within Article 3(2) of the Prospectus Directive, provided that no such offer of shares of our common stock shall result in a requirement for the publication by us or any underwriter of a prospectus pursuant to Article 3 of the Prospectus Directive.

For the purposes of this provision, the expression an "offer to the public" in relation to any shares of our common stock in any Relevant Member State means the communication in any form and by any means of sufficient information on the terms of the offer and any shares of our common stock to be offered so as

Table of Contents

to enable an investor to decide to purchase any shares of our common stock, as the same may be varied in that Member State by any measure implementing the Prospectus Directive in that Member State, the expression "Prospectus Directive" means Directive 2003/71/EC (and amendments thereto, including the 2010 PD Amending Directive, to the extent implemented in the Relevant Member State), and includes any relevant implementing measure in the Relevant Member State, and the expression "2010 PD Amending Directive" means Directive 2010/73/EU.

United Kingdom

Each underwriter has represented and agreed that:

(a) it has only communicated or caused to be communicated and will only communicate or cause to be communicated an invitation or inducement to engage in investment activity (within the meaning of Section 21 of the Financial Services and Markets Act 2000 ("FSMA") received by it in connection with the issue or sale of the shares of our common stock in circumstances in which Section 21(1) of the FSMA does not apply to us; and

(b) it has complied and will comply with all applicable provisions of the FSMA with respect to anything done by it in relation to the shares of our common stock in, from or otherwise involving the United Kingdom.

Switzerland

This prospectus supplement does not constitute an issue prospectus pursuant to Article 652a or Article 1156 of the Swiss Code of Obligations ("CO") and the shares will not be listed on the SIX Swiss Exchange. Therefore, this prospectus supplement may not comply with the disclosure standards of the CO and/or the listing rules (including any prospectus schemes) of the SIX Swiss Exchange. Accordingly, the shares may not be offered to the public in or from Switzerland, but only to a selected and limited circle of investors, which do not subscribe to the shares with a view to distribution.

Japan

Our securities have not been and will not be registered under the Financial Instruments and Exchange Law of Japan (the "Financial Instruments and Exchange Law") and our securities will not be offered or sold, directly or indirectly, in Japan, or to, or for the benefit of, any resident of Japan (which term as used herein means any person resident in Japan, including any corporation or other entity organized under the laws of Japan), or to others for re-offering or resale, directly or indirectly, in Japan, or to a resident of Japan, except pursuant to an exemption from the registration requirements of, and otherwise in compliance with, the Financial Instruments and Exchange Law and any other applicable laws, regulations and ministerial guidelines of Japan.

LEGAL MATTERS

The validity of the shares of common stock offered hereby will be passed upon for us by Ropes & Gray LLP, Boston, Massachusetts. Certain legal matters will be passed upon for the underwriters by Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C., Boston, Massachusetts.

EXPERTS

The consolidated financial statements of Acceleron Pharma Inc. appearing in Acceleron Pharma Inc.'s Annual Report (Form 10-K) for the year ended December 31, 2014, and the effectiveness of Acceleron Pharma Inc.'s internal control over financial reporting as of December 31, 2014 have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their reports thereon, included therein, and incorporated herein by reference. Such consolidated financial statements are incorporated herein by reference in reliance upon such reports given on the authority of such firm as experts in accounting and auditing.

Table of Contents

PROSPECTUS

ACCELERON PHARMA INC.

$300,000,000

Common Stock

We may offer and sell from time to time, in one or more series or issuances and on terms determined at the time of the offering, any combination of the securities described in this prospectus. In addition, selling security holders to be named in a prospectus supplement may offer our securities from time to time. The aggregate offering price of all securities sold under this prospectus will not exceed $300,000,000.

Specific terms of any offering will be provided in a supplement to this prospectus. Any prospectus supplement may also add, update or change information contained in this prospectus. You should carefully read this prospectus and the applicable prospectus supplement as well as the documents incorporated or deemed to be incorporated by reference in this prospectus before you purchase any of the securities offered hereby.

These securities may be offered and sold in the same offering or in separate offerings, to or through underwriters, dealers or agents or directly to purchasers. The names of any underwriters, dealers or agents involved in the sale of our securities and their compensation will be described in the applicable prospectus supplement.

General Information

Our common stock is traded on the NASDAQ Global Market under the symbol "XLRN". On December 31, 2015, the closing price of our common stock was $48.76.

Investing in our securities involves risks. See "Risk Factors" on page 3 and in any applicable prospectus supplement and in the documents incorporated by reference in this prospectus for a discussion of the factors you should carefully consider before deciding to purchase these securities.

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

The date of this prospectus is January 4, 2016.

Table of Contents

TABLE OF CONTENTS

ABOUT THIS PROSPECTUS	1
OUR BUSINESS	2
RISK FACTORS	3
CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS	3
USE OF PROCEEDS	5
PLAN OF DISTRIBUTION	6
WHERE YOU CAN FIND MORE INFORMATION	7
INCORPORATION OF CERTAIN DOCUMENTS BY REFERENCE	7
LEGAL MATTERS	8
EXPERTS	8

Table of Contents

ABOUT THIS PROSPECTUS

This prospectus is a part of a registration statement that we filed with the Securities and Exchange Commission (the "SEC") using a "shelf" registration process. Under this shelf registration process, any combination of the securities described in this prospectus may be sold in one or more offerings. The aggregate public offering price of the securities we sell in these transactions will not exceed $300,000,000. Each time securities are sold under this shelf registration, we will provide a prospectus supplement that will contain specific information about the terms of that offering. The prospectus supplement may also add, update or change information contained in this prospectus. You should read both this prospectus and the applicable prospectus supplement, including all documents incorporated herein by reference, together with additional information described under "Where You Can Find More Information" below.

We have not authorized any dealer, agent or other person to give any information or to make any representation other than those contained or incorporated by reference in this prospectus and any accompanying prospectus supplement. You must not rely upon any information or representation not contained or incorporated by reference in this prospectus or an accompanying prospectus supplement. This prospectus and the accompanying prospectus supplement, if any, do not constitute an offer to sell or the solicitation of an offer to buy any securities other than the registered securities to which they relate, nor do this prospectus and any accompanying prospectus supplement constitute an offer to sell or the solicitation of an offer to buy securities in any jurisdiction to any person to whom it is unlawful to make such offer or solicitation in such jurisdiction. You should not assume that the information contained in this prospectus and the accompanying prospectus supplement, if any, is accurate on any date subsequent to the date set forth on the front of the document or that any information we have incorporated by reference is correct on any date subsequent to the date of the document incorporated by reference, even though this prospectus and any accompanying prospectus supplement is delivered or securities are sold on a later date.

Unless the context otherwise requires, "Acceleron", the "Company", "we", "us", "our" and similar names refer to Acceleron Pharma Inc. and its wholly owned subsidiary.

Table of Contents

OUR BUSINESS

Our Company

We are a clinical stage biopharmaceutical company focused on the discovery, development and commercialization of novel therapeutic candidates that are based on the mechanisms that the human body uses to regulate the growth and repair of its cells and tissues. Our research focuses on key natural regulators of cellular growth and repair, particularly the Transforming Growth Factor-Beta, or TGF-ß protein superfamily. We believe that we are a leading company in discovering and developing therapeutic candidates that regulate cellular growth and repair. By combining our discovery and development expertise, including our proprietary knowledge of the TGF-ß superfamily, and our internal protein engineering and manufacturing capabilities, we have built a highly productive discovery and development platform that has generated innovative therapeutic candidates with novel mechanisms of action. These differentiated therapeutic candidates have the potential to significantly improve clinical outcomes for patients across many fields of medicine, and we have focused our discovery and development efforts on treatments for cancer and rare diseases.

Our common stock is listed on the NASDAQ Global Market under the symbol "XLRN". Our principal executive offices are located at 128 Sidney Street, Cambridge, Massachusetts 02139, and our telephone number is (617) 649-9200. Our website address is www.acceleronpharma.com. The information found on our website is not part of this prospectus.

Table of Contents

RISK FACTORS

Investing in our securities involves risk. Prior to making a decision about investing in our securities, you should carefully consider the specific risk factors discussed under the heading "Risk Factors" in our Annual Report on Form 10-K for the year ended December 31, 2014, on file with the SEC, which is incorporated by reference into this prospectus and any prospectus supplement in its entirety, as the same may be amended, supplemented or superseded from time to time by our filings under the Securities Exchange Act of 1934, as amended (the "Exchange Act"), together with those under the heading "Risk Factors" in any applicable prospectus supplement and all of the other information contained or incorporated by reference in this prospectus or such prospectus supplement. See "Where You Can Find More Information." The risks and uncertainties we describe are not the only ones we face. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also affect our operations. If any of these risks were to occur, our business, financial condition or results of operations would likely suffer. In that event, the trading price of our common stock could decline, and you could lose all or part of your investment.

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus, any prospectus supplement and the other documents we have filed with the SEC that are incorporated herein by reference contain forward-looking statements that involve risks and uncertainties, as well as assumptions that, if they never materialize or prove incorrect, could cause our results to differ materially from those expressed or implied by such forward-looking statements. In some cases, these forward-looking statements can be identified by the use of forward-looking terminology. The statements contained in this prospectus that are not purely historical are "forward-looking statements" within the meaning of Section 27A of the Securities Act. The terms "anticipate", "believe", "contemplate", "continue", "could", "estimate", "expect", "forecast", "goal", "intend", "may", "plan", "potential", "predict", "project", "should", "strategy", "target", "will", "would", "vision", or, in each case, the negative or other variations thereon or other similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

The forward-looking statements in this prospectus, any prospectus supplement and the other documents we have filed with the SEC that are incorporated herein by reference include, among other things, statements regarding our intentions, beliefs, projections, outlook, analyses or current expectations concerning, among other things:

- our ongoing and planned preclinical studies and clinical trials;
- clinical trial data and the timing of results of our ongoing clinical trials;
- our plans to develop and commercialize dalantercept, ACE-083 and other potential therapeutic candidates, and our and Celgene's plans to develop and commercialize luspatercept and sotatercept;
- the potential benefits of strategic partnership agreements and our ability to enter into selective strategic partnership arrangements;
- the timing of, and our and Celgene's ability to, obtain and maintain regulatory approvals for our therapeutic candidates;
- the rate and degree of market acceptance and clinical utility of any approved therapeutic candidate, particularly in specific patient populations;
- our ability to expand our development capabilities and our ability to quickly and efficiently identify and develop therapeutic candidates, including antibodies and proteins from our IntelliTrap™ platform;

Table of Contents

our commercialization, marketing and manufacturing capabilities and strategy;

our intellectual property position; and

our estimates regarding our results of operations, financial condition, liquidity, capital requirements, prospects, growth and strategies.

Given these uncertainties, you should not place undue reliance on these forward-looking statements. You should read this prospectus, any supplements to this prospectus and the documents that we reference in this prospectus with the understanding that our actual future results may be materially different from what we expect. Except as required by law, we do not undertake any obligation to update or revise any forward-looking statements contained in this prospectus or any supplement to this prospectus, whether as a result of new information, future events or otherwise.

Table of Contents

USE OF PROCEEDS

Except as otherwise provided in the applicable prospectus supplement, we intend to use the net proceeds from the sale of the securities offered by us by this prospectus for general corporate purposes, including working capital, capital expenditures, research, development and manufacturing expenditures, clinical trial expenditures, general and administrative expenses, or commercial expenditures. We may temporarily invest the net proceeds in short-term, interest-bearing, investment-grade securities, certificates of deposit or government securities until they are used for their stated purpose. We have not determined the amount of net proceeds to be used specifically for such purposes. As a result, management will retain broad discretion over the allocation of net proceeds.

Additional information on the use of net proceeds from the sale of securities offered by us by this prospectus may be set forth in the prospectus supplement relating to the specific offering.

Table of Contents

PLAN OF DISTRIBUTION

We and any selling security holders may sell securities in any of the ways described below or in any combination:

- to or through underwriters or dealers;
- through one or more agents; or
- directly to purchasers or to a single purchaser.

The distribution of the securities may be effected from time to time in one or more transactions:

- at a fixed price, or prices, which may be changed from time to time;
- at market prices prevailing at the time of sale;
- at prices related to such prevailing market prices; or
- at negotiated prices.

Each prospectus supplement will describe the method of distribution of the securities and any applicable restrictions.

The prospectus supplement with respect to the securities of a particular series will describe the terms of the offering of the securities, including the following:

- the name or names of any underwriters, dealers or agents and the amounts of securities underwritten or purchased by each of them;
- the public offering price of the securities and the proceeds to us and any discounts, commissions or concessions allowed or reallowed or paid to dealers; and
- any securities exchanges on which the securities may be listed.

Any offering price and any discounts or concessions allowed or reallowed or paid to dealers may be changed from time to time.

Only the agents or underwriters named in each prospectus supplement are agents or underwriters in connection with the securities being offered thereby.

We may authorize underwriters, dealers or other persons acting as our agents to solicit offers by certain institutions to purchase securities from us pursuant to delayed delivery contracts providing for payment and delivery on the date stated in each applicable prospectus supplement. Each contract will be for an amount not less than, and the aggregate amount of securities sold pursuant to such contracts shall not be less nor more than, the respective amounts stated in each applicable prospectus supplement. Institutions with whom the contracts, when authorized, may be made include commercial and savings banks, insurance companies, pension funds, investment companies, educational and charitable institutions and other institutions, but shall in all cases be subject to our approval. Delayed delivery contracts will be subject only to those conditions set forth in each applicable prospectus supplement, and each prospectus supplement will set forth any commissions we pay for

solicitation of these contracts.

Agents, underwriters and other third parties described above may be entitled to indemnification by us against certain civil liabilities, including liabilities under the Securities Act, or to contribution from us with respect to payments that the agents, underwriters or other third parties may be required to make in respect thereof. Agents, underwriters and such other third parties may be customers of, engage in transactions with, or perform services for us in the ordinary course of business.

Table of Contents

One or more firms, referred to as "remarketing firms," may also offer or sell the securities, if a prospectus supplement so indicates, in connection with a remarketing arrangement upon their purchase. Remarketing firms will act as principals for their own accounts or as our agents. These remarketing firms will offer or sell the securities in accordance with the terms of the securities. Each prospectus supplement will identify and describe any remarketing firm and the terms of its agreement, if any, with us and will describe the remarketing firm's compensation. Remarketing firms may be deemed to be underwriters in connection with the securities they remarket. Remarketing firms may be entitled under agreements that may be entered into with us to indemnification by us against certain civil liabilities, including liabilities under the Securities Act, and may be customers of, engage in transactions with or perform services for us in the ordinary course of business.

Certain underwriters may use this prospectus and any accompanying prospectus supplement for offers and sales related to market-making transactions in the securities. These underwriters may act as principal or agent in these transactions, and the sales will be made at prices related to prevailing market prices at the time of sale.

The securities may be new issues of securities and may have no established trading market. The securities may or may not be listed on a securities exchange. Underwriters may make a market in these securities, but will not be obligated to do so and may discontinue any market making at any time without notice. We can make no assurance as to the liquidity of, or the existence of trading markets for, any of the securities.

Certain persons participating in an offering may engage in overallotment, stabilizing transactions, short covering transactions and penalty bids in accordance with rules and regulations under the Securities Exchange Act. Overallotment involves sales in excess of the offering size, which create a short position. Stabilizing transactions permit bids to purchase the underlying security so long as the stabilizing bids do not exceed a specified maximum. Short covering transactions involve purchases of the securities in the open market after the distribution is completed to cover short positions. Penalty bids permit the underwriters to reclaim a selling concession from a dealer when the securities originally sold by the dealer are purchased in a short covering transaction to cover short positions. Those activities may cause the price of the securities to be higher than it would otherwise be. If commenced, the underwriters may discontinue any of the activities at any time.

WHERE YOU CAN FIND MORE INFORMATION

We file annual and quarterly reports, current reports, proxy statements, and other information with the SEC. We make these documents publicly available, free of charge, on our website at www.acceleronpharma.com as soon as reasonably practicable after filing such documents with the SEC.

You may read and copy any materials that we file with the SEC at its Public Reference Room, 100 F Street, N.E., Washington, D.C. 20549. You may obtain information on the operation of the Public Reference Room by calling the SEC at (800) 732-0330. Our filings are also available to the public from the website maintained by the SEC at http://www.sec.gov.

INCORPORATION OF CERTAIN DOCUMENTS BY REFERENCE

The SEC allows us to "incorporate by reference" into this prospectus the information we file with it, which means that we can disclose important information to you by referring you to those documents. The information incorporated by reference is considered to be part of this prospectus, and information in documents that we file later with the SEC will automatically update and supersede information in this prospectus. We incorporate by reference into this prospectus the documents listed below and any future filings made by us with the SEC under Section 13(a), 13(c), 14 or 15(d) of the Exchange Act until we terminate or complete this offering (other than documents or information deemed to have

Table of Contents

been furnished and not filed in accordance with SEC rules). We hereby incorporate by reference the following documents:

- Our Annual Report on Form 10-K for the year ended December 31, 2014, filed March 2, 2015;
- Our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2015, June 30, 2015 and September 30, 2015, filed with the SEC on May 7, 2015, August 6, 2015 and November 4, 2015, respectively;
- Our Definitive Proxy Statement on Schedule 14A, filed with the SEC on April 17, 2015;
- Our Current Reports on Form 8-K filed with the SEC on March 6, 2015, May 5, 2015 (as amended on May 6, 2015), June 9, 2015, June 15, 2015, September 11, 2015, October 23, 2015, December 10, 2015; and December 17, 2015; and
- The description of our common stock contained in our Registration Statement on Form 8-A, filed September 9, 2013, including any amendments or reports filed for the purpose of updating such description.

A statement contained in a document incorporated by reference into this prospectus shall be deemed to be modified or superseded for purposes of this prospectus to the extent that a statement contained in this prospectus, any future prospectus supplement or in any other subsequently filed document that is also incorporated in this prospectus modifies or replaces such statement. Any statements so modified or superseded shall not be deemed, except as so modified or superseded, to constitute a part of this prospectus. You should not assume that the information in this prospectus or in the documents incorporated by reference is accurate as of any date other than the date on the front of this prospectus or those documents.

You may request a copy of these documents, which will be provided to you at no cost, by contacting:

Acceleron Pharma Inc.
128 Sidney Street
Cambridge, Massachusetts 02139
(617) 649-9200

Copies of these filings are also available, without charge, through the "Investors & Media" section of our website (www.acceleronpharma.com) as soon as reasonably practicable after they are filed electronically with the SEC. The information contained on our website is not a part of this prospectus.

LEGAL MATTERS

The validity of the issuance of the securities offered hereby will be passed upon for us by Ropes & Gray LLP, Boston, Massachusetts. The validity of any securities will be passed upon for any underwriters or agents by counsel that we will name in the applicable prospectus supplement.

EXPERTS

The consolidated financial statements of Acceleron Pharma Inc. appearing in Acceleron Pharma Inc.'s Annual Report (Form 10-K) for the year ended December 31, 2014, and the effectiveness of Acceleron Pharma Inc.'s internal control over financial reporting as of December 31, 2014 have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their reports thereon, included therein, and incorporated herein by reference. Such consolidated financial statements are incorporated herein by reference in reliance upon such reports given on the authority of such firm as experts in accounting and auditing.

Table of Contents

$150,000,000

Acceleron Pharma Inc.

COMMON STOCK

Prospectus Supplement

MORGAN STANLEY
LEERINK PARTNERS
UBS INVESTMENT BANK
JMP SECURITIES