

ACCELERON PHARMA INC

FORM 424B5

(Prospectus filed pursuant to Rule 424(b)(5))

Filed 09/19/17

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| Telephone | 617-649-9200 |
| CIK | 0001280600 |
| Symbol | XLRN |
| SIC Code | 2836 - Biological Products, (No Diagnostic Substances) |
| Industry | Biotechnology & Medical Research |
| Sector | Healthcare |
| Fiscal Year | 12/31 |

Subject to completion, dated September 19, 2017

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.

Preliminary prospectus supplement

(To prospectus dated September 19, 2017)

\$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 September 18, 2017, the last reported sale price of our common stock was \$39.38 per share.

Our collaboration partner and one of our principal stockholders, Celgene Corporation, or 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-50 of this prospectus supplement, in an amount that will result in Celgene owning up to its current percentage ownership of our total outstanding common stock as of the date of this 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-11 of this prospectus supplement, the accompanying prospectus and the other documents that are incorporated by reference herein.

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.

| | 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.

The shares of common stock will be ready for delivery on or about September , 2017.

J.P. Morgan

Citigroup

Leerink Partners

September , 2017.

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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.

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 ACE-083 and our other preclinical 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 anticipated milestone payments under our collaboration agreements with Celgene;
- 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 quickly and efficiently identify and develop therapeutic candidates;
- our commercialization, marketing and manufacturing capabilities and strategy;
- our intellectual property position; and
- our estimates regarding our operating capital requirements, 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-11 of this prospectus supplement to better understand the risks and uncertainties inherent in our business and underlying any forward-looking statements.

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, 2017, filed with the SEC on March 1, 2017;
- Our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2017 and June 30, 2017, filed with the SEC on May 8, 2017 and August 3, 2017, respectively;
- The information specifically incorporated by reference into our Annual Report on Form 10-K for the fiscal year ended December 31, 2016 from our Definitive Proxy Statement on Schedule 14A, filed with the SEC on April 13, 2017;
- Our Current Reports on Form 8-K filed with the SEC on April 27, 2017, May 2, 2017, May 10, 2017, June 6, 2017, June 15, 2017, June 30, 2017, July 19, 2017 and September 19, 2017; and
- The description of our common stock contained in our Registration Statement on Form 8-A, filed with the SEC on September 13, 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.

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.

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 leading biopharmaceutical company in the discovery and development of TGF-beta therapeutics to treat serious and rare diseases. Our research focuses on key natural regulators of cellular growth and repair, particularly the Transforming Growth Factor-Beta, or TGF-beta, protein superfamily. By combining our discovery and development expertise, including our proprietary knowledge of the TGF-beta superfamily, and our internal protein engineering and manufacturing capabilities, we have generated several innovative therapeutic candidates, all of which encompass novel potential first-in-class mechanisms of action. We have focused and prioritized our research and development activities within three key therapeutic areas, and if successful, these candidates could have the potential to significantly improve clinical outcomes for patients across these areas of high, unmet need.

Luspatercept, our lead program, and sotatercept, are partnered with Celgene Corporation, or Celgene. Luspatercept is designed to promote red blood cell production through a novel mechanism, and is being developed to treat chronic anemia and associated complications in myelodysplastic syndromes, or MDS, beta-thalassemia, and myelofibrosis. Celgene is currently conducting two Phase 3 clinical trials with luspatercept; one for the treatment of patients with lower risk MDS, known as the "MEDALIST" trial, and another for the treatment of patients with beta-thalassemia, also known as the "BELIEVE" trial. Celgene recently initiated a Phase 2 clinical trial for the treatment of patients with myelofibrosis, a rare bone marrow disorder, and we expect Celgene to enroll the first patient in this study by the end of this year. We further expect Celgene to initiate a Phase 3 clinical trial, the "COMMANDS" trial, in first-line, lower-risk MDS patients in early 2018. In addition, a Phase 2 trial in non-transfusion-dependent beta-thalassemia patients, referred to as the "BEYOND" trial, is in the planning stages and we expect Celgene to initiate the BEYOND trial by the end of this year. If luspatercept were to receive regulatory approval for each of these indications in the United States and Europe, we believe that there is an aggregate sales opportunity for this product in excess of \$2 billion.

For sotatercept, we recently announced that Celgene granted back to us the rights to fund, develop, and lead the global commercialization of sotatercept in pulmonary arterial hypertension, or PAH. PAH is a rare and chronic, rapidly progressing disorder characterized by the constriction of small pulmonary arteries, resulting in abnormally high blood pressure in the pulmonary arteries. We expect to initiate a Phase 2 clinical trial for the treatment of patients with PAH in the first half of 2018.

Celgene is responsible for paying 100% of the development costs for all clinical trials for luspatercept as well as clinical trials with sotatercept, outside of pulmonary hypertension. We may receive a maximum of \$545.0 million for the potential development, regulatory and commercial milestone payments. If these therapeutic candidates are commercialized, we are eligible to receive a royalty on net sales in the low-to-mid 20% range. We have the right to co-promote luspatercept and, outside of pulmonary hypertension, sotatercept, if approved, in North America, for which our commercialization costs will be

entirely funded by Celgene. See "Recent Developments" below for additional details concerning the terms of our rights to develop and commercialize sotatercept in pulmonary hypertension.

We are independently developing our wholly-owned neuromuscular candidate, ACE-083. ACE-083 is designed for the treatment of focal muscle disorders, and we are currently conducting a Phase 2 clinical trial with ACE-083 in patients with facioscapulohumeral dystrophy, or FSHD, as well as a Phase 2 clinical trial with ACE-083 in patients with Charcot-Marie-Tooth disease, or CMT. We expect to report part 1 preliminary results from cohort 1 of our Phase 2 clinical trial in patients with FSHD in late 2017, and we expect to report preliminary results from part 1 of all dose-escalation cohorts in both of our Phase 2 clinical trials with ACE-083 in 2018. We previously reported data from the Phase 1 clinical trial of ACE-083 showing marked increases in the volume of muscles treated with ACE-083, measured using magnetic resonance imaging or MRI.

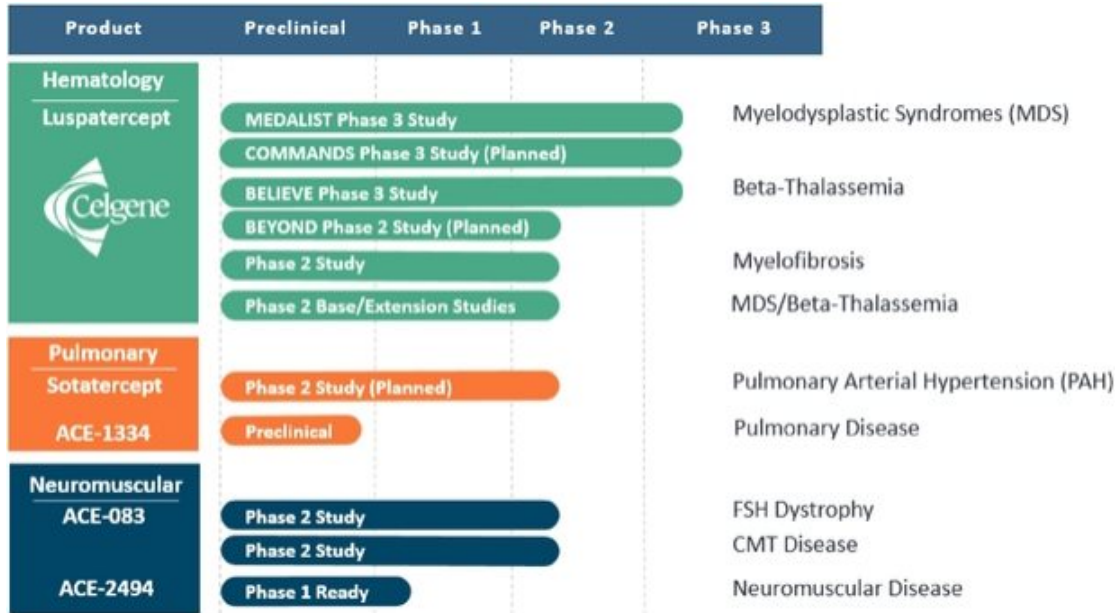
In addition to our clinical programs, we are conducting research within our three focused disease areas—hematologic, neuromuscular and pulmonary—in order to identify new therapeutic candidates to advance into clinical trials. To this end, we expanded our discovery efforts with our proprietary platform technology, IntelliTrap™. We have nominated an IntelliTrap™ molecule, ACE-2494, a systemic muscle agent, as a candidate for clinical development, and we expect to initiate a Phase 1 healthy volunteer study in late 2017.

As of June 30, 2017, our operations have been primarily funded by \$105.1 million in equity investments from venture investors, \$337.3 million from public investors, \$96.2 million in equity investments from our collaboration partners, and \$268.0 million in upfront payments, milestones, and net research and development payments from our collaboration partners.

Recent developments

On September 18, 2017, we and Celgene amended and restated the sotatercept collaboration, license and option agreement, originally executed on February 20, 2008 and amended on August 2, 2011. The amended agreement provides us with global access to sotatercept for development and commercialization in pulmonary hypertension. Under the amended agreement, we will fund and conduct all research and development activities for sotatercept in pulmonary hypertension. If sotatercept is commercialized to treat pulmonary hypertension and we recognize such revenue, then Celgene will be eligible to receive a royalty in the low 20% range on global net sales. In certain circumstances Celgene may recognize revenue related to the commercialization of sotatercept in pulmonary hypertension, and in this scenario we will be eligible to receive a royalty from Celgene such that the economic position of the parties is equivalent to the scenario in which we recognize such revenue. With respect to development and commercialization of sotatercept outside of pulmonary hypertension, the original collaboration deal terms remain in place, and accordingly Celgene will fund and conduct all research, development and commercialization activities, and we are eligible to receive tiered royalty payments in the low to mid-20% range on global net sales.

Our product pipeline



Luspatercept

Luspatercept is designed to promote red blood cell production through a novel mechanism. We are developing luspatercept, through our collaborations with Celgene, as a treatment for anemia and associated complications in diseases in which erythropoiesis-stimulating agents are either not approved or are not well-suited to treat the underlying anemia, such as beta-thalassemia and MDS.

Myelodysplastic Syndromes (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. Celgene is currently conducting a Phase 3 clinical trial with luspatercept in patients with very low, low and intermediate risk MDS per the Revised International Prognostic Scoring System, the "MEDALIST" trial. 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, a 3-month base study, 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. We have completed patient enrollment in all of the dose escalation cohorts as well as the first two expansion cohorts of the trial, for a total of 107 patients.

We believe that preliminary results from the Phase 2 MDS study, including the two additional cohorts, are encouraging. We presented these results using a data cut-off date of April 13, 2017 at the 22nd Congress of the European Hematology Association, or EHA, in June 2017. As of April 13, 2017, a total of 88 patients were treated in the base study with doses of luspatercept of at least 0.75 mg/kg, once every three weeks. All 88 patients were evaluable pursuant to the International Working Group, or IWG, Hematologic Improvement Erythroid, or HI-E, response criterion and 60 patients were evaluable for whether they

achieved red blood cell, or RBC, transfusion independence, or RBC-TI. For patients evaluable for HI-E, the median hemoglobin was 8.3 grams per deciliter (g/dL) (range 6-10 g/dL) and the median RBC transfusion burden was 2 units of RBC during each 8 week period (2U RBC/8 weeks) (range 0-18 RBC units). Among patients evaluable for RBC-TI, the median RBC transfusion burden was 4U RBC/8 weeks (range 4-18 RBC units). A total of 64% of patients were ring sideroblast positive, or RS+, 33% were ring sideroblast negative, or RS-, and the remainder were indeterminate as to ring sideroblast status.

Patient response was evaluated using the IWG HI-E response criterion. To achieve IWG HI-E criterion, a low transfusion burden (< 4 U RBC/8 week, Hb <10 g/dL) patient must have a hemoglobin increase of ≥ 1.5 g/dL for ≥ 8 weeks, and a high transfusion burden (> 4 U RBC/8 weeks) patient must have a reduction of ≥ 4 units RBC over 8 weeks. The preliminary IWG HI-E response rates for patients treated with luspatercept dose levels of ≥ 0.75 mg/kg were 66% (23/35) for RS+ patients with erythropoietin, or EPO, levels < 200 U/L, 50% (4/8) for RS- patients with EPO levels < 200 U/L, 58% (7/12) for RS+ patients with EPO levels 200-500 U/L, 50% (4/8) for RS- patients with EPO levels 200-500 U/L, 56% (5/9) for RS+ patients with EPO levels > 500 U/L, and 8% (1/13) for RS- patients with EPO levels > 500 U/L.

Patients were also evaluated on the basis of whether they achieved RBC transfusion independence, or RBC-TI, for ≥ 8 weeks. The RBC-TI rates for patients treated with luspatercept dose levels of ≥ 0.75 mg/kg were 62% (13/21) for RS+ patients with EPO levels < 200 U/L, 25% (1/4) for RS- patients with EPO levels < 200 U/L, 38% (3/8) for RS+ patients with EPO levels 200-500 U/L, 60% (3/5) for RS- patients with EPO levels 200-500 U/L, 22% (2/9) for RS+ patients with EPO levels > 500 U/L and 9% (1/11) for RS- patients with EPO levels > 500 U/L.

With regard to safety, as reported at EHA in June 15, 2017, the majority of adverse events (AEs) were grade 1 or 2 and luspatercept was generally well-tolerated. There were seven possibly related grade 3, non-serious adverse events (in one patient each): ascites, blast cell count increase, blood bilirubin increase, bone pain, hypertension, platelet count increase and pleural effusion. There were four possibly related serious adverse events: ataxia, general physical health deterioration, muscle weakness and myalgia. Adverse events which may be related to luspatercept observed in > 2 patients in these studies were headache, fatigue, hypertension, bone pain, diarrhea, arthralgia, injection site erythema, myalgia, and peripheral edema.

Based on these data, we conclude that lower risk MDS patients treated with luspatercept continue to demonstrate increases in hemoglobin and decreases in transfusion burden (per IWG HI-E) and a high rate of RBC transfusion independence, and encouraging response rates were observed across all baseline EPO levels. Response rates were similar in patients who received prior ESA compared to those who were ESA naïve. The IWG HI-E response rates were similar in RS+ and RS-, except when EPO levels were > 500 U/L, in which case the RS+ group showed a higher response rate. These data continue to support the initiation of a new Phase 3 trial in first line, lower-risk MDS patients. This trial in first line, lower-risk MDS patients is now being planned, and is referred to as the COMMANDS trial.

The COMMANDS trial is being designed as a Phase 3 trial to evaluate luspatercept versus standard-of-care in the first-line treatment setting for lower-risk MDS patients. We expect that the COMMANDS trial will be initiated in early 2018.

Beta-thalassemia

With respect to beta-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. Celgene is

currently conducting a Phase 3 clinical trial with luspatercept in regularly transfused patients with beta-thalassemia, also known as the "BELIEVE" trial. The BELIEVE trial targets adult beta-thalassemia patients who are regularly transfused.

In addition to the Phase 3 clinical trial, we are currently conducting two Phase 2 clinical trials of luspatercept in patients with beta-thalassemia. The first clinical trial, a 3-month base study, is designed as a two-part trial, with an ascending dose part to evaluate the safety and efficacy of luspatercept in patients with beta-thalassemia, and an expansion part in which additional patients are enrolled at a selected dose level. We have completed enrollment and treatment of all of the dose escalation cohorts as well as the expansion cohort of the base trial. Patients enrolled in the base trial are eligible to enroll in a second Phase 2 trial (extension study) that permits dosing with luspatercept for up to an additional five years. This trial is currently being conducted at sites in Italy and Greece.

We believe that the preliminary results from the Phase 2 clinical trials are encouraging. We presented these results, using a data cut-off date of April 13, 2017, at the 22nd Congress of the EHA in June 2017. As of the cut-off date, a total of 63 patients had been treated with luspatercept dose levels ≥ 0.6 mg/kg. Luspatercept was administered subcutaneously, once every 3 weeks. Of these 63 patients, 32 were transfusion dependent and 31 were non-transfusion dependent. For the transfusion dependent patients treated with luspatercept dose levels ≥ 0.6 mg/kg, 69% of patients had a $\geq 33\%$ reduction in transfusion burden over any 12-week period compared to baseline.

For the non-transfusion dependent patients treated with luspatercept dose levels ≥ 0.6 mg/kg, 71%, respectively, achieved ≥ 1.0 g/dL increases, and 52% achieved ≥ 1.5 g/dL increases, in mean hemoglobin over any 12-week period compared to baseline.

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 patient-reported quality of life in non-transfusion dependent patients correlated with increases in hemoglobin. Rapid healing and partial healing of leg ulcers, a serious complication of beta-thalassemia, was observed in some patients. To date, we have received no reports of related serious adverse events and we have received reports of related grade 3 adverse events consisting of bone pain, asthenia, and headache. The most common adverse events which may be related to luspatercept observed in $\geq 10\%$ of patients were bone pain, myalgia, headache, arthralgia, musculoskeletal pain, asthenia, back pain and injection site pain.

Additional clinical trials in patients with beta-thalassemia are being planned. A Phase 2 trial in non-transfusion-dependent beta-thalassemia patients, referred to as the "BEYOND" trial, is in the planning stages and we expect Celgene to initiate the BEYOND trial by the end of this year.

Myelofibrosis

Myelofibrosis is an acquired disease of the bone marrow that results in replacement of the bone marrow with fibrotic tissue leading to bone marrow failure and inability to make new blood cells, including red blood cells, which leads to anemia. Epidemiological databases suggest that there are approximately 30,000 myelofibrosis patients in the United States and Europe. Approximately 30% of myelofibrosis patients present primarily with anemia when diagnosed and nearly all patients will develop anemia with progression of the disease. There is no approved drug therapy to treat anemia in myelofibrosis. Our and Celgene's objective is to develop luspatercept as a treatment for the anemia in myelofibrosis patients, and Celgene recently initiated a Phase 2 clinical trial in patients with myelofibrosis.

Sotatercept

Sotatercept is designed to inhibit the group of TGF-beta ligands referred to as the activins, as well as certain other ligands that signal in a similar manner. In phase 1 and phase 2 clinical trials involving approximately 400 patients, sotatercept has been shown in humans to promote the formation of red blood cells, increase bone mineral density and reduce calcified blockages in the vasculature (vascular calcification). We have recently discovered that sotatercept has a potent effect in improving cardiovascular health in mouse models of a disease termed pulmonary arterial hypertension, or PAH.

Pulmonary hypertension is a group of diseases characterized by elevated blood pressure in the pulmonary circulation resulting from a variety of causes. PAH is a type of pulmonary hypertension. It is a rare, chronic, rapidly progressing disorder characterized by the constriction of small pulmonary arteries, resulting in abnormally high blood pressure in these vessels. Patients typically present with exercise fatigue and shortness of breath. Progressive obstruction and constriction of the pulmonary vasculature leads to elevated blood pressure in the pulmonary circulation and strain on the right side of the heart. In later stages of disease, right heart failure may develop, and heart failure is the major cause of death in PAH patients. The major classes of drugs used to treat PAH are: the phosphodiesterase 5 inhibitors (PDE5i), the endothelin receptor antagonists (ERAs), the soluble guanylate cyclase stimulators (sGCs) and the prostacyclins. Despite the availability of therapeutic options, the disease progresses rapidly and the five-year survival rate for patients is approximately 57%. All classes of currently approved therapies are designed to promote the dilation of blood vessels, a mechanism referred to as vasodilation. As evident from the high mortality rate, therapies that promote vasodilation improve many aspects of the disease, but do not fundamentally modify or halt the progression of the disease. Accordingly, there is significant unmet need for therapies that address more fundamental aspects of the disease.

Heritable forms of PAH are known, and the underlying genetic defects have been identified. In most cases, the underlying mutations map to a gene that encodes the BMP receptor type II (BMPRII) or genes encoding other proteins that participate in the BMPRII signaling pathway. BMPRII is a key receptor for ligands referred to as the BMPs, and these are part of the TGF-beta superfamily. The BMP-BMPRII signaling pathway activates transcription factors called Smad1/5/8 that coordinate changes in the expression of certain genes. A deficiency in BMP-BMPRII signaling, and the attendant activation of Smad1/5/8, is thought to lead to increased proliferation of cell types that line the vessels, including endothelial cells, smooth muscle cells and fibroblasts. This increased proliferation leads to an overgrowth of smooth muscle and fibrotic tissue around the small arterioles, leading to the formation of muscularized vessels and so-called plexiform lesions. The vessels become constricted and obstructed. Plexiform lesions are arterioles that have become almost completely obstructed by an over-proliferation of endothelial cells, smooth muscle cells and fibrotic tissue. Although the association between BMP-BMPRII signaling and PAH was first identified through the study of patients with heritable forms of the disease, it is now understood that BMP-BMPRII signaling is deficient in patients with non-heritable forms of the disease, including idiopathic and associated forms of PAH. For these reasons, it is expected that a therapeutic agent that improves the signaling deficits in the BMP-BMPRII pathway, activating Smad1/5/8, could rectify key defective molecular signaling events causing the disease, with the potential to modify the course of disease.

It has been reported that a group of proteins targeted by sotatercept, the activins, are present at increased levels in PAH patients. Recently, we and others have found that activins can suppress signaling through the BMP-BMPRII pathway, as measured by assessing Smad1/5/8 activation. We further found that sotatercept, by inhibiting activins, can stimulate the BMP-BMPRII signaling pathway in isolated cells. We evaluated sotatercept for its effects on the establishment of PAH in two mouse models of the disease, and we found that sotatercept had a more profound benefit than representatives of any of the classes of

standard-of-care therapies. As a result, we believe that sotatercept has the potential to correct the BMP-BMPRII signaling deficit that is fundamental to disease in PAH patients and thereby modify the course of disease. Further, because sotatercept works by a distinct mechanism from the available vasodilator agents, we believe that sotatercept can be used in combination with these other agents.

The worldwide PAH patient population is expanding, with approximately 30,000 patients in the United States and 40,000 patients in the European Union. PAH represents one of the largest specialty pharmaceutical markets with more than \$4 billion in sales in the United States in 2016.

We recently amended our agreement with Celgene to secure the right to develop and commercialize sotatercept in patients with pulmonary hypertension, and we expect to initiate a phase 2 clinical trial with sotatercept in patients with PAH during the first half of 2018. In addition to other patents and patent applications related to sotatercept, we have filed patent applications relating to the use of sotatercept in the treatment of pulmonary hypertension. The expected expiration date for these method of treatment patents is 2037, exclusive of possible patent term extensions.

Celgene has the rights to continue to develop and commercialize sotatercept outside the pulmonary hypertension field. Sotatercept is being studied through investigator-initiated clinical trials in multiple myeloma, Diamond-Blackfan anemia and myelofibrosis. Investigators at the MD Anderson Cancer Center are conducting a trial to determine the safety and efficacy of sotatercept in patients with myeloproliferative neoplasm-associated myelofibrosis and anemia. Based on data from this investigator-sponsored trial presented at the 58th ASH Annual Meeting and Exposition in December 2016, and taking into account mechanistic similarities between sotatercept and luspatercept, Celgene initiated a Phase 2 clinical trial with luspatercept in patients with myelofibrosis.

ACE-083

Our third clinical stage therapeutic candidate, ACE-083, is designed to promote muscle growth and function in specific, targeted muscles. ACE-083 uses the myostatin+ approach to promote muscle growth, meaning that ACE-083 inhibits myostatin, a well-characterized regulator of muscle size, as well as other factors that suppress muscle growth. Through the inhibition of multiple suppressors of muscle growth, ACE-083 promotes a substantially greater muscle mass increase than simple myostatin antagonists. We completed a Phase 1 clinical trial with ACE-083 in healthy volunteers. ACE-083 was well tolerated in the Phase 1 clinical trial and no serious adverse events were reported. Data from cohorts 1 through 5 in 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 injected rectus femoris muscle of the quadriceps. Data from cohorts 6 and 7 demonstrated that, at the highest dose level tested, ACE-083 generated a mean increase in muscle volume of approximately 8.9% in the injected tibialis anterior muscle of the lower leg. We have completed the Phase 1 clinical trial and we are currently conducting a Phase 2 clinical trial with ACE-083 in patients with facioscapulohumeral dystrophy, or FSHD, and a Phase 2 clinical trial with ACE-083 in patients with CMT disease.

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 fusion protein platform, which includes the IntelliTrap™ platform, and identifying novel antibodies. We have selected our first IntelliTrap™ therapeutic candidate, ACE-2494, a systemic muscle agent, for advancement to clinical trials and we expect to initiate

a Phase 1 healthy volunteer study in 2017. We are also evaluating ACE-1334, a selective TGF-beta antagonist, for treatment of disorders with a fibrotic component, and additional molecules from our IntelliTrap™ platform for undisclosed therapeutic areas.

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-11 of this prospectus supplement and in our Annual Report on Form 10-K for the year ended December 31, 2016 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.

The offering

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| Issuer | Accelaron Pharma Inc. |
| Securities | 3,809,040 shares of common stock based on an assumed public offering price of \$39.38 per share, the last reported sale price of our common stock on the NASDAQ Global Market on September 18, 2017 (or 4,380,396 shares if the underwriters exercise their option to purchase additional shares of common stock in full). |
| Common stock outstanding after this offering | 42,445,545 shares of common stock based on an assumed public offering price of \$39.38 per share, the last reported sale price of our common stock on the NASDAQ Global Market on September 18, 2017 (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 \$140.6 million (or approximately \$161.8 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 potential therapeutic candidates from our existing research pipeline and for general and administrative expenses (including personnel-related costs), capital expenditures and working capital and other general corporate purposes, including potential acquisitions of rights to additional programs from third parties. 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 United States Federal 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 38,636,505 shares of our common stock outstanding as of June 30, 2017, and excludes:

- 3,541,003 shares of common stock issuable upon the exercise of stock options outstanding as of June 30, 2017, at a weighted-average exercise price of \$28.57 per share;
- 63,296 shares of common stock issuable upon the exercise of warrants to purchase shares of common stock outstanding as of June 30, 2017, at a weighted-average exercise price of \$5.94 per share;

- 809,599 shares of common stock issuable upon vesting of outstanding restricted stock units as of June 30, 2017;
- 2,862,062 shares of common stock reserved for future issuance under our 2013 Equity Incentive Plan as of June 30, 2017; and
- 199,739 shares of common stock reserved for future issuance under our Employee Stock Purchase Plan as of June 30, 2017.

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

- no exercise by the underwriters of their option to purchase up to \$22,500,000 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 June 30, 2017.

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

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 \$31.63 per share as of June 30, 2017, based on an assumed public offering price of \$39.38 per share, the last reported sale price of our common stock on the NASDAQ Global Market on September 18, 2017, 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, including this offering, may result in material additional limitations on our ability to use our net operating loss and tax credit carryforwards.

As of December 31, 2016, we had U.S. federal and state net operating loss carryforwards, or NOL carryforwards, of \$339.3 million and \$293.7 million, respectively, available to reduce future taxable income, if any. These federal and state NOL carryforwards expire at various times through 2036. 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 (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.

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 December 31, 2016, we had an accumulated deficit of \$364.5 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 ACE-083, ACE-2494 or other therapeutic candidates. If we do not receive the anticipated milestone payments or do not enter into partnerships for ACE-083, ACE-2494 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 December 31, 2016, our cash, cash equivalents and investments were \$234.4 million. We believe that we will continue to expend substantial resources for the foreseeable future developing sotatercept for pulmonary hypertension, ACE-083, ACE-2494 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 generally pays development, manufacturing and commercialization and certain patent costs for luspatercept and for sotatercept outside of pulmonary hypertension. Other than those costs, our future capital requirements depend on many factors, particularly in connection with the development of our other therapeutic candidates including sotatercept for pulmonary hypertension, ACE-083 and ACE-2494:

- the scope, progress, results and costs of researching and developing our other therapeutic candidates, and conducting preclinical studies and clinical trials;
- 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, will be sufficient to fund our projected operating requirements until the end of 2020. 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 terms unfavorable 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 ACE-083, ACE-2494, sotatercept for pulmonary hypertension or any therapeutic candidates other than luspatercept or sotatercept outside of pulmonary hypertension, 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 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, ACE-083, ACE-2494 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;

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- 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 of our therapeutic candidates, 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 and ACE-083, and our encouraging preclinical results to date for ACE-2494, are not necessarily predictive of the results of our ongoing or future clinical trials. Promising results in preclinical studies of a drug candidate may not be predictive of similar results in humans during clinical trials, and successful results from early clinical trials of a drug candidate may not be replicated in later and larger clinical trials or in clinical trials for different indications. If the results of our or our 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, for our Celgene partnered programs, 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 their policies and guidance 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 or Celgene's 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 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 policies of the FDA and other regulatory agencies 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 beta-thalassemia, and for the treatment of patients with non-transfusion-dependent beta-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 eligible for such designation, the FDA could decide not to grant it. Even though luspatercept has received Fast Track designation, 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.

Celgene is currently conducting two Phase 3 clinical trials with luspatercept: one for the treatment of patients with lower risk MDS, the "MEDALIST" trial, and another for the treatment of patients with beta-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 of our current or future partners 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.

Risks related to our reliance on third parties

We are dependent on Celgene for the successful development and commercialization of our most advanced therapeutic candidate, luspatercept. If Celgene does not devote sufficient resources to the development of luspatercept, discontinues development of luspatercept, is unsuccessful in its efforts, or chooses to terminate the luspatercept agreement with us, our business will be materially harmed.

We have entered into collaboration agreements with Celgene to develop and commercialize sotatercept and luspatercept. Pursuant to the sotatercept agreement, responsibility for all clinical and other product development activities for all indications other than for pulmonary hypertension 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. Celgene is responsible for paying 100% of worldwide development costs for

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luspatercept and for sotatercept outside of pulmonary hypertension. We will co-promote sotatercept outside of pulmonary hypertension 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 outside of pulmonary hypertension 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. This may occur for many reasons, including internal business reasons or because of unfavorable regulatory feedback. Further, on review of the safety and efficacy data available to date, the FDA may impose requirements on a clinical trial program that would render the program commercially nonviable. In the event of any such decision, we would be unable to advance such program ourselves.

Under our collaboration agreements, when 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 sotatercept and/or 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, including lenalidomide and azacitidine, for certain MDS patients for which luspatercept is also being developed.
- Celgene may terminate its partnership with us without cause and for circumstances outside of our control, which could make it difficult for us to attract new strategic partners or adversely affect how we are perceived in scientific and financial communities.
- 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.

We and Celgene share the obligations to commercialize luspatercept and sotatercept outside of pulmonary hypertension in the United States and we are solely dependent on Celgene to commercialize luspatercept and sotatercept outside of pulmonary hypertension 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 outside of pulmonary hypertension in the United States, we will need to rely extensively on Celgene, and we will need to establish our own adequate marketing, sales and distribution capabilities. In addition, to successfully commercialize sotatercept in pulmonary hypertension in jurisdictions where it is approved, we will need to establish our own 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 ACE-083 and will do so for any future unpartnered therapeutic candidates such as ACE-2494, and we will continue to work with Celgene on any ongoing or future 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.

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.

In addition to our internal manufacturing, we rely on third-party manufacturers in the production and testing of 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, 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 agree. 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 manufacture, or contract for the manufacture of, bulk drug substance and finished drug product for use in late stage clinical trials and for commercial supplies of these product candidates, if approved. 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.

Celgene is responsible for manufacturing sotatercept outside of pulmonary hypertension and luspatercept for future late-stage clinical trials and may elect to be responsible for manufacture of sotatercept for clinical trials for pulmonary hypertension. 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 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 Celgene has 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 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 ACE-083, ACE-2494 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

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 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, and may in the future in-license, 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. See "Business—Intellectual Property—In-Licenses" in our Annual Report on Form 10-K for the year ended December 31, 2016 for a description of our license agreements.

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 any of our existing therapeutic candidates or any 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;
- 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, including those in the United States, 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 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, and as evidenced by public discourse on the topic. 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:

- public and market perceptions of our future business prospects, including future revenue and profitability;
- 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;

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- 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, 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 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 beta-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 beta-thalassemia patients could materially reduce the potential patient population for luspatercept, especially in transfusion dependent patients.

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 are conducting 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. (See "Business—Competition").

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. In the case of placebo-controlled clinical trials, if the rate of an adverse event or serious adverse event observed in the treatment group exceeds the rate of such adverse event or serious adverse event observed in the placebo-controlled group, then the FDA or other regulatory authorities may require the delay or termination of such clinical trial, or require the conduct of one or more additional clinical trials to further demonstrate the safety of the therapeutic candidate.

For a more complete description of the safety profile for our therapeutic candidates, see the description of each of our therapeutic candidates in the "Business" section of this Annual Report on Form 10-K.

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;

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- 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.

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.

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. Except for ACE-2494, we have not otherwise previously manufactured or developed antibodies or IntelliTrap™ proteins, and we may not be successful at doing so. We may be unable to manufacture these therapeutic candidates, these therapeutic candidates 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. 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 experience a disruption of our business activities due to the transition to a new Chief Executive Officer.

Effective as of December 1, 2016, our board of directors appointed Habib Dable as President, Chief Executive Officer and a director following the retirement and resignation of John Knopf, Ph.D. as President, Chief Executive Officer, and a director. If we fail to effectively manage our leadership change, our financial condition, clinical program development, results of operations, and reputation, as well as our ability to successfully attract, motivate and retain key employees, could be harmed.

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 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.

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. 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 data breaches and cyber-attacks, which could compromise our intellectual property or other sensitive information and could result in a material disruption of our therapeutic candidate development programs.

In the ordinary course of our business, we collect, maintain and transmit sensitive data on our networks and systems and on the networks and systems of our partners, third-party CROs and other contractors or consultants, including our intellectual property and proprietary or confidential business information (such as research data and employee personal information) and confidential information with respect to our vendors and our partners. The secure maintenance of this information is critical to our business and reputation. We believe that companies have been increasingly subject to a wide variety of security incidents, cyber-attacks and other attempts to gain unauthorized access. These threats can come from a variety of sources, ranging in sophistication from an individual hacker to a state-sponsored attack. Cyber threats may be generic, or they may be custom-crafted against our information systems. Over the past few years, cyber-attacks have become more prevalent and much harder to detect and defend against.

Our network and storage applications and those of our clinical research organizations, collaborators and vendors may be subject to unauthorized access by hackers or breached due to operator error, malfeasance or other system disruptions. It is often difficult to anticipate or immediately detect such incidents and the damage caused by such incidents. These data breaches and any unauthorized access or disclosure of our

information or intellectual property could compromise our intellectual property and expose sensitive business information. A data security breach could also lead to public exposure of personal information of our employees. Cyber-attacks could cause us to incur significant remediation costs, result in product development delays, disrupt key business operations and divert attention of management and key information technology resources. Our network security and data recovery measures and those of our clinical research organizations, collaborators and vendors may not be adequate to protect against such security breaches and disruptions. These incidents could also subject us to liability, expose us to significant expense and cause significant harm to our reputation and business. While we have not experienced any such material security breaches or disruptions 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.

Risks related to our common stock

The market price of our common stock may be highly volatile, and you may not be able to resell your shares at or above the price at which you purchased them.

Since our initial public offering, the price of our common stock as reported on The NASDAQ Global Market has ranged from a low of \$16.78 on November 6 and 8, 2013 to a high of \$57.89 on January 22, 2014. The market price of shares of our common stock could be subject to wide fluctuations in response to many risk factors listed in this section, and others beyond our control, including:

- results of clinical trials of our therapeutic candidates, including sotatercept, luspatercept and ACE-083;
- the timing of the release of results of our clinical trials that are being conducted by Celgene;
- results of clinical trials of our competitors' products;
- regulatory actions with respect to our products or our competitors' products;
- actual or anticipated fluctuations in our financial condition and operating results;
- publication of research reports by securities analysts about us or our competitors or our industry;
- our failure or the failure of our competitors to meet analysts' projections or guidance that we or our competitors may give to the market;
- additions and departures of key personnel;
- strategic decisions by us or our competitors, such as acquisitions, divestitures, spin-offs, joint ventures, strategic investments or changes in business strategy;
- the passage of legislation or other regulatory developments affecting us or our industry;
- fluctuations in the valuation of companies perceived by investors to be comparable to us;
- sales of our common stock by us, our insiders or our other stockholders;
- speculation in the press or investment community;
- announcement or expectation of additional financing efforts;

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- changes in accounting principles;
- terrorist acts, acts of war or periods of widespread civil unrest;
- natural disasters and other calamities;
- actual or perceived changes in current or future market conditions for biopharmaceutical stocks; and
- changes in general market and economic conditions.

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

We incur significant costs as a result of operating as a public company and complying with the Sarbanes-Oxley Act, and our management is required to devote substantial time to compliance initiatives. 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.

As a public company, we incur significant legal, accounting and other expenses. 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. 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.

The Sarbanes-Oxley Act requires, among other things, that we maintain effective internal controls for financial reporting and disclosure controls and procedures. 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. In addition, we are required to have our independent registered public accounting firm attest to the effectiveness of our internal control over financial reporting.

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 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.

We do not expect to pay any cash dividends for the foreseeable future.

You should not rely on an investment in our common stock to provide dividend income. We do not anticipate that we will pay any cash dividends to holders of our common stock in the foreseeable future. Instead, we plan to retain any earnings to maintain and expand our operations. 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. Accordingly, investors must rely on sales of their common stock after price appreciation, which may never occur, as the only way to realize any return on their investment. As a result, investors seeking cash dividends should not purchase our common stock.

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.

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 analysts do not publish research or reports about our business or if they publish negative, or inaccurate, evaluations of our stock, the price of our stock 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.

Use of proceeds

We estimate that the net proceeds from this offering will be approximately \$140.6 million (or approximately \$161.8 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 \$45 million to conduct clinical trials and associated activities in connection with our therapeutic candidates in our pulmonary hypertension program;
- approximately \$30 million to conduct clinical trials and associated activities in connection with our therapeutic candidates in our neuromuscular program; 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, including potential acquisitions of rights to additional programs from third parties.

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.

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 |
|----------------|-------------|------------|
| 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 |
| 2016 | | |
| First Quarter | \$ 48.05 | \$ 22.67 |
| Second Quarter | \$ 37.67 | \$ 25.49 |
| Third Quarter | \$ 40.70 | \$ 28.29 |
| Fourth Quarter | \$ 41.69 | \$ 24.77 |
| 2017 | | |
| First Quarter | \$ 32.57 | \$ 23.07 |
| Second Quarter | \$ 34.91 | \$ 24.37 |

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.

Capitalization

The following table sets forth our cash and cash equivalents and investments and capitalization as of June 30, 2017:

- 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 \$39.38 per share, the last reported price of our common stock on the NASDAQ Global Market on September 18, 2017), 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.

| (in thousands, except share and per share data) | As of June 30, 2017 | |
|--|---------------------|-------------------|
| | Actual | As adjusted |
| Cash, cash equivalents and short-term and long-term investments | \$ 194,038 | \$ 334,638 |
| Warrants to purchase common stock | \$ 1,516 | \$ 1,516 |
| 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; 38,636,505 shares issued and outstanding, actual, and 42,445,545 shares issued and outstanding, as adjusted(1) | 39 | 43 |
| Additional paid-in capital | 608,493 | 749,089 |
| Accumulated deficit | (419,646) | (419,646) |
| Accumulated other comprehensive loss | (354) | (354) |
| Total stockholders' equity | 188,532 | 329,132 |
| Total capitalization | \$ 190,048 | \$ 330,648 |

(1) The actual and as adjusted common stock information excludes (i) 3,541,003 shares of common stock issuable upon the exercise of stock options outstanding as of June 30, 2017 at a weighted-average exercise price of \$28.57 per share, (ii) 63,296 shares of common stock issuable upon the exercise of warrants to purchase shares of common stock outstanding as of June 30, 2017 at a weighted-average exercise price of \$5.94 per share, (iii) 809,599 shares of common stock issuable upon vesting of outstanding restricted stock units as of June 30, 2017, (iv) 2,862,062 shares of common stock reserved for future issuance under our 2013 Equity Incentive Plan as of June 30, 2017, and (v) 199,739 shares of common stock reserved for future issuance under our Employee Stock Purchase Plan as of June 30, 2017.

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 June 30, 2017 was approximately \$188.5 million, or approximately \$4.88 per share of common stock based upon 38,636,505 shares outstanding as of June 30, 2017. 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 \$150.0 million of shares of common stock at an assumed offering price of \$39.38 per share, the last reported price of our common stock on the NASDAQ Global Market on September 18, 2017, and after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us, our as adjusted net tangible book value as of June 30, 2017 would have been approximately \$329.1 million, or \$7.75 per share. This would represent an immediate increase in net tangible book value of \$2.87 per share to our existing stockholders and an immediate dilution in net tangible book value of \$31.63 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 | \$ 39.38 |
| Net tangible book value per share as of June 30, 2017 | \$ 4.88 |
| Increase in net tangible book value per share attributable to the offering | <u>2.87</u> |
| As adjusted net tangible book value per share after giving effect to the offering | \$ 7.75 |
| Dilution in net tangible book value per share to new investors in the offering | <u>\$ 31.63</u> |

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 June 30, 2017 and no issuance of up to 571,356 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 \$39.38 per share, the last reported sale price of our common stock on the NASDAQ Global Market on September 18, 2017. 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 their option to purchase \$22,500,000 of shares of common stock in full at the assumed public offering price of \$39.38 per share, the last reported sale price of our common stock on the NASDAQ Global Market on September 18, 2017, the pro forma as adjusted net tangible book value after this offering would be approximately \$8.14 per share, representing an increase in net tangible book value of approximately \$3.26 per share to existing stockholders and immediate dilution in net tangible book value of approximately \$31.24 per share to investors purchasing our common stock in this offering at the public offering price.

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 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.

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, is attributable to a permanent establishment maintained by such Non-U.S. Holder in the United States), 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 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, 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 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.

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.

Underwriting

J.P. Morgan Securities LLC, Citigroup Global Markets Inc., and Leerink Partners LLC are acting as joint book-running managers of the offering and as representatives of the underwriters named below. Subject to the terms and conditions stated in the underwriting agreement dated the date of this prospectus supplement, each underwriter named below has severally agreed to purchase, and we have agreed to sell to that underwriter, the number of shares set forth opposite the underwriter's name.

| Underwriter | Number of Shares |
|-------------------------------|-------------------------|
| J.P. Morgan Securities LLC | |
| Citigroup Global Markets Inc. | |
| Leerink Partners LLC | |
| Total | |

The underwriting agreement provides that the obligations of the underwriters to purchase the shares included in this offering are subject to approval of legal matters by counsel and to other conditions. The underwriters are obligated to purchase all the shares (other than those covered by the option to purchase additional shares described below) if they purchase any of the shares.

Shares sold by the underwriters to the public will initially be offered at the public offering price set forth on the cover of this prospectus supplement. Any shares sold by the underwriters to securities dealers may be sold at a discount from the public offering price not to exceed \$ _____ per share. If all the shares are not sold at the initial offering price, the underwriters may change the offering price and the other selling terms. The representatives have advised us that the underwriters do not intend to make sales to discretionary accounts.

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 at the public offering price less the underwriting discount. To the extent the option is exercised, each underwriter must purchase a number of additional shares approximately proportionate to that underwriter's initial purchase commitment. Any shares issued or sold under the option will be issued and sold on the same terms and conditions as the other shares that are the subject of this offering.

We, and our officers and directors have agreed that, for a period of 60 days from the date of this prospectus supplement, we and they will not, without the prior written consent of J.P. Morgan, Citigroup and Leerink, among other things, dispose of or hedge any shares or any securities convertible into or exchangeable for our common stock. J.P. Morgan, Citigroup and Leerink in their sole discretion may release any of the securities subject to these lock-up agreements at any time, which, in the case of officers and directors, shall be without notice.

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

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The following table shows the underwriting discounts and commissions that we are to pay to the underwriters in connection with this offering. These amounts are shown assuming both no exercise and full exercise of the underwriters' option to purchase additional shares of common stock.

| | Paid by Acceleron | |
|-----------|-------------------|---------------|
| | No exercise | Full exercise |
| Per share | \$ | \$ |
| Total | \$ | \$ |

We estimate that our portion of the total expenses of this offering will be approximately \$400,000.

We have also agreed to reimburse the underwriters for certain of their expenses in an amount up to \$30,000 as set forth in the underwriting agreement.

In connection with the offering, the underwriters may purchase and sell shares in the open market. Purchases and sales in the open market may include short sales, purchases to cover short positions, which may include purchases pursuant to the underwriters' option to purchase additional shares, and stabilizing purchases.

- Short sales involve secondary market sales by the underwriters of a greater number of shares than they are required to purchase in the offering.
 - "Covered" short sales are sales of shares in an amount up to the number of shares represented by the underwriters' option to purchase additional shares.
 - "Naked" short sales are sales of shares in an amount in excess of the number of shares represented by the underwriters' option to purchase additional shares.
- Covering transactions involve purchases of shares either pursuant to the underwriters' option to purchase additional shares or in the open market in order to cover short positions.
 - To close a naked short position, the underwriters must purchase 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 shares in the open market after pricing that could adversely affect investors who purchase in the offering.
 - To close a covered short position, the underwriters must purchase shares in the open market or must exercise the option to purchase additional shares. In determining the source of shares to close the covered short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market as compared to the price at which they may purchase shares through the option to purchase additional shares.
- Stabilizing transactions involve bids to purchase shares so long as the stabilizing bids do not exceed a specified maximum.

Purchases to cover short positions and stabilizing purchases, as well as other purchases by the underwriters for their own accounts, may have the effect of preventing or retarding a decline in the market price of the shares. They may also cause the price of the shares to be higher than the price that would otherwise exist in the open market in the absence of these transactions. The underwriters may conduct these transactions on the NASDAQ Global Market, in the over-the-counter market or otherwise. If the underwriters commence any of these transactions, they may discontinue them at any time.

Other relationships

Some of the underwriters and their affiliates have engaged in, and may in the future engage in, investment banking and other commercial dealings in the ordinary course of business with us or our affiliates, including serving as underwriters for our initial public offering in September 2013, for which they received, or may in the future receive, customary fees and commissions for these transactions.

Conflicts of interest

The underwriters are full service financial institutions engaged in various activities, which may include securities trading, commercial and investment banking, financial advisory, investment management, principal investment, hedging, financing and brokerage activities. Certain of the underwriters and their respective affiliates may, from time to time, engage in transactions with and perform services for us in the ordinary course of their business for which they may receive customary fees and reimbursement of expenses. 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 (which may include bank loans and/or credit default swaps) 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 investments and securities activities may involve securities and/or instruments of ours or our affiliates. The underwriters and their affiliates may also make investment recommendations and/or publish or express independent research views in respect of such securities or financial instruments and may hold, or recommend to clients that they acquire, long and/or short positions in such securities and instruments.

We have agreed to indemnify the underwriters against certain liabilities, including liabilities under the Securities Act, or to contribute to payments the underwriters may be required to make because of any of those liabilities

Notice to prospective investors in the European Economic Area

In relation to each member state of the European Economic Area that has implemented the Prospectus Directive (each, a relevant member state), with effect from and including the date on which the Prospectus Directive is implemented in that relevant member state (the relevant implementation date), an offer of shares described in this prospectus supplement may not be made to the public in that relevant member state other than:

- to any legal entity which is a qualified investor as defined in the Prospectus Directive;
- 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 relevant Dealer or Dealers nominated by us for any such offer; or
- in any other circumstances falling within Article 3(2) of the Prospectus Directive,

provided that no such offer of securities shall require us or any underwriter to publish a prospectus pursuant to Article 3 of the Prospectus Directive.

For purposes of this provision, the expression an "offer of securities to the public" 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 the shares to be offered so as to enable an investor to decide to purchase or subscribe for the shares, as the expression may be varied in that member state by any measure implementing the Prospectus Directive in that member state, and 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. The expression 2010 PD Amending Directive means Directive 2010/73/EU.

The sellers of the shares have not authorized and do not authorize the making of any offer of shares through any financial intermediary on their behalf, other than offers made by the underwriters with a view to the final placement of the shares as contemplated in this prospectus supplement. Accordingly, no purchaser of the shares, other than the underwriters, is authorized to make any further offer of the shares on behalf of the sellers or the underwriters.

Notice to prospective investors in the United Kingdom

This prospectus supplement is only being distributed to, and is only directed at, persons in the United Kingdom that are qualified investors within the meaning of Article 2(1)(e) of the Prospectus Directive that are also (i) investment professionals falling within Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005 (the Order) or (ii) high net worth entities, and other persons to whom it may lawfully be communicated, falling within Article 49(2)(a) to (d) of the Order (each such person being referred to as a "relevant person"). This prospectus supplement and its contents are confidential and should not be distributed, published or reproduced (in whole or in part) or disclosed by recipients to any other persons in the United Kingdom. Any person in the United Kingdom that is not a relevant person should not act or rely on this document or any of its contents.

Notice to prospective investors in France

Neither this prospectus supplement nor any other offering material relating to the shares described in this prospectus supplement has been submitted to the clearance procedures of the *Autorité des Marchés Financiers* or of the competent authority of another member state of the European Economic Area and notified to the *Autorité des Marchés Financiers*. The shares have not been offered or sold and will not be offered or sold, directly or indirectly, to the public in France. Neither this prospectus supplement nor any other offering material relating to the shares has been or will be:

- released, issued, distributed or caused to be released, issued or distributed to the public in France; or
- used in connection with any offer for subscription or sale of the shares to the public in France.

Such offers, sales and distributions will be made in France only:

- to qualified investors (*investisseurs qualifiés*) and/or to a restricted circle of investors (*cercle restreint d'investisseurs*), in each case investing for their own account, all as defined in, and in accordance with, articles L.411-2, D.411-1, D.411-2, D.734-1, D.744-1, D.754-1 and D.764-1 of the French *Code monétaire et financier* ;
- to investment services providers authorized to engage in portfolio management on behalf of third parties; or
- in a transaction that, in accordance with article L.411-2-II-1°-or-2°-or 3° of the French *Code monétaire et financier* and article 211-2 of the General Regulations (*Règlement Général*) of the *Autorité des Marchés Financiers* , does not constitute a public offer (*appel public à l'épargne*).

The ordinary shares may be resold directly or indirectly, only in compliance with articles L.411-1, L.411-2, L.412-1 and L.621-8 through L.621-8-3 of the French *Code monétaire et financier*.

Notice to prospective investors in Australia

No prospectus or other disclosure document (as defined in the Corporations Act 2001 (Cth) of Australia (Corporations Act)) in relation to the common stock has been or will be lodged with the Australian Securities & Investments Commission (ASIC). This document has not been lodged with ASIC and is only directed to certain categories of exempt persons. Accordingly, if you receive this document in Australia:

- (a) you confirm and warrant that you are either:
 - (i) a "sophisticated investor" under section 708(8)(a) or (b) of the Corporations Act;
 - (ii) a "sophisticated investor" under section 708(8)(c) or (d) of the Corporations Act and that you have provided an accountant's certificate to us which complies with the requirements of section 708(8)(c)(i) or (ii) of the Corporations Act and related regulations before the offer has been made;
 - (iii) a person associated with the company under section 708(12) of the Corporations Act; or
 - (iv) a "professional investor" within the meaning of section 708(11)(a) or (b) of the Corporations Act, and to the extent that you are unable to confirm or warrant that you are an exempt sophisticated investor, associated person or professional investor under the Corporations Act any offer made to you under this document is void and incapable of acceptance; and
- (b) you warrant and agree that you will not offer any of the common stock for resale in Australia within 12 months of that common stock being issued unless any such resale offer is exempt from the requirement to issue a disclosure document under section 708 of the Corporations Act.

Notice to prospective investors in Hong Kong

The shares may not be offered or sold in Hong Kong by means of any document other than (i) in circumstances which do not constitute an offer to the public within the meaning of the Companies Ordinance (Cap. 32, Laws of Hong Kong), or (ii) to "professional investors" within the meaning of the Securities and Futures Ordinance (Cap. 571, Laws of Hong Kong) and any rules made thereunder, or (iii) in other circumstances which do not result in the document being a "prospectus" within the meaning of the Companies Ordinance (Cap. 32, Laws of Hong Kong) and no advertisement, invitation or document relating to the shares may be issued or may be in the possession of any person for the purpose of issue (in each case whether in Hong Kong or elsewhere), which is directed at, or the contents of which are likely to be accessed or read by, the public in Hong Kong (except if permitted to do so under the laws of Hong Kong) other than with respect to shares which are or are intended to be disposed of only to persons outside Hong Kong or only to "professional investors" within the meaning of the Securities and Futures Ordinance (Cap. 571, Laws of Hong Kong) and any rules made thereunder.

Notice to prospective investors in Japan

The shares offered in this prospectus supplement have not been and will not be registered under the Financial Instruments and Exchange Law of Japan. The shares have not been offered or sold and will not be offered or sold, directly or indirectly, in Japan or to or for the account of any resident of Japan (including any corporation or other entity organized under the laws of Japan), except (i) pursuant to an

exemption from the registration requirements of the Financial Instruments and Exchange Law and (ii) in compliance with any other applicable requirements of Japanese law.

Notice to prospective investors in Canada

The shares may be sold 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 shares 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 supplement (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.

Notice to prospective investors in Singapore

This prospectus supplement has not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus supplement and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of the shares may not be circulated or distributed, nor may the shares be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to persons in Singapore other than (i) to an institutional investor under Section 274 of the Securities and Futures Act, Chapter 289 of Singapore (the SFA), (ii) to a relevant person pursuant to Section 275(1), or any person pursuant to Section 275(1A), and in accordance with the conditions specified in Section 275 of the SFA or (iii) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA, in each case subject to compliance with conditions set forth in the SFA.

Where the shares are subscribed or purchased under Section 275 of the SFA by a relevant person which is:

- a corporation (which is not an accredited investor (as defined in Section 4A of the SFA)) the sole business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor; or
- a trust (where the trustee is not an accredited investor) whose sole purpose is to hold investments and each beneficiary of the trust is an individual who is an accredited investor,
- shares, debentures and units of shares and debentures of that corporation or the beneficiaries' rights and interest (howsoever described) in that trust shall not be transferred within six months after that

corporation or that trust has acquired the shares pursuant to an offer made under Section 275 of the SFA except:

- to an institutional investor (for corporations, under Section 274 of the SFA) or to a relevant person defined in Section 275(2) of the SFA, or to any person pursuant to an offer that is made on terms that such shares, debentures and units of shares and debentures of that corporation or such rights and interest in that trust are acquired at a consideration of not less than S\$200,000 (or its equivalent in a foreign currency) for each transaction, whether such amount is to be paid for in cash or by exchange of securities or other assets, and further for corporations, in accordance with the conditions specified in Section 275 of the SFA;
- where no consideration is or will be given for the transfer; or
- where the transfer is by operation of law.

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, 2016, and the effectiveness of Acceleron Pharma Inc.'s internal control over financial reporting as of December 31, 2016 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.

PROSPECTUS

ACCELERON PHARMA INC.

Common Stock

Preferred Stock

Warrants

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.

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 September 18, 2017, the closing price of our common stock was \$39.38.

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 September 19, 2017.

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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. 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, "Accelaron", the "Company", "we", "us", "our" and similar names refer to Accelaron Pharma Inc. and its wholly owned subsidiary.

OUR BUSINESS

Our Company

We are a leading biopharmaceutical company in the discovery and development of TGF-beta therapeutics to treat serious and rare diseases. Our research focuses on key natural regulators of cellular growth and repair, particularly the Transforming Growth Factor-Beta, or TGF-beta, protein superfamily. By combining our discovery and development expertise, including our proprietary knowledge of the TGF-beta superfamily, and our internal protein engineering and manufacturing capabilities, we have generated several innovative therapeutic candidates, all of which encompass novel potential first-in-class mechanisms of action. We have focused and prioritized our research and development activities within three key therapeutic areas, and if successful, these candidates could have the potential to significantly improve clinical outcomes for patients across these areas of high, unmet need.

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.

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, 2016, 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 ACE-083 and our other preclinical 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 quickly and efficiently identify and develop therapeutic candidates;
- 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.

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.

RATIO OF COMBINED FIXED CHARGES AND PREFERRED STOCK DIVIDENDS TO EARNINGS

The following table sets forth our historical ratios of fixed charges and preferred stock dividends to earnings for the periods indicated. You should read this table in conjunction with the financial statements and notes incorporated by reference in this prospectus.

| | Year Ended December 31, | | | | | Six Months Ended |
|--|-------------------------|------|------|------|------|------------------|
| | 2012 | 2013 | 2014 | 2015 | 2016 | June 30, 2017 |
| Ratio of combined fixed charges and preferred stock dividends to earnings(1) | — | — | — | — | — | — |

- (1) Earnings were inadequate to cover fixed charges and preferred dividends for the years ended December 31, 2012, 2013, 2014, 2015 and 2016 by \$59.6 million, \$39.0 million, \$51.3 million, \$63.9 million and \$57.0 million, respectively, and for the six months ended June 30, 2017, by \$55.1 million.

PLAN OF DISTRIBUTION

We 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 reallocated 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 reallocated 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

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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.

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.

DESCRIPTION OF CAPITAL STOCK

General

The following description of our capital stock is intended as a summary only and is qualified in its entirety by reference to our restated certificate of incorporation and amended and restated by-laws,

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which are filed as exhibits to the registration statement of which this prospectus is a part, and to the applicable provisions of the Delaware General Corporation Law. We refer in this section to our restated certificate of incorporation as our certificate of incorporation, and we refer to our amended and restated by-laws as our by-laws.

Our authorized capital stock consists of 175,000,000 shares of our common stock, par value \$0.001 per share, and 25,000,000 shares of our preferred stock, par value \$0.001 per share, all of which preferred stock is undesignated.

As of June 30, 2017, we had issued and outstanding:

- 38,636,505 shares of our common stock;
- options to purchase a total of 3,541,003 shares of our common stock with a weighted-average exercise price of \$28.57 per share; and
- warrants to purchase a total of 63,296 shares of our common stock with a weighted-average exercise price of \$5.94 per share.

As of June 30, 2017, we had 92 stockholders of record.

Common Stock

Dividend Rights. Subject to preferences that may apply to shares of preferred stock outstanding at the time, holders of outstanding shares of common stock will be entitled to receive dividends out of assets legally available at the times and in the amounts as the board of directors may from time to time determine.

Voting Rights. Each outstanding share of common stock will be entitled to one vote on all matters submitted to a vote of stockholders. Holders of shares of our common stock shall have no cumulative voting rights.

Preemptive Rights. Our common stock will not be entitled to preemptive or other similar subscription rights to purchase any of our securities.

Conversion or Redemption Rights. Our common stock will be neither convertible nor redeemable.

Liquidation Rights. Upon our liquidation, the holders of our common stock will be entitled to receive pro rata our assets which are legally available for distribution, after payment of all debts and other liabilities and subject to the prior rights of any holders of preferred stock then outstanding.

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

Preferred Stock

Our board of directors may, without further action by our stockholders, from time to time, direct the issuance of shares of preferred stock in series and may, at the time of issuance, determine the designations, powers, preferences, privileges, and relative participating, optional or special rights as well as the qualifications, limitations or restrictions thereof, including dividend rights, conversion rights, voting rights, terms of redemption and liquidation preferences, any or all of which may be greater than the rights of the common stock. Satisfaction of any dividend preferences of outstanding shares of preferred stock would reduce the amount of funds available for the payment of dividends on shares of our common stock. Holders of shares of preferred stock may be entitled to receive a preference payment in the event of our liquidation before any payment is made to the holders of shares of our common stock. Under certain circumstances, the issuance of shares of preferred stock may render more difficult or tend to discourage a merger, tender offer or proxy contest, the assumption of control by a holder of a large block of our securities or the removal of incumbent management. Upon the

affirmative vote of a majority of the total number of directors then in office, our board of directors, without stockholder approval, may issue shares of preferred stock with voting and conversion rights which could adversely affect the holders of shares of our common stock and the market value of our common stock. There are no shares of preferred stock outstanding, and we have no present intention to issue any shares of preferred stock.

Registration Rights

We are party to an amended and restated registration rights agreement with certain holders of our common stock.

Under the amended and restated registration rights agreement, holders of registrable shares can demand that we file a registration statement or request that their shares be included on a registration statement that we are otherwise filing, in either case, registering the resale of their shares of common stock. These registration rights are subject to conditions and limitations, including the right, in certain circumstances, of the underwriters of an offering to limit the number of shares included in such registration and our right, in certain circumstances, not to effect a requested S-1 or S-3 registration within 60 days before the Company's estimated date of filing a registration statement or six months following the effective date of a registration statement pertaining to an underwritten public offering of securities for the account of the Company, including this offering.

Demand Registration Rights

The holders of at least a majority of the registrable shares may require us to file a registration statement under the Securities Act at our expense with respect to the resale of their registrable shares, and we are required to use our best efforts to effect the registration.

Piggyback Registration Rights

If we propose to register any of our securities under the Securities Act for our own account or the account of any other holder, the holders of registrable shares are entitled to notice of such registration and to request that we include registrable shares for resale on such registration statement, subject to the right of any underwriter to limit the number of shares included in such registration.

We will pay all registration expenses, other than underwriting discounts and commissions, related to any demand or piggyback registration. The amended and restated registration rights agreement contains customary cross-indemnification provisions, pursuant to which we are obligated to indemnify the selling stockholders, in the event of misstatements or omissions in the registration statement attributable to us and they are obligated to indemnify us for misstatements or omissions attributable to them, in each case, except in the event of fraud. The registration rights will not terminate until all registrable shares have been sold or no longer qualify as registrable shares.

Anti-Takeover Effects of Our Certificate of Incorporation and Our By-Laws

Our certificate of incorporation and by-laws contain certain provisions that are intended to enhance the likelihood of continuity and stability in the composition of our board of directors and which may have the effect of delaying, deferring or preventing a future takeover or change in control of the company unless such takeover or change in control is approved by our board of directors.

These provisions include:

Classified Board. Our certificate of incorporation provides that our board of directors be divided into three classes of directors, with the classes as nearly equal in number as possible. As a result, approximately one-third of our board of directors will be elected each year. The classification of directors has the effect of making it more difficult for stockholders to change the composition of our

board. Our certificate of incorporation also provides that, subject to any rights of holders of preferred stock to elect additional directors under specified circumstances, the number of directors is fixed exclusively pursuant to a resolution adopted by our board of directors.

Action by Written Consent; Special Meetings of Stockholders. Our certificate of incorporation provides that, except as otherwise provided for by a resolution of the board of directors providing for the issuance of a series of preferred stock, stockholder action can be taken only at an annual or special meeting of stockholders and cannot be taken by written consent in lieu of a meeting. Our certificate of incorporation and the by-laws also provide that, except as otherwise required by law, and subject to any special rights of the holders of preferred stock, special meetings of the stockholders can only be called pursuant to a resolution adopted by a majority of the board of directors. Except as described above, stockholders are not permitted to call a special meeting or to require the board of directors to call a special meeting.

Removal of Directors. Our certificate of incorporation provides that, subject to any special rights of holders of preferred stock, our directors may be removed only for cause by the affirmative vote of at least 75% of the voting power of our outstanding shares of capital stock, voting together as a single class. This requirement of a supermajority vote to remove directors could enable holders of a minority of our capital stock to prevent a change in the composition of our board.

Advance Notice Procedures. Our by-laws establish an advance notice procedure for stockholder proposals to be brought before an annual meeting of our stockholders, including proposed nominations of persons for election to the board of directors. Stockholders at an annual meeting will only be able to consider proposals or nominations specified in the notice of meeting or brought before the meeting by or at the direction of the board of directors or by a stockholder who was a stockholder of record on the record date for the meeting, who is entitled to vote at the meeting and who has given our Secretary timely written notice, in proper form, of the stockholder's intention to bring that business before the meeting. Although the by-laws do not give the board of directors the power to approve or disapprove stockholder nominations of candidates or proposals regarding other business to be conducted at a special or annual meeting, the by-laws may have the effect of precluding the conduct of certain business at a meeting if the proper procedures are not followed or may discourage or deter a potential acquiror from conducting a solicitation of proxies to elect its own slate of directors or otherwise attempting to obtain control of the company.

Supermajority Approval Requirements. The Delaware General Corporation Law generally provides that the affirmative vote of a majority of the shares entitled to vote on any matter is required to amend a corporation's certificate of incorporation or by-laws, unless either a corporation's certificate of incorporation or by-laws require a greater percentage. Our certificate of incorporation provides that the affirmative vote of holders of at least 75% of the voting power of the outstanding shares of our capital stock is required to amend, alter, change or repeal our by-laws. This requirement of a supermajority vote to approve amendments to our by-laws could enable holders of a minority of our capital stock to exercise veto power over any such amendments.

Authorized but Unissued Shares. Our authorized but unissued shares of common stock and preferred stock will be available for future issuance without stockholder approval. These additional shares may be utilized for a variety of corporate purposes, including future public offerings to raise additional capital, corporate acquisitions and employee benefit plans. The existence of authorized but unissued shares of common stock and preferred stock could render more difficult or discourage an attempt to obtain control of a majority of our common stock by means of a proxy contest, tender offer, merger or otherwise.

Exclusive Forum. Our certificate of incorporation provides that, subject to limited exceptions, the state or federal court located within the State of Delaware is the sole and exclusive forum 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 certificate of incorporation or our 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 certificate of incorporation described above. Although we believe these provisions benefit us by providing increased consistency in the application of Delaware law for the specified types of actions and proceedings, the provisions may have the effect of discouraging lawsuits against our directors and officers. The enforceability of similar choice of forum provisions in other companies' certificates of incorporation has been challenged in legal proceedings, and it is possible that, in connection with one or more actions or proceedings described above, a court could find the choice of forum provisions contained in our certificate of incorporation to be inapplicable or unenforceable.

Section 203 of the Delaware General Corporation Law. We are subject to the provisions of Section 203 of the Delaware General Corporation Law. In general, Section 203 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. A "business combination" includes, among other things, a merger, asset or stock sale or other transaction resulting in a financial benefit to the interested stockholder. An "interested stockholder" is a person who, together with affiliates and associates, owns, or did own within three years prior to the determination of interested stockholder status, 15% or more of the corporation's voting stock.

Under Section 203, a business combination between a corporation and an interested stockholder is prohibited unless it satisfies one of the following conditions: before the stockholder became interested, the board of directors approved either the business combination or the transaction which resulted in the stockholder becoming an interested stockholder; upon consummation of the transaction which resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the voting stock outstanding, shares owned by persons who are directors and also officers, and employee stock plans, in some instances; or at or after the time the stockholder became interested, the business combination was approved by the board of directors of the corporation and authorized at an annual or special meeting of the stockholders by the affirmative vote of at least two-thirds of the outstanding voting stock which is not owned by the interested stockholder.

A Delaware corporation may "opt out" of these provisions with an express provision in its original certificate of incorporation or an express provision in its certificate of incorporation or by-laws resulting from a stockholders' amendment approved by at least a majority of the outstanding voting shares. We have not opted out of these provisions. As a result, mergers or other takeover or change in control attempts of us may be discouraged or prevented.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is Computershare Trust Company, N.A. The transfer agent and registrar's address is 462 South 4th Street, Suite 1600, Louisville, Kentucky 40202.

DESCRIPTION OF WARRANTS

The following description, together with the additional information that we include in any applicable prospectus supplements and in any related free writing prospectuses that we may authorize

to be distributed to purchasers, summarizes the material terms and provisions of the warrants that we may offer under this prospectus. While the terms we have summarized below will apply generally to any warrants that we may offer under this prospectus, we will describe the particular terms of any series of warrants in more detail in the applicable prospectus supplement. The terms of any warrants offered under a prospectus supplement may differ from the terms described below.

We will file as exhibits to the registration statement of which this prospectus is a part, or will incorporate by reference from reports that we file with the SEC, the form of warrant agreement that describes the terms of the series of warrants we are offering, and any supplemental agreements, before the issuance of the related series of warrants. The following summaries of material terms and provisions of the warrants are subject to, and qualified in their entirety by reference to, all the provisions of the warrant agreement and any supplemental agreements applicable to a particular series of warrants. We urge purchasers to read the applicable prospectus supplements related to the particular series of warrants that we may offer under this prospectus, as well as any related free writing prospectuses and the complete warrant agreement and any supplemental agreements that contain the terms of the warrants.

General Terms. We may issue warrants to purchase common stock or preferred stock. We may offer warrants separately or together with one or more additional warrants, common stock or preferred stock, or any combination of those securities in the form of units, as described in the applicable prospectus supplement. If we issue warrants as part of a unit, the accompanying prospectus supplement will specify whether those warrants may be separated from the other securities in the unit prior to the expiration date of the warrants.

We will specify in a prospectus supplement the terms of the series of warrants, including, if applicable, the following:

- the specific designation and aggregate number of, and the offering price at which we will issue, the warrants;
- the currency or currency units in which the offering price, if any, and the exercise price are payable;
- the date on which the right to exercise the warrants will begin and the date on which that right will expire or, if a holder may not continuously exercise the warrants throughout that period, the specific date or dates on which such holder may exercise the warrants;
- whether the warrants are to be sold separately or with other securities as parts of units;
- whether the warrants will be issued in definitive or global form or in any combination of these forms, although, in any case, the form of a warrant included in a unit will correspond to the form of the unit and of any security included in that unit;
- any applicable material U.S. federal income tax consequences;
- the identity of the warrant agent for the warrants and of any other depositaries, execution or paying agents, transfer agents, registrars or other agents;
- the proposed listing, if any, of the warrants or any securities purchasable upon exercise of the warrants on any securities exchange;
- the designation and terms of any equity securities purchasable upon exercise of the warrants;
- if applicable, the designation and terms of the preferred stock or common stock with which the warrants are issued and, the number of warrants issued with each security;
- if applicable, the date from and after which the warrants and common stock and/or preferred stock will be separately transferable;

- the number of shares of preferred stock or the number of shares of common stock purchasable upon exercise of a warrant and the price at which those shares may be purchased;
- if applicable, the minimum or maximum amount of the warrants that may be exercised at any one time;
- information with respect to book-entry procedures, if any;
- the antidilution provisions of, and other provisions for changes to or adjustment in the exercise price of, the warrants, if any;
- any redemption or call provisions; and
- any additional terms of the warrants, including terms, procedures and limitations relating to the exchange or exercise of the warrants.

Before exercising their warrants, holders of warrants will not have any of the rights of holders of the securities purchasable upon such exercise, including, in the case of warrants to purchase common stock or preferred stock, the right to receive dividends, if any, or payments upon our liquidation, dissolution or winding up or to exercise voting rights, if any.

The provisions described in this section, as well as those described under "Description of Capital Stock" will apply to each warrant, as applicable, and to any common stock or preferred stock included in each warrant, as applicable.

Enforceability of Rights by Holders of Warrants. Each warrant agent will act solely as our agent under the applicable warrant agreement and will not assume any obligation or relationship of agency or trust with any holder or any warrant. A single bank or trust company may act as a warrant agent for more than one issue of warrants. A warrant agent will have no duty or responsibility in case of any default by us under the applicable warrant agreement or warrant, including any duty or responsibility to initiate any proceedings at law or otherwise, or to make any demand upon us. Any holder of a warrant may, without the consent of the related warrant agent or the holder of any other warrant, enforce by appropriate legal action its right to exercise, and receive the securities purchasable upon exercise of, its warrants.

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

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, 2016, filed with the SEC on March 1, 2017;
- Our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2017 and June 30, 2017, filed with the SEC on May 8, 2017 and August 3, 2017, respectively;
- The information specifically incorporated by reference into our Annual Report on Form 10-K for the fiscal year ended December 31, 2016 from our Definitive Proxy Statement on Schedule 14A, filed with the SEC on April 13, 2017;
- Our Current Reports on Form 8-K filed with the SEC on April 27, 2017, May 2, 2017, May 10, 2017, June 6, 2017, June 15, 2017, June 30, 2017, July 19, 2017 and September 19, 2017; and
- The description of our common stock contained in our Registration Statement on Form 8-A, filed with the SEC on September 13, 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, 2016, and the effectiveness of Acceleron Pharma Inc.'s internal control over financial reporting as of December 31, 2016 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.

\$150,000,000



Acceleron Pharma Inc.

Common stock

Prospectus supplement

J.P. Morgan

, 2017

Citigroup

Leerink Partners
