Aeglea BioTherapeutics, Inc.
Form S-3/A
February 11, 2019
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As filed with the Securities and Exchange Commission on February 11, 2019

Registration No. 333-228967

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, D.C. 20549

Amendment No. 1

to

FORM S-3

REGISTRATION STATEMENT

UNDER

THE SECURITIES ACT OF 1933

Aeglea BioTherapeutics, Inc.

(Exact name of registrant as specified in its charter)

Delaware	46-4312787
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)

901 S. MoPac Expressway

Barton Oaks Plaza One

Suite 250

Austin, TX 78746

(512) 942-2935

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

Anthony G. Quinn, M.B Ch.B, Ph.D.

Chief Executive Officer

Aeglea BioTherapeutics, Inc.

901 S. MoPac Expressway

Barton Oaks Plaza One

Suite 250

Austin, TX 78746

(512) 942-2935

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

Copies to:

Robert A. Freedman, Esq.	Charles N. York II
Effie Toshav, Esq.	Chief Financial Officer

Fenwick & West LLP

801 California Street

Mountain View, California 94041

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Aeglea BioTherapeutics, Inc.

901 S. MoPac Expressway

Barton Oaks Plaza One

Suite 250

Austin, TX 78746

(512) 942-2935

Approximate date of commencement of proposed sale to the public: From time to time after the effective date of this Registration Statement.

If the only securities being registered on this Form are being offered pursuant to dividend or interest reinvestment plans, please check the following box:

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, other than securities offered only in connection with dividend or interest reinvestment plans, check the following box:

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

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

If this Form is a registration statement pursuant to General Instruction I.D. or a post-effective amendment thereto that shall become effective upon filing with the Commission pursuant to Rule 462(e) under the Securities Act, check the following box.

If this Form is a post-effective amendment to a registration statement filed pursuant to General Instruction I. D. filed to register additional securities or additional classes of securities pursuant to Rule 413(b) under the Securities Act, check the following box.

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

Large accelerated filer	Accelerated filer
Non-accelerated filer	Smaller reporting company
Emerging growth company	

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 7(a)(2)(B) of the Securities Act.

CALCULATION OF REGISTRATION FEE

Title of Each Class of Securities to be Registered (1)	Amount to be Registered (1)(2)	Proposed Maximum Offering Price Per Security (3)	Proposed Maximum Aggregate Offering Price (3)	Amount of Registration Fee (4)
Common stock, $0.0001 par value per share				
Preferred stock, $0.0001 par value per share				
Debt securities				
Warrants				
Subscription rights				
Units				
Total			$200,000,000	$24,240

(1) There is being registered hereunder an indeterminate number of shares of (a) common stock, (b) preferred stock, (c) debt securities, (d) warrants to purchase common stock, preferred stock or debt securities of the Registrant, (e) subscription rights to purchase common stock, preferred stock or debt securities of the Registrant, and (f) units, consisting of some or all of these securities in any combination, as may be sold from time to time by the Registrant. Any securities registered hereunder may be sold separately or as units with other securities registered hereunder. There are also being registered hereunder an indeterminate number of shares of common stock, preferred stock and debt securities as shall be issuable upon conversion, exchange or exercise of any securities that provide for such issuance. In no event will the aggregate offering price of all types of securities issued by the Registrant pursuant to this registration statement exceed $200,000,000.

(2) Pursuant to Rule 416(a), this registration statement also covers any additional securities that may be offered or issued in connection with any stock split, stock dividend or similar transaction.

(3) The proposed maximum offering price per share and proposed maximum aggregate offering price for each type of security will be determined from time to time by the Registrant in connection with the issuance by the Registrant of the securities registered hereunder.

(4) Calculated pursuant to Rule 457(o) under the Securities Act of 1933, as amended. The registrant previously paid $23,595 of the registration fee in connection with the prior filing of the Registration Statement.

The Registrant hereby amends this registration statement on such date or dates as may be necessary to delay its effective date until the Registrant shall file a further amendment which specifically states that this

registration statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933, as amended, or until the registration statement shall become effective on such date as the Commission, acting pursuant to said Section 8(a), may determine.

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EXPLANATORY NOTE

This registration statement contains two prospectuses:

- a base prospectus, which covers the offering, issuance and sale by us of up to a maximum aggregate offering price of $200,000,000 of our common stock, preferred stock, debt securities, warrants to purchase our common stock, preferred stock or debt securities, subscription rights to purchase our common stock, preferred stock or debt securities and/or units consisting of some or all of these securities; and

- a sales agreement prospectus supplement covering the offering, issuance and sale by us of up to a maximum aggregate offering price of $60,000,000 of our common stock that may be issued and sold under an Open Market Sale Agreement[SM] dated December 21, 2018 with Jefferies LLC.

The base prospectus immediately follows this explanatory note. The specific terms of any securities to be offered pursuant to the base prospectus will be specified in a prospectus supplement to the base prospectus. The sales agreement prospectus supplement immediately follows the base prospectus. The $60,000,000 of common stock that may be offered, issued and sold under the sales agreement prospectus supplement is included in the $200,000,000 of securities that may be offered, issued and sold by us under the base prospectus.

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The information in this prospectus is not complete and may be changed. We may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. This prospectus is not an offer to sell these securities, and it is not soliciting an offer to buy these securities, in any state where the offer or sale is not permitted.

SUBJECT TO COMPLETION, DATED FEBRUARY 11, 2019

PROSPECTUS

$200,000,000

Aeglea BioTherapeutics, Inc.

Common Stock, Preferred Stock,

Debt Securities, Warrants, Subscription Rights and Units

From time to time, we may offer up to $200,000,000 aggregate dollar amount of shares of our common stock or preferred stock, debt securities, warrants to purchase our common stock, preferred stock or debt securities, subscription rights to purchase our common stock, preferred stock or debt securities and/or units consisting of some or all of these securities, in any combination, together or separately, in one or more offerings, in amounts, at prices and on the terms that we will determine at the time of the offering and which will be set forth in a prospectus supplement and any related free writing prospectus. The prospectus supplement and any related free writing prospectus may also add, update or change information contained in this prospectus. The total amount of these securities will have an initial aggregate offering price of up to $200,000,000.

You should read this prospectus, the information incorporated, or deemed to be incorporated, by reference in this prospectus, and any applicable prospectus supplement and related free writing prospectus carefully before you invest.

Our common stock is traded on The Nasdaq Global Market under the symbol AGLE. On February 8, 2019 the last reported sales price for our common stock was $7.83 per share. None of the other securities we may offer are currently traded on any securities exchange. The applicable prospectus supplement and any related free writing prospectus will contain information, where applicable, as to any other listing on The Nasdaq Global Market or any securities market or exchange of the securities covered by the prospectus supplement and any related free writing prospectus.

An investment in our securities involves a high degree of risk. You should carefully consider the information under the heading Risk Factors beginning on page 7 of this prospectus before investing in our securities.

Common stock, preferred stock, debt securities, warrants, subscription rights and/or units may be sold by us to or through underwriters or dealers, directly to purchasers or through agents designated from time to time. For additional information on the methods of sale, you should refer to the section entitled Plan of Distribution in this prospectus. If any underwriters, dealers or agents are involved in the sale of any securities with respect to which this prospectus is being delivered, the names of such underwriters or agents and any applicable fees, discounts or commissions, details regarding over-allotment options, if any, and the net proceeds to us will be set forth in a prospectus supplement. The price to the public of such securities and the net proceeds we expect to receive from such sale will also be set forth in a prospectus supplement.

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

The date of this prospectus is , 2019

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ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission, or the SEC, using a shelf registration process. Under this shelf registration process, from time to time, we may sell any combination of the securities described in this prospectus in one or more offerings, up to a total dollar amount of $200,000,000. We have provided to you in this prospectus a general description of the securities we may offer. Each time we sell securities under this shelf registration process, we will provide a prospectus supplement that will contain specific information about the terms of the offering. We may also add, update or change in the prospectus supplement any of the information contained in this prospectus. To the extent there is a conflict between the information contained in this prospectus and the prospectus supplement, you should rely on the information in the prospectus supplement; *provided* that, if any statement in one of these documents is inconsistent with a statement in another document having a later date for example, a document incorporated by reference in this prospectus or any prospectus supplement the statement in the document having the later date modifies or supersedes the earlier statement. You should read both this prospectus and any prospectus supplement together with additional information described under the next heading Where You Can Find More Information.

You should rely only on the information contained in or incorporated by reference into this prospectus or any applicable prospectus supplement. No dealer, salesperson or any other person is authorized to give any information or to make any representation other than the information and representations contained in or incorporated by reference into this prospectus or any applicable prospectus supplement. If different information is given or different representations are made, you may not rely on that information or those representations as having been authorized by us. You may not imply from the delivery of this prospectus and any applicable prospectus supplement, nor from a sale made under this prospectus and any applicable prospectus supplement, that our affairs are unchanged since the date of this prospectus and any applicable prospectus supplement or that the information contained in any document incorporated by reference is accurate as of any date other than the date of the document incorporated by reference, regardless of the time of delivery of this prospectus and any applicable prospectus supplement or any sale of a security. This prospectus and any applicable prospectus supplement may only be used where it is legal to sell the securities.

THIS PROSPECTUS MAY NOT BE USED TO OFFER AND SELL SECURITIES UNLESS IT IS ACCOMPANIED BY AN ADDITIONAL PROSPECTUS OR A PROSPECTUS SUPPLEMENT.

In this prospectus, unless the context otherwise requires, the terms Aeglea, the Company, we, us, and our refer t Aeglea BioTherapeutics, Inc., a Delaware corporation, and its consolidated subsidiaries.

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PROSPECTUS SUMMARY

This summary may not contain all the information that you should consider before investing in securities. You should read the entire prospectus and the information incorporated by reference in this prospectus carefully, including Risk Factors and the financial data and related notes and other information incorporated by reference, before making an investment decision.

Company Overview

We are a biotechnology company that designs and develops innovative human enzyme therapeutics for patients with rare genetic diseases and cancer. We believe our novel approach of utilizing human enzymes offers advantages that provide a greater likelihood of clinical success and commercial adoption.

Our drug-hunting capabilities in enzyme engineering, preclinical disease modeling, and drug development in both rare genetic disease and cancer allow us to identify and advance innovative opportunities to address important unmet medical needs for the benefit of patients. Our programs and the decisions we make to progress assets into clinical studies are driven by the following considerations:

- Potential for enhancement of human enzymatic activity
- Ability to create novel human enzymatic activity
- Strong preclinical data and rationale
- Limited or no competition
- Meaningful commercial opportunities
- Worldwide commercial rights

We are a patient-focused organization conscious of the fact that people with a rare genetic disease or cancer have limited treatment options, and we recognize that their lives and well-being are highly dependent upon our efforts to develop improved therapies. For this reason, we are passionate about designing and developing novel therapeutics to address significant unmet medical need for rare genetic disease and cancer.

Our lead product candidate, pegzilarginase, is engineered to degrade the amino acid arginine and is being developed to exploit two aspects of arginine metabolism, including arginine excess in patients with Arginase 1 Deficiency, a rare genetic disease, as well as the arginine dependence of some cancers. We expect to start a single, global pivotal Phase 3 trial of pegzilarginase in patients with Arginase 1 Deficiency in the second quarter of 2019. We are currently evaluating pegzilarginase in multiple ongoing clinical trials, including a Phase 1/2 clinical trial for the treatment of Arginase 1 Deficiency, an open-label extension study for patients with Arginase 1 Deficiency, a Phase 1 clinical trial for the treatment of advanced solid tumors, and a Phase 1/2 combination clinical trial of pegzilarginase with

pembrolizumab for the treatment of patients with small cell lung cancer (SCLC). We are also building a pipeline of additional product candidates targeting key amino acids and other metabolites, including AEB4104 for the treatment of homocystinuria, AEB5100 for the treatment of cystinuria, and AEB2109 for the treatment of cancer.

Rare Genetic Diseases

Pegzilarginase in Patients with Arginase 1 Deficiency

Arginase 1 Deficiency is a debilitating disease that progresses despite current medical management leading to severe complications and early death. Pegzilarginase is the first ever investigative therapy that addresses the elevated levels of arginine, which is the key driver of Arginase 1 Deficiency.

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In December 2018, we announced the design of our single, global pivotal Phase 3 PEACE (Pegzilarginase Effect on Arginase 1 Deficiency Clinical Endpoints) trial with a primary endpoint of plasma arginine reduction and secondary endpoints which include assessments of clinical outcomes on mobility and adaptive behavior, safety and pharmacokinetics. The Phase 3 PEACE trial is designed to assess the effects of treatment with pegzilarginase versus placebo over 24 weeks, and we expect to enroll 30 patients with Arginase 1 Deficiency. We finalized the design of the Phase 3 PEACE trial to be a single, global pivotal trial based on the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) feedback. Patients enrolled in the trial will be randomized on a two-to-one basis to receive weekly infusions of pegzilarginase, or placebo for the double-blind treatment period of 24 weeks. Patients will be considered eligible for the PEACE trial if they exhibit average plasma arginine of greater than 250 μM, are greater than two years of age and have a deficit of mobility or adaptive behavior. All assessments and dose adjustments will be conducted in a blinded fashion at pre-specified intervals. Patients will remain on current disease management for the duration of the Phase 3 PEACE trial. We expect to dose the first patient in the PEACE trial in the second quarter of 2019 and expect that data from the Phase 3 PEACE trial will be available in the first quarter of 2021. The FDA indicated that data from this Phase 3 PEACE trial showing plasma arginine reduction in conjunction with improvements in clinically meaningful aspects of the disease may be sufficient to support a marketing application for pegzilarginase in Arginine 1 Deficiency. Additional interim clinical data from our Phase 1/2 clinical trial reporting repeat dose administration of pegzilarginase is expected in the first half of 2019.

In October 2018, we announced new positive interim clinical data at the 2018 American Society of Human Genetics (ASHG) Conference from our ongoing Phase 1/2 trial of pegzilarginase in patients with Arginase 1 Deficiency. We reported clinical improvements with repeat dose administration of pegzilarginase after only eight weeks, including consistent reduction of arginine and improvement in mobility or adaptive behavior. Pegzilarginase was generally well tolerated; most treatment-related adverse events were mild, and while investigators considered some of the hypersensitivity events as serious adverse events, the hypersensitivity reactions were generally manageable with standard measures and all patients continued study treatment. Additionally, we completed and exceeded our enrollment target with 16 patients in the Phase 1/2 clinical trial.

In addition, we announced in October 2018 that the FDA granted a rare pediatric disease designation to our lead product candidate, pegzilarginase, for the treatment of Arginase 1 Deficiency. This designation by the FDA confirms our eligibility to receive a rare pediatric disease priority review voucher upon approval of a biologics license application for pegzilarginase if completed before October 1, 2022.

AEB4104 in Patients with Homocystinuria

Homocystinuria is an inherited disorder of methionine metabolism caused by mutations in CBS and other genes leading to elevated levels of plasma and tissue homocysteine and homocystine, which affect multiple organ systems and cause early mortality. Current disease management, which includes dietary protein (methionine) restriction, vitamins, and betaine supplementation, is insufficient to effectively control the more severe forms of the disease. Given the severity of the disease, the limitations of current disease management approaches, and the data demonstrating improved survival in a preclinical model of the disease, we intend to advance AEB4104 into IND-enabling studies in the first half of 2019. The patent rights to AEB4104 were exclusively licensed to us from the Board of Regents of The University of Texas System, or the University, pursuant to the Amended and Restated License Agreement dated January 31, 2017, as amended, or the Restated License. For more information on the Restated License, see section titled Item 1. Business Licensing in our Annual Report on Form 10-K for the fiscal year ended December 31, 2017.

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In October 2018, we announced preclinical efficacy data on our AEB4104 homocystinuria program at the 2018 American Society of Human Genetics (ASHG) Conference, demonstrating that AEB4104 improved survival and important disease-related abnormalities in a preclinical model of homocystinuria. AEB4104 decreased homocysteine and homocystine levels in the plasma, including the CBS deficient model (CBS-/-) and the high methionine diet-induced model of homocystinuria. Treatment with AEB4104 prevented early mortality, stopped disease progression, and reversed liver pathology.

AEB5100 in Patients with Cystinuria

AEB5100 is a novel recombinant human enzyme that degrades plasma cystine and cysteine. We are developing AEB5100 for the treatment of patients with cystinuria, a rare genetic disease characterized by frequent and recurrent kidney stone formation requiring multiple procedural interventions and by an increased risk of chronic kidney disease. Cystinuria occurs due to genetic mutations in amino acid transporters that lead to increased amounts of cystine in the urine. This results in high cystine concentrations in the urine and formation of kidney stones.

In October 2018, we announced preclinical efficacy data on our AEB5100 cystinuria therapeutic program at the 2018 American Society of Nephrology (ASN) Conference, demonstrating that AEB5100 lowered blood levels of cystine and cysteine, decreased the amount of cystine in the urine and reduced kidney stone formation in a preclinical model of cystinuria. Given the compelling preclinical data and the limitations of current disease management approaches, we intend to advance AEB5100 into IND-enabling studies and we anticipate beginning GLP manufacturing for toxicology studies in the first half of 2019. The patent rights to AEB5100 were exclusively licensed to us from the University pursuant to the Restated License. For more information on the Restated License, see section titled Item 1. Business Licensing in our Annual Report on Form 10-K for the fiscal year ended December 31, 2017.

Cancer

Pegzilarginase with Pembrolizumab in Patients with Small Cell Lung Cancer

In the first quarter of 2018, we initiated a Phase 1 clinical collaboration with Merck to evaluate the combination of pegzilarginase with Merck s anti-PD1 therapy, pembrolizumab, for the treatment of patients with SCLC, with the primary objectives of determining the safety and dose of pegzilarginase that can be combined with pembrolizumab to be used in Phase 2. The Phase 2 primary objective is objective response rate (ORR) and secondary objectives include safety, clinical benefit rate, time to response, duration of response, progression free survival (PFS), overall survival, pegzilarginase pharmacokinetics, and exploring the correlation of tumor expression of ASS1 and PD-L1 with clinical activity. We dosed the first patient in the first quarter of 2018, expect to initiate Phase 2 in the second quarter of 2019, and expect to report topline safety and clinical activity for Phase 1 in the first quarter of 2019.

Pegzilarginase in Patients with Advanced Solid Tumors

In October 2018, we presented interim clinical data at the European Society for Medical Oncology (ESMO) 2018 Congress, demonstrating that pegzilarginase monotherapy resulted in anti-tumor activity in heavily pre-treated patients with advanced melanoma. The investigator-assessed responses in 13 cutaneous melanoma patients and 15 uveal melanoma patients revealed that one patient achieved a confirmed partial response (PR) at week 20 and eight patients had stable disease (SD) at week 8 or later. Three patients experienced treatment-related, Serious Grade 3 adverse events, including asthenia and failure to thrive, vomiting and dehydration. Six patients remained on treatment at the time of the data cutoff. Anti-tumor activity appeared greater in tumors lacking argininosuccinate synthetase 1 (ASS1) expression, which is consistent with preclinical studies that suggest tumors lacking ASS1 expression are dependent on extracellular arginine for survival.

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In addition, pegzilarginase was shown to rapidly and sustainably deplete plasma arginine with a manageable safety profile. The results, combined with preclinical evidence of synergy with immune checkpoint inhibitors, support further clinical evaluation of pegzilarginase in immunotherapy combinations.

The Securities We May Offer

With this prospectus, we may offer common stock, preferred stock, debt securities, warrants, subscription rights to purchase our common stock, preferred stock or debt securities, and/or units consisting of some or all of these securities in any combination. The aggregate offering price of securities that we offer with this prospectus will not exceed $200,000,000. Each time we offer securities with this prospectus, we will provide offerees with a prospectus supplement that will contain the specific terms of the securities being offered. The following is a summary of the securities we may offer with this prospectus.

Common Stock

We may offer shares of our common stock, par value $0.0001 per share.

Preferred Stock

We may offer shares of our preferred stock, par value $0.0001 per share, in one or more series. Our board of directors or a committee designated by the board will determine the dividend, voting, conversion and other rights of the series of shares of preferred stock being offered. Each series of preferred stock will be more fully described in the particular prospectus supplement that will accompany this prospectus, including redemption provisions, rights in the event of our liquidation, dissolution or the winding up, voting rights and rights to convert into common stock.

Debt Securities

We may offer general obligations, which may be secured or unsecured, senior or subordinated and convertible into shares of our common stock or preferred stock. In this prospectus, we refer to the senior debt securities and the subordinated debt securities together as the debt securities. Our board of directors will determine the terms of each series of debt securities being offered.

We will issue the debt securities under an indenture between us and a trustee. In this document, we have summarized general features of the debt securities from the indenture. We encourage you to read the indenture, which is an exhibit to the registration statement of which this prospectus is a part.

Warrants

We may offer warrants for the purchase of debt securities, shares of preferred stock or shares of common stock. We may issue warrants independently or together with other securities. Our board of directors will determine the terms of the warrants.

Subscription Rights

We may offer subscription rights for the purchase of common stock, preferred stock or debt securities. We may issue subscription rights independently or together with other securities. Our board of directors will determine the terms of the subscription rights.

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Units

We may offer units consisting of some or all of the securities described above, in any combination, including common stock, preferred stock, warrants and/or debt securities. The terms of these units will be set forth in a prospectus supplement. The description of the terms of these units in the related prospectus supplement will not be complete. You should refer to the applicable form of unit and unit agreement for complete information with respect to these units.

* * *

We were formed as a limited liability company under the laws of the State of Delaware in December 2013 and converted to a Delaware corporation in March 2015. In connection with our conversion to a Delaware corporation, each of our outstanding shares of the members of the limited liability company was converted into shares of capital stock. On the date of conversion, each Series A convertible preferred share converted into a share of Series A convertible preferred stock, and each Common A share, Common A-1 share and Common B share converted into shares of common stock. Our principal executive offices are located at 901 S. MoPac Expressway, Barton Oaks Plaza One, Suite 250, Austin, Texas 78746, and our telephone number is (512) 942-2935. We have research and development operations and corporate offices in Austin, TX.

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RISK FACTORS

An investment in our securities involves a high degree of risk. The prospectus supplement applicable to each offering of securities will contain a discussion of the risks applicable to an investment in our securities. Prior to making a decision about investing in our securities, you should carefully consider the specific factors discussed under the heading Risk Factors in the applicable prospectus supplement, together with all of the other information contained or incorporated by reference in the prospectus supplement or appearing or incorporated by reference in this prospectus. You should also consider the risks, uncertainties and assumptions discussed under Part II, Item 1A, Risk Factors, in our Quarterly Report on Form 10-Q for the quarter ended September 30, 2018, which is incorporated herein by reference, and may be amended, supplemented or superseded from time to time by other reports we file with the SEC in the future. The risks and uncertainties we have described 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.

FORWARD-LOOKING STATEMENTS

This prospectus and documents incorporated herein by reference contain forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements involve a number of risks and uncertainties. We caution readers that any forward-looking statement is not a guarantee of future performance and that actual results could differ materially from those contained in the forward-looking statement. These statements are based on current expectations of future events.

Such statements include, but are not limited to, statements regarding expectations and intentions, costs and expenses, outcome of contingencies, financial condition, results of operations, liquidity, cost savings, objectives of management, debt financing, our future results of operations and financial position, business strategies, market size, potential growth opportunities, clinical development activities, efficacy and safety profile of our product candidates, our ability to maintain and recognize the benefits of certain designations received by product candidates, timing and results of our nonclinical studies and clinical trials, the receipt and timing of potential regulatory designations, the achievement of clinical and commercial milestones, the advancement of our technologies and our proprietary product candidates, approvals and commercialization of product candidates and other statements that are not historical facts. You can find many of these statements by looking for words like believes, expects, anticipates, estimates, may, might, sh could, plan, intend, project, seek or similar expressions in this prospectus, in documents incorporated by referen this prospectus or any free writing prospectus. We intend that such forward-looking statements be subject to the safe harbors created thereby.

These forward-looking statements are based on the current beliefs and expectations of our management and are subject to significant risks and uncertainties. If underlying assumptions prove inaccurate or unknown risks or uncertainties materialize, actual results may differ materially from current expectations and projections. Factors that might cause such a difference include those discussed in Part II, Item 1A, Risk Factors, in our Quarterly Report on Form 10-Q for the quarter ended September 30, 2018, as well as those discussed in this prospectus, the documents incorporated by reference into this prospectus and any free writing prospectus. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date of this prospectus or, in the case of documents referred to or incorporated by reference, the date of those documents.

All subsequent written or oral forward-looking statements attributable to us or any person acting on our behalf are expressly qualified in their entirety by the cautionary statements contained or referred to in this section. We do not undertake any obligation to release publicly any revisions to these forward-looking statements to reflect events or circumstances after the date of this prospectus or to reflect the occurrence of unanticipated events, except as may be required under applicable U.S. securities law. If we do update one or more forward-looking statements, no inference

should be drawn that we will make additional updates with respect to those or other forward-looking statements.

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WHERE YOU CAN FIND MORE INFORMATION

We are subject to the informational requirements of the Securities Exchange Act of 1934, as amended, or the Exchange Act and are required to file annual, quarterly and other reports, proxy statements and other information with the SEC. The SEC maintains an Internet site (http://www.sec.gov) that contains reports, proxy and information statements, and various other information about us. You may also inspect the documents described herein at our principal executive offices, 901 S. MoPac Expressway, Barton Oaks Plaza One, Suite 250, Austin, TX 78746, during normal business hours.

Information about us is also available at our website at http://www.aegleabio.com. However, the information on our website is not a part of this prospectus and is not incorporated by reference into this prospectus.

INCORPORATION OF INFORMATION BY REFERENCE

The SEC allows us to incorporate by reference information that we file with the SEC, which means that we can disclose important information to you by referring you to those other documents. The information incorporated by reference is an important part of this prospectus, and information we file later with the SEC will automatically update and supersede this information. A Current Report (or portion thereof) furnished, but not filed, on Form 8-K shall not be incorporated by reference into this prospectus. We incorporate by reference the documents listed below and any future filings we make with the SEC under Section 13(a), 13(c), 14, or 15(d) of the Exchange Act prior to the termination of any offering of securities made by this prospectus:

- our Annual Report on Form 10-K for the fiscal year ended December 31, 2017, filed with the SEC on March 13, 2018, including certain information incorporated by reference therein from our Definitive Proxy Statement for our 2018 annual meeting of stockholders filed with the SEC on April 16, 2018;

- our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2018, June 30, 2018 and September 30, 2018, filed with the SEC on May 8, 2018, August 9, 2018 and November 8, 2018, respectively;

- our Current Reports on Form 8-K filed on March 26, 2018, April 16, 2018, April 19, 2018, June 8, 2018, July 16, 2018, July 23, 2018, October 10, 2018, November 29, 2018, December 21, 2018 and February 7, 2019 (in each case, except for information contained therein which is furnished rather than filed);

- the description of our common stock contained in our registration statement on Form 8-A filed with the SEC on March 28, 2016 under Section 12 of the Exchange Act, including any amendment or report filed for the purpose of updating such description; and

- filings we make with the SEC pursuant to the Exchange Act after the date of the initial registration statement, of which this prospectus is a part, and prior to the effectiveness of the registration statement.

We will furnish without charge to you, on written or oral request, a copy of any or all of such documents that has been incorporated herein by reference (other than exhibits to such documents unless such exhibits are specifically

incorporated by reference into the documents that this prospectus incorporates). Written or oral requests for copies should be directed Aeglea BioTherapeutics, Inc., Attn: Investor Relations, 901 S. MoPac Expressway, Barton Oaks Plaza One, Suite 250, Austin, Texas 78746, telephone number (512) 942-2935. See the section of this prospectus entitled Where You Can Find More Information for information concerning how to read and obtain copies of materials that we file with the SEC.

Any statement contained in this prospectus, or in a document all or a portion of which is incorporated by reference, shall be modified or superseded for purposes of this prospectus to the extent that a statement contained in this prospectus, any prospectus supplement or any document incorporated by reference modifies or supersedes such statement. Any such statement so modified or superseded shall not, except as so modified or superseded, constitute a part of this prospectus.

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USE OF PROCEEDS

We will retain broad discretion over the use of the net proceeds to us from the sale of our securities under this prospectus. Unless otherwise provided in the applicable prospectus supplement, we intend to use the net proceeds from the sale of securities under this prospectus for general corporate purposes, which may include funding research and development, increasing our working capital, reducing indebtedness, acquisitions or investments in businesses, products or technologies that are complementary to our own and capital expenditures. We will set forth in the prospectus supplement our intended use for the net proceeds received from the sale of any securities. Pending the application of the net proceeds, we intend to invest the net proceeds in short-term or long-term, investment-grade, interest-bearing securities.

PLAN OF DISTRIBUTION

We may sell the securities covered by this prospectus to one or more underwriters for public offering and sale by them, and may also sell the securities to investors directly or through agents. We will name any underwriter or agent involved in the offer and sale of securities in the applicable prospectus supplement. We have reserved the right to sell or exchange securities directly to investors on our own behalf in jurisdictions where we are authorized to do so. We may distribute the securities from time to time in one or more transactions:

at a fixed price or prices, which may be changed;

at market prices prevailing at the time of sale;

at prices related to such prevailing market prices; or

at negotiated prices.

We may directly solicit offers to purchase the securities being offered by this prospectus. We may also designate agents to solicit offers to purchase the securities from time to time. We will name in a prospectus supplement any agent involved in the offer or sale of our securities. Unless otherwise indicated in a prospectus supplement, an agent will be acting on a best efforts basis, and a dealer will purchase securities as a principal for resale at varying prices to be determined by the dealer.

If we utilize an underwriter in the sale of the securities being offered by this prospectus, we will execute an underwriting agreement with the underwriter at the time of sale and we will provide the name of any underwriter in the prospectus supplement that the underwriter will use to make resales of the securities to the public. In connection with the sale of the securities, we, or the purchasers of securities for whom the underwriter may act as agent, may compensate the underwriter in the form of underwriting discounts or commissions. The underwriter may sell the securities to or through dealers, and those dealers may receive compensation in the form of discounts, concessions or commissions from the underwriters or commissions from the purchasers for whom they may act as agent.

We will provide in the applicable prospectus supplement any compensation we pay to underwriters, dealers, or agents in connection with the offering of the securities, and any discounts, concessions or commissions allowed by underwriters to participating dealers. Underwriters, dealers and agents participating in the distribution of the securities

may be deemed to be underwriters within the meaning of the Securities Act of 1933, as amended, or the Securities Act, and any discounts and commissions received by them and any profit realized by them on resale of the securities may be deemed to be underwriting discounts and commissions. We may enter into agreements to indemnify underwriters, dealers and agents against civil liabilities, including liabilities under the Securities Act, and to reimburse them for certain expenses. We may grant underwriters who participate in the distribution of our securities under this prospectus an option to purchase additional securities to cover any over-allotments in connection with the distribution.

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The securities we offer under this prospectus may or may not be listed through The Nasdaq Global Market or any other securities exchange. To facilitate the offering of securities, certain persons participating in the offering may engage in transactions that stabilize, maintain or otherwise affect the price of the securities. This may include short sales of the securities, which involves the sale by persons participating in the offering of more securities than we sold to them. In these circumstances, these persons would cover such short positions by making purchases in the open market or by exercising their option to purchase additional securities. In addition, these persons may stabilize or maintain the price of the securities by bidding for or purchasing securities in the open market or by imposing penalty bids, whereby selling concessions allowed to dealers participating in the offering may be reclaimed if securities sold by them are repurchased in connection with stabilization transactions. The effect of these transactions may be to stabilize or maintain the market price of the securities at a level above that which might otherwise prevail in the open market. These transactions may be discontinued at any time.

We may engage in at the market offerings into an existing trading market in accordance with Rule 415(a)(4) under the Securities Act. In addition, we may enter into derivative transactions with third parties, or sell securities not covered by this prospectus to third parties in privately negotiated transactions. If the applicable prospectus supplement indicates, in connection with those derivatives, the third parties may sell securities covered by this prospectus and the applicable prospectus supplement, including short sale transactions. If so, the third party may use securities pledged by us or borrowed from us or others to settle those sales or to close out any related open borrowings of stock, and they may use securities received from us in settlement of those derivatives to close out any related open borrowings of stock. The third party in these sale transactions will be an underwriter and will be identified in the applicable prospectus supplement. In addition, we may otherwise loan or pledge securities to a financial institution or other third party that in turn may sell the securities short using this prospectus. The financial institution or other third party may transfer its economic short position to investors in our securities or in connection with a concurrent offering of other securities.

We will file a prospectus supplement to describe the terms of any offering of our securities covered by this prospectus. The prospectus supplement will disclose:

- the terms of the offer;
- the names of any underwriters, including any managing underwriters, as well as any dealers or agents;
- the purchase price of the securities from us;
- the net proceeds to us from the sale of the securities;
- any delayed delivery arrangements;
- any over-allotment or other options under which underwriters, if any, may purchase additional securities from us;

any underwriting discounts, commissions or other items constituting underwriters compensation, and any commissions paid to agents;

in a subscription rights offering, whether we have engaged dealer-managers to facilitate the offering or subscription, including their name or names and compensation;

any public offering price; and

other facts material to the transaction.

We will bear all or substantially all of the costs, expenses and fees in connection with the registration of our securities under this prospectus. The underwriters, dealers and agents may engage in transactions with us, or perform services for us, in the ordinary course of business.

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DESCRIPTION OF CAPITAL STOCK

General

Our authorized capital stock consists of 500,000,000 shares of common stock, $0.0001 par value per share, and 10,000,000 shares of undesignated preferred stock, $0.0001 par value per share. The following description summarizes the most important terms of our capital stock. Because it is only a summary, it does not contain all the information that may be important to you. For a complete description, you should refer to our restated certificate of incorporation and restated bylaws, which are included as exhibits to the registration statement of which this prospectus forms a part, and to the applicable provisions of Delaware law.

As of September 30, 2018, there were 22,098,218 shares of our common stock outstanding, and no shares of preferred stock outstanding.

Common Stock

Dividend rights

Subject to preferences that may apply to any shares of preferred stock outstanding at the time, the holders of our common stock are entitled to receive dividends out of funds legally available if our board of directors, in its discretion, determines to issue dividends and then only at the times and in the amounts that our board of directors may determine. For more information about our dividend policy, see Dividend Policy in our Annual Report on Form 10-K for the year ended December 31, 2017, which is incorporated by reference in this prospectus.

Voting rights

Holders of our common stock are entitled to one vote for each share held on all matters submitted to a vote of stockholders. We have not provided for cumulative voting for the election of directors in our restated certificate of incorporation. Accordingly, pursuant to our restated certificate of incorporation holders of a majority of the shares of our common stock are able to elect all of our directors. Our restated certificate of incorporation establishes a classified board of directors, divided into three classes with staggered three-year terms. Only one class of directors will be elected at each annual meeting of our stockholders, with the other classes continuing for the remainder of their respective three-year terms.

No preemptive or similar rights

Our common stock is not entitled to preemptive rights, and is not subject to conversion, redemption or sinking fund provisions.

Right to receive liquidation distributions

Upon our liquidation, dissolution or winding-up, the assets legally available for distribution to our stockholders would be distributable ratably among the holders of our common stock and any participating preferred stock outstanding at that time, subject to prior satisfaction of all outstanding debt and liabilities and the preferential rights of and the payment of liquidation preferences, if any, on any outstanding shares of preferred stock.

Preferred Stock

Our board of directors is authorized, subject to limitations prescribed by Delaware law, to issue preferred stock in one or more series, to establish from time to time the number of shares to be included in each series and to fix the designation, powers, preferences and rights of the shares of each series and any of their qualifications, limitations or restrictions, in each case without further vote or action by our stockholders. Our board of directors

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can also increase or decrease the number of shares of any series of preferred stock, but not below the number of shares of that series then outstanding, without any further vote or action by our stockholders. Our board of directors may authorize the issuance of preferred stock with voting or conversion rights that could adversely affect the voting power or other rights of the holders of our common stock. The issuance of preferred stock, while providing flexibility in connection with possible acquisitions and other corporate purposes, could, among other things, have the effect of delaying, deferring or preventing a change in control of our company and might adversely affect the market price of our common stock and the voting and other rights of the holders of our common stock. We have no current plan to issue any shares of preferred stock.

Registration Rights

Pursuant to the terms of our investors rights agreement entered into in March 2015, as subsequently amended, certain of our stock holders are entitled to rights with respect to the registration of their shares under the Securities Act until the earliest of (a) April 12, 2021, (b) the date on which such holder ceases to hold registrable securities, or (c) such holder s registrable securities could be sold without any restriction on volume or manner of sale in any three-month period under Rule 144 or any successor rule, as described below. We refer to these shares collectively as registrable securities.

Demand registration rights

The holders of at least 62% of the shares of common stock issued upon the conversion of Series B convertible preferred stock in connection with our initial public offering may make a written request to us for the registration of any of the registrable securities under the Securities Act. We are only required to file two registration statements that are declared effective upon exercise of these demand registration rights. We may postpone the filing of a registration statement once during any 12-month period for a total cumulative period of not more than 90 days if our board of directors determines that the filing would be seriously detrimental to us and our stockholders, provided that we do not register any securities for our own account or any other stockholder during such 90-day period.

Form S-3 registration rights

The holders of at least 20% of the outstanding shares of common stock that were issued upon the conversion of shares of preferred stock in connection with our initial public offering can request that we register all or part of their shares on Form S-3 if we are eligible to file a registration statement on Form S-3 and if the aggregate price to the public of the shares offered is at least $1,000,000. We may postpone the filing of a registration statement on Form S-3 once during any 12-month period for a total cumulative period of not more than 90 days if our board of directors determines that the filing would be seriously detrimental to us and our stockholders, provided that we do not register any securities for our own account or any other stockholder during such 90-day period.

Piggyback registration rights

If we register any of our securities for public sale in an offering pursuant to this prospectus, holders of registrable securities will have the right to include their shares in the registration statement. However, this right does not apply to a registration relating to employee benefit plans or a registration on Form S-4 relating solely to a transaction under Rule 145 of the Securities Act. The underwriters of any underwritten offering will have the right to limit the number of shares registered by these holders if they determine that marketing factors require limitation, in which case the number of shares to be registered will be apportioned pro rata among these holders, according to the total amount of securities entitled to be included by each holder. However, the number of shares to be registered by these holders cannot be reduced below 25% of the total shares covered by the registration statement.

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Expenses of registration rights

We generally will pay all expenses related to the registrations, other than underwriting discounts and commissions.

Expiration of registration rights

The registration rights described above will expire, with respect to any particular holder of these rights, on the earlier of the fifth anniversary of the closing of our initial public offering, or when that holder ceases to hold such registrable securities.

Anti-Takeover Provisions

The provisions of Delaware law, our restated certificate of incorporation and our restated bylaws could have the effect of delaying, deferring or discouraging another person from acquiring control of our company. These provisions, which are summarized below, may have the effect of discouraging takeover bids. They are also designed, in part, to encourage persons seeking to acquire control of us to negotiate first with our board of directors. We believe that the benefits of increased protection of our potential ability to negotiate with an unfriendly or unsolicited acquirer outweigh the disadvantages of discouraging a proposal to acquire us because negotiation of these proposals could result in an improvement of their terms.

Delaware law

We are subject to the provisions of Section 203 of the Delaware General Corporation Law regulating corporate takeovers. In general, Section 203 prohibits a publicly-held Delaware corporation from engaging in a business combination with an interested stockholder for a period of three years following the date on which the person became an interested stockholder unless:

Prior to the date of the transaction, the board of directors of the corporation approved either the business combination or 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, but not the outstanding voting stock owned by the interested stockholder, (1) shares owned by persons who are directors and also officers and (2) shares owned by employee stock plans in which employee participants do not have the right to determine confidentially whether shares held subject to the plan will be tendered in a tender or exchange offer; or

At or subsequent to the date of the transaction, the business combination is approved by the board of directors of the corporation and authorized at an annual or special meeting of stockholders, and not by written consent, by the affirmative vote of at least 66.67% of the outstanding voting stock that is not owned by the interested stockholder.

Restated Certificate of Incorporation and Restated Bylaw Provisions

Our restated certificate of incorporation and our restated bylaws include a number of provisions that could deter hostile takeovers or delay or prevent changes in control of our company, including the following:

Board of Directors vacancies. Our restated certificate of incorporation and restated bylaws authorize our board of directors to fill vacant directorships, including newly created seats unless the board of directors determines that any such vacancies shall be filled by the stockholders. In addition, the number of directors constituting our board of directors is permitted to be set only by a resolution adopted by a

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majority vote of our entire board of directors. These provisions prevent a stockholder from increasing the size of our board of directors and then gaining control of our board of directors by filling the resulting vacancies with its own nominees. This makes it more difficult to change the composition of our board of directors but promotes continuity of management.

Classified board. Our restated certificate of incorporation and restated bylaws provide that our board is classified into three classes of directors, each with staggered three-year terms. A third party may be discouraged from making a tender offer or otherwise attempting to obtain control of us as it is more difficult and time consuming for stockholders to replace a majority of the directors on a classified board of directors.

Stockholder action; special meetings of stockholders. Our restated certificate of incorporation provides that our stockholders may not take action by written consent, but may only take action at annual or special meetings of our stockholders. As a result, a holder controlling a majority of our capital stock would not be able to amend our restated bylaws or remove directors without holding a meeting of our stockholders called in accordance with our restated bylaws. Further, our restated bylaws provide that special meetings of our stockholders may be called only by a majority of our board of directors, the chairperson of our board of directors, our Chief Executive Officer or our President, thus prohibiting a stockholder from calling a special meeting. These provisions might delay the ability of our stockholders to force consideration of a proposal or for stockholders controlling a majority of our capital stock to take any action, including the removal of directors.

Advance notice requirements for stockholder proposals and director nominations. Our restated bylaws provide advance notice procedures for stockholders seeking to bring business before our annual meeting of stockholders or to nominate candidates for election as directors at our annual meeting of stockholders. Our restated bylaws also specify certain requirements regarding the form and content of a stockholder s notice. These provisions might preclude our stockholders from bringing matters before our annual meeting of stockholders or from making nominations for directors at our annual meeting of stockholders if the proper procedures are not followed. We expect that these provisions might also discourage or deter a potential acquirer from conducting a solicitation of proxies to elect the acquirer s own slate of directors or otherwise attempting to obtain control of our company.

No cumulative voting. The Delaware General Corporation Law provides that stockholders are not entitled to the right to cumulate votes in the election of directors unless a corporation s certificate of incorporation provides otherwise. Our restated certificate of incorporation and restated bylaws do not provide for cumulative voting.

Directors removed only for cause. Our restated certificate of incorporation provides that stockholders may remove directors only for cause.

Amendment of charter provisions. Any amendment of the above provisions in our restated certificate of incorporation requires approval by holders of at least two-thirds of our outstanding common stock, provided that if two-thirds of our board of directors approves such an amendment, then only the approval of a majority

of holders is required.

Issuance of undesignated preferred stock. Our board of directors has the authority, without further action by the stockholders, to issue up to 10,000,000 shares of undesignated preferred stock with rights and preferences, including voting rights, designated from time to time by our board of directors. The existence of authorized but unissued shares of preferred stock enables our board of directors to render more difficult or to discourage an attempt to obtain control of us by merger, tender offer, proxy contest or other means.

Choice of forum. Our restated certificate of incorporation provides that the Court of Chancery of the State of Delaware is the exclusive forum for any derivative action or proceeding brought on our behalf; any action asserting a breach of fiduciary duty; any action asserting a claim against us arising pursuant to the Delaware General Corporation Law, our restated certificate of incorporation or our restated bylaws; or any action asserting a claim against us that is governed by the internal affairs doctrine.

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Transfer Agent and Registrar

The transfer agent and registrar for our common stock is American Stock Transfer and Trust Company, LLC. The transfer agent s address is 6201 15th Avenue, Brooklyn, New York 11219, and its telephone number is (800) 937-5449.

Exchange Listing

Our common stock is listed on The Nasdaq Global Market under the symbol AGLE.

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DESCRIPTION OF DEBT SECURITIES

General

We will issue the debt securities offered by this prospectus and any accompanying prospectus supplement under an indenture to be entered into between us and the trustee identified in the applicable prospectus supplement. The terms of the debt securities will include those stated in the indenture and those made part of the indenture by reference to the Trust Indenture Act of 1939, as in effect on the date of the indenture. We have filed a copy of the form of indenture as an exhibit to the registration statement in which this prospectus is included. The indenture will be subject to and governed by the terms of the Trust Indenture Act of 1939.

We may offer under this prospectus up to an aggregate principal amount of $200,000,000 in debt securities, or if debt securities are issued at a discount, or in a foreign currency, foreign currency units or composite currency, the principal amount as may be sold for an aggregate public offering price of up to $200,000,000. Unless otherwise specified in the applicable prospectus supplement, the debt securities will represent our direct, unsecured obligations and will rank equally with all of our other unsecured indebtedness.

We may issue the debt securities in one or more series with the same or various maturities, at par, at a premium, or at a discount. We will describe the particular terms of each series of debt securities in a prospectus supplement relating to that series, which we will file with the SEC. The prospectus supplement relating to the particular series of debt securities being offered will specify the particular amounts, prices and terms of those debt securities. These terms may include:

- the title of the series;
- the aggregate principal amount, and, if a series, the total amount authorized and the total amount outstanding;
- the issue price or prices, expressed as a percentage of the aggregate principal amount of the debt securities;
- any limit on the aggregate principal amount;
- the date or dates on which principal is payable;
- the interest rate or rates (which may be fixed or variable) or, if applicable, the method used to determine such rate or rates;
- the date or dates from which interest, if any, will be payable and any regular record date for the interest payable;

the place or places where principal and, if applicable, premium and interest, is payable;

the terms and conditions upon which we may, or the holders may require us to, redeem or repurchase the debt securities;

the denominations in which such debt securities may be issuable, if other than denominations of $1,000 or any integral multiple of that number;

whether the debt securities are to be issuable in the form of certificated securities (as described below) or global securities (as described below);

the portion of principal amount that will be payable upon declaration of acceleration of the maturity date if other than the principal amount of the debt securities;

the currency of denomination;

the designation of the currency, currencies or currency units in which payment of principal and, if applicable, premium and interest, will be made;

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if payments of principal and, if applicable, premium or interest, on the debt securities are to be made in one or more currencies or currency units other than the currency of denomination, the manner in which the exchange rate with respect to such payments will be determined;

if amounts of principal and, if applicable, premium and interest may be determined by reference to an index based on a currency or currencies or by reference to a commodity, commodity index, stock exchange index or financial index, then the manner in which such amounts will be determined;

the provisions, if any, relating to any collateral provided for such debt securities;

any addition to or change in the covenants and/or the acceleration provisions described in this prospectus or in the indenture;

any events of default, if not otherwise described below under Events of Default ;

the terms and conditions, if any, for conversion into or exchange for shares of our common stock or preferred stock;

any depositaries, interest rate calculation agents, exchange rate calculation agents or other agents; and

the terms and conditions, if any, upon which the debt securities shall be subordinated in right of payment to our other indebtedness.

We may issue discount debt securities that provide for an amount less than the stated principal amount to be due and payable upon acceleration of the maturity of such debt securities in accordance with the terms of the indenture. We may also issue debt securities in bearer form, with or without coupons. If we issue discount debt securities or debt securities in bearer form, we will describe material U.S. federal income tax considerations and other material special considerations which apply to these debt securities in the applicable prospectus supplement.

We may issue debt securities denominated in or payable in a foreign currency or currencies or a foreign currency unit or units. If we do, we will describe the restrictions, elections, and general tax considerations relating to the debt securities and the foreign currency or currencies or foreign currency unit or units in the applicable prospectus supplement.

Debt securities offered under this prospectus and any prospectus supplement will be subordinated in right of payment to certain of our outstanding senior indebtedness. In addition, we will seek the consent of the holders of any such senior indebtedness prior to issuing any debt securities under this prospectus to the extent required by the agreements evidencing such senior indebtedness.

Registrar and Paying Agent

The debt securities may be presented for registration of transfer or for exchange at the corporate trust office of the security registrar or at any other office or agency that we maintain for those purposes. In addition, the debt securities may be presented for payment of principal, interest and any premium at the office of the paying agent or at any office or agency that we maintain for those purposes.

Conversion or Exchange Rights

Debt securities may be convertible into or exchangeable for shares of our common stock. The terms and conditions of conversion or exchange will be stated in the applicable prospectus supplement. The terms will include, among others, the following:

the conversion or exchange price;

the conversion or exchange period;

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provisions regarding the convertibility or exchangeability of the debt securities, including who may convert or exchange;

events requiring adjustment to the conversion or exchange price;

provisions affecting conversion or exchange in the event of our redemption of the debt securities; and

any anti-dilution provisions, if applicable.

Registered Global Securities

If we decide to issue debt securities in the form of one or more global securities, then we will register the global securities in the name of the depositary for the global securities or the nominee of the depositary, and the global securities will be delivered by the trustee to the depositary for credit to the accounts of the holders of beneficial interests in the debt securities.

The prospectus supplement will describe the specific terms of the depositary arrangement for debt securities of a series that are issued in global form. None of us, the trustee, any payment agent or the security registrar will have any responsibility or liability for any aspect of the records relating to or payments made on account of beneficial ownership interests in a global debt security or for maintaining, supervising or reviewing any records relating to these beneficial ownership interests.

No Protection in the Event of Change of Control

The indenture does not have any covenants or other provisions providing for a put or increased interest or otherwise that would afford holders of our debt securities additional protection in the event of a recapitalization transaction, a change of control or a highly leveraged transaction. If we offer any covenants or provisions of this type with respect to any debt securities covered by this prospectus, we will describe them in the applicable prospectus supplement.

Covenants

Unless otherwise indicated in this prospectus or the applicable prospectus supplement, our debt securities will not have the benefit of any covenants that limit or restrict our business or operations, the pledging of our assets or the incurrence by us of indebtedness. We will describe in the applicable prospectus supplement any material covenants in respect of a series of debt securities.

Merger, Consolidation or Sale of Assets

The form of indenture provides that we will not consolidate with or merge into any other person or convey, transfer, sell or lease our properties and assets substantially as an entirety to any person, unless:

we are the surviving person of such merger or consolidation, or if we are not the surviving person, the person formed by the consolidation or into or with which we are merged or the person to which our properties and assets are conveyed, transferred, sold or leased, is a corporation organized and existing under the laws of the

U.S., any state or the District of Columbia or a corporation or comparable legal entity organized under the laws of a foreign jurisdiction and has expressly assumed all of our obligations, including the payment of the principal of and, premium, if any, and interest on the debt securities and the performance of the other covenants under the indenture; and

immediately before and immediately after giving effect to the transaction on a pro forma basis, no event of default, and no event which, after notice or lapse of time or both, would become an event of default, has occurred and is continuing under the indenture.

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Events of Default

Unless otherwise specified in the applicable prospectus supplement, the following events will be events of default under the indenture with respect to debt securities of any series:

- we fail to pay any principal or premium, if any, when it becomes due;
- we fail to pay any interest within 30 days after it becomes due;
- we fail to observe or perform any other covenant in the debt securities or the indenture for 60 days after written notice specifying the failure from the trustee or the holders of not less than 25% in aggregate principal amount of the outstanding debt securities of that series; and
- certain events involving bankruptcy, insolvency or reorganization of us or any of our significant subsidiaries.

The trustee may withhold notice to the holders of the debt securities of any series of any default, except in payment of principal of or premium, if any, or interest on the debt securities of a series, if the trustee considers it to be in the best interest of the holders of the debt securities of that series to do so.

If an event of default (other than an event of default resulting from certain events of bankruptcy, insolvency or reorganization) occurs, and is continuing, then the trustee or the holders of not less than 25% in aggregate principal amount of the outstanding debt securities of any series may accelerate the maturity of the debt securities. If this happens, the entire principal amount, plus the premium, if any, of all the outstanding debt securities of the affected series plus accrued interest to the date of acceleration will be immediately due and payable. At any time after the acceleration, but before a judgment or decree based on such acceleration is obtained by the trustee, the holders of a majority in aggregate principal amount of outstanding debt securities of such series may rescind and annul such acceleration if:

- all events of default (other than nonpayment of accelerated principal, premium or interest) have been cured or waived;
- all lawful interest on overdue interest and overdue principal has been paid; and
- the rescission would not conflict with any judgment or decree.

In addition, if the acceleration occurs at any time when we have outstanding indebtedness that is senior to the debt securities, the payment of the principal amount of outstanding debt securities may be subordinated in right of payment to the prior payment of any amounts due under the senior indebtedness, in which case the holders of debt securities will be entitled to payment under the terms prescribed in the instruments evidencing the senior indebtedness and the indenture.

If an event of default resulting from certain events of bankruptcy, insolvency or reorganization occurs, the principal, premium and interest amount with respect to all of the debt securities of any series will be due and payable immediately without any declaration or other act on the part of the trustee or the holders of the debt securities of that series.

The holders of a majority in principal amount of the outstanding debt securities of a series will have the right to waive any existing default or compliance with any provision of the indenture or the debt securities of that series and to direct the time, method and place of conducting any proceeding for any remedy available to the trustee, subject to certain limitations specified in the indenture.

No holder of any debt security of a series will have any right to institute any proceeding with respect to the indenture or for any remedy under the indenture, unless:

the holder gives to the trustee written notice of a continuing event of default;

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the holders of at least 25% in aggregate principal amount of the outstanding debt securities of the affected series make a written request and offer reasonable indemnity to the trustee to institute a proceeding as trustee;

the trustee fails to institute a proceeding within 60 days after such request; and

the holders of a majority in aggregate principal amount of the outstanding debt securities of the affected series do not give the trustee a direction inconsistent with such request during such 60-day period.

These limitations do not, however, apply to a suit instituted for payment on debt securities of any series on or after the due dates expressed in the debt securities.

We will periodically deliver certificates to the trustee regarding our compliance with our obligations under the indenture.

Modification and Waiver

From time to time, we and the trustee may, without the consent of holders of the debt securities of one or more series, amend the indenture or the debt securities of one or more series, or supplement the indenture, for certain specified purposes, including:

to provide that the surviving entity following a change of control permitted under the indenture will assume all of our obligations under the indenture and debt securities;

to provide for certificated debt securities in addition to uncertificated debt securities;

to comply with any requirements of the SEC under the Trust Indenture Act of 1939;

to provide for the issuance of and establish the form and terms and conditions of debt securities of any series as permitted by the indenture;

to cure any ambiguity, defect or inconsistency, or make any other change that does not materially and adversely affect the rights of any holder; and

to appoint a successor trustee under the indenture with respect to one or more series.

From time to time we and the trustee may, with the consent of holders of at least a majority in principal amount of an outstanding series of debt securities, amend or supplement the indenture or the debt securities series, or waive compliance in a particular instance by us with any provision of the indenture or the debt securities. We may not, however, without the consent of each holder affected by such action, modify or supplement the indenture or the debt securities or waive compliance with any provision of the indenture or the debt securities in order to:

reduce the amount of debt securities whose holders must consent to an amendment, supplement, or waiver to the indenture or such debt security;

reduce the rate of or change the time for payment of interest or reduce the amount of or postpone the date for payment of sinking fund or analogous obligations;

reduce the principal of or change the stated maturity of the debt securities;

make any debt security payable in money other than that stated in the debt security;

change the amount or time of any payment required or reduce the premium payable upon any redemption, or change the time before which no such redemption may be made;

waive a default in the payment of the principal of, premium, if any, or interest on the debt securities or a redemption payment;

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waive a redemption payment with respect to any debt securities or change any provision with respect to redemption of debt securities; or

take any other action otherwise prohibited by the indenture to be taken without the consent of each holder affected by the action.

Defeasance of Debt Securities and Certain Covenants in Certain Circumstances

The indenture permits us, at any time, to elect to discharge our obligations with respect to one or more series of debt securities by following certain procedures described in the indenture. These procedures will allow us either:

to defease and be discharged from any and all of our obligations with respect to any debt securities except for the following obligations (which discharge is referred to as legal defeasance):

1. to register the transfer or exchange of such debt securities;

2. to replace temporary or mutilated, destroyed, lost or stolen debt securities;

3. to compensate and indemnify the trustee; or

4. to maintain an office or agency in respect of the debt securities and to hold monies for payment in trust; or

to be released from our obligations with respect to the debt securities under certain covenants contained in the indenture, as well as any additional covenants which may be contained in the applicable supplemental indenture (which release is referred to as covenant defeasance).

In order to exercise either defeasance option, we must irrevocably deposit with the trustee or other qualifying trustee, in trust for that purpose:

money;

U.S. Government Obligations (as described below) or Foreign Government Obligations (as described below) that through the scheduled payment of principal and interest in accordance with their terms will provide money; or

a combination of money and/or U.S. Government Obligations and/or Foreign Government Obligations sufficient in the written opinion of a nationally-recognized firm of independent accountants to provide

money;

that, in each case specified above, provides a sufficient amount to pay the principal of, premium, if any, and interest, if any, on the debt securities of the series, on the scheduled due dates or on a selected date of redemption in accordance with the terms of the indenture.

In addition, defeasance may be effected only if, among other things:

in the case of either legal or covenant defeasance, we deliver to the trustee an opinion of counsel, as specified in the indenture, stating that as a result of the defeasance neither the trust nor the trustee will be required to register as an investment company under the Investment Company Act of 1940;

in the case of legal defeasance, we deliver to the trustee an opinion of counsel stating that we have received from, or there has been published by, the Internal Revenue Service a ruling to the effect that, or there has been a change in any applicable federal income tax law with the effect that (and the opinion shall confirm that), the holders of outstanding debt securities will not recognize income, gain or loss for U.S. federal income tax purposes solely as a result of such legal defeasance and will be subject to U.S. federal income tax on the same amounts, in the same manner, including as a result of prepayment, and at the same times as would have been the case if legal defeasance had not occurred;

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in the case of covenant defeasance, we deliver to the trustee an opinion of counsel to the effect that the holders of the outstanding debt securities will not recognize income, gain or loss for U.S. federal income tax purposes as a result of covenant defeasance and will be subject to U.S. federal income tax on the same amounts, in the same manner and at the same times as would have been the case if covenant defeasance had not occurred; and

certain other conditions described in the indenture are satisfied.

If we fail to comply with our remaining obligations under the indenture and applicable supplemental indenture after a covenant defeasance of the indenture and applicable supplemental indenture, and the debt securities are declared due and payable because of the occurrence of any undefeased event of default, the amount of money and/or U.S. Government Obligations and/or Foreign Government Obligations on deposit with the trustee could be insufficient to pay amounts due under the debt securities of the affected series at the time of acceleration. We will, however, remain liable in respect of these payments.

The term U.S. Government Obligations as used in the above discussion means securities that are direct obligations of or non-callable obligations guaranteed by the United States of America for the payment of which obligation or guarantee the full faith and credit of the United States of America is pledged.

The term Foreign Government Obligations as used in the above discussion means, with respect to debt securities of any series that are denominated in a currency other than U.S. dollars, (1) direct obligations of the government that issued or caused to be issued such currency for the payment of which obligations its full faith and credit is pledged or (2) obligations of a person controlled or supervised by or acting as an agent or instrumentality of such government the timely payment of which is unconditionally guaranteed as a full faith and credit obligation by that government, which in either case under clauses (1) or (2), are not callable or redeemable at the option of the issuer.

Regarding the Trustee

We will identify the trustee with respect to any series of debt securities in the prospectus supplement relating to the applicable debt securities. You should note that if the trustee becomes a creditor of ours, the indenture and the Trust Indenture Act of 1939 limit the rights of the trustee to obtain payment of claims in certain cases, or to realize on certain property received in respect of any such claim, as security or otherwise. The trustee and its affiliates may engage in, and will be permitted to continue to engage in, other transactions with us and our affiliates. If, however, the trustee acquires any conflicting interest within the meaning of the Trust Indenture Act of 1939, it must eliminate such conflict or resign.

The holders of a majority in principal amount of the then outstanding debt securities of any series may direct the time, method and place of conducting any proceeding for exercising any remedy available to the trustee. If an event of default occurs and is continuing, the trustee, in the exercise of its rights and powers, must use the degree of care and skill of a prudent person in the conduct of his or her own affairs. Subject to that provision, the trustee will be under no obligation to exercise any of its rights or powers under the indenture at the request of any of the holders of the debt securities, unless they have offered to the trustee reasonable indemnity or security.

No Individual Liability of Incorporators, Stockholders, Officers or Directors

Each indenture provides that no incorporator and no past, present or future stockholder, officer or director of our company or any successor corporation in those capacities will have any individual liability for any of our obligations, covenants or agreements under the debt securities or such indenture.

Governing Law

The indentures and the debt securities will be governed by, and construed in accordance with, the laws of the State of New York.

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DESCRIPTION OF WARRANTS

General

We may issue warrants for the purchase of our debt securities, preferred stock, common stock, or any combination thereof. Warrants may be issued independently or together with our debt securities, preferred stock or common stock and may be attached to or separate from any offered securities. Each series of warrants will be issued under a separate warrant agreement to be entered into between us and a bank or trust company, as warrant agent. The warrant agent will act solely as our agent in connection with the warrants. The warrant agent will not have any obligation or relationship of agency or trust for or with any holders or beneficial owners of warrants. This summary of certain provisions of the warrants is not complete. For the terms of a particular series of warrants, you should refer to the prospectus supplement for that series of warrants and the warrant agreement for that particular series.

Debt Warrants

The prospectus supplement relating to a particular issue of warrants to purchase debt securities will describe the terms of the debt warrants, including the following:

- the title of the debt warrants;
- the offering price for the debt warrants, if any;
- the aggregate number of the debt warrants;
- the designation and terms of the debt securities, including any conversion rights, purchasable upon exercise of the debt warrants;
- if applicable, the date from and after which the debt warrants and any debt securities issued with them will be separately transferable;
- the principal amount of debt securities that may be purchased upon exercise of a debt warrant and the exercise price for the warrants, which may be payable in cash, securities or other property;
- the dates on which the right to exercise the debt warrants will commence and expire;
- if applicable, the minimum or maximum amount of the debt warrants that may be exercised at any one time;

whether the debt warrants represented by the debt warrant certificates or debt securities that may be issued upon exercise of the debt warrants will be issued in registered or bearer form;

information with respect to book-entry procedures, if any;

the currency or currency units in which the offering price, if any, and the exercise price are payable;

if applicable, a discussion of material U.S. federal income tax considerations;

the antidilution provisions of the debt warrants, if any;

the redemption or call provisions, if any, applicable to the debt warrants;

any provisions with respect to the holder s right to require us to repurchase the debt warrants upon a change in control or similar event; and

any additional terms of the debt warrants, including procedures and limitations relating to the exchange, exercise, and settlement of the debt warrants.

Debt warrant certificates will be exchangeable for new debt warrant certificates of different denominations. Debt warrants may be exercised at the corporate trust office of the warrant agent or any other office indicated in

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the prospectus supplement. Prior to the exercise of their debt warrants, holders of debt warrants will not have any of the rights of holders of the debt securities purchasable upon exercise and will not be entitled to payment of principal or any premium, if any, or interest on the debt securities purchasable upon exercise.

Equity Warrants

The prospectus supplement relating to a particular series of warrants to purchase our common stock or preferred stock will describe the terms of the warrants, including the following:

- the title of the warrants;
- the offering price for the warrants, if any;
- the aggregate number of warrants;
- the designation and terms of the common stock or preferred stock that may be purchased upon exercise of the warrants;
- if applicable, the designation and terms of the securities 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 any securities issued with the warrants will be separately transferable;
- the number of shares of common stock or preferred stock that may be purchased upon exercise of a warrant and the exercise price for the warrants;
- the dates on which the right to exercise the warrants shall commence and expire;
- if applicable, the minimum or maximum amount of the warrants that may be exercised at any one time;
- the currency or currency units in which the offering price, if any, and the exercise price are payable;
- if applicable, a discussion of material U.S. federal income tax considerations;

the antidilution provisions of the warrants, if any;

the redemption or call provisions, if any, applicable to the warrants;

any provisions with respect to a holder s right to require us to repurchase the warrants upon a change in control or similar event; and

any additional terms of the warrants, including procedures and limitations relating to the exchange, exercise and settlement of the warrants.

Holders of equity warrants will not be entitled:

to vote, consent, or receive dividends;

receive notice as stockholders with respect to any meeting of stockholders for the election of our directors or any other matter; or

exercise any rights as stockholders.

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DESCRIPTION OF SUBSCRIPTION RIGHTS

We may issue subscription rights to purchase our common stock, preferred stock or debt securities. These subscription rights may be offered independently or together with any other security offered hereby and may or may not be transferable by the stockholder receiving the subscription rights in such offering. In connection with any offering of subscription rights, we may enter into a standby arrangement with one or more underwriters or other purchasers pursuant to which the underwriters or other purchasers may be required to purchase any securities remaining unsubscribed for after such offering.

The prospectus supplement relating to any subscription rights we offer, if any, will, to the extent applicable, include specific terms relating to the offering, including some or all of the following:

- the price, if any, for the subscription rights;
- the exercise price payable for our common stock, preferred stock or debt securities upon the exercise of the subscription rights;
- the number of subscription rights to be issued to each stockholder;
- the number and terms of our common stock, preferred stock or debt securities which may be purchased per each subscription right;
- the extent to which the subscription rights are transferable;
- any other terms of the subscription rights, including the terms, procedures and limitations relating to the exchange and exercise of the subscription rights;
- the date on which the right to exercise the subscription rights shall commence, and the date on which the subscription rights shall expire;
- the extent to which the subscription rights may include an over-subscription privilege with respect to unsubscribed securities or an over-allotment privilege to the extent the securities are fully subscribed; and
- if applicable, the material terms of any standby underwriting or purchase arrangement which may be entered into by us in connection with the offering of subscription rights.

The description in the applicable prospectus supplement of any subscription rights we offer will not necessarily be complete and will be qualified in its entirety by reference to the applicable subscription rights certificate, which will be filed with the SEC if we offer subscription rights. We urge you to read the applicable subscription rights certificate

and any applicable prospectus supplement in their entirety.

DESCRIPTION OF UNITS

We may issue units consisting of some or all of the securities described above, in any combination, including common stock, preferred stock, warrants and/or debt securities. The terms of these units will be set forth in a prospectus supplement. The description of the terms of these units in the related prospectus supplement will not be complete. You should refer to the applicable form of unit and unit agreement for complete information with respect to these units.

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LEGAL MATTERS

Fenwick & West LLP, Mountain View, California, will issue an opinion about certain legal matters with respect to the securities. Any underwriters or agents will be advised about legal matters relating to any offering by their own counsel.

EXPERTS

The financial statements incorporated in this Prospectus by reference to the Annual Report on Form 10-K for the year ended December 31, 2017 have been so incorporated in reliance on the report of PricewaterhouseCoopers LLP, an independent registered public accounting firm, given on the authority of said firm as experts in auditing and accounting.

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The information in this preliminary prospectus supplement and the accompanying prospectus is not complete and may be changed. We may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. This preliminary prospectus supplement and accompanying prospectus are not an offer to sell these securities and they are not soliciting an offer to buy these securities in any state where the offer or sale is not permitted.

Subject to completion, dated February 11, 2019

PROSPECTUS SUPPLEMENT

Up to $60,000,000

Common Stock

We have entered into an Open Market Sale Agreement[SM], or sales agreement, with Jefferies LLC, or Jefferies, dated December 21, 2018, relating to the sale of shares of our common stock offered by this prospectus supplement. In accordance with the terms of the sales agreement, under this prospectus supplement we may offer and sell shares of our common stock, $0.0001 par value per share, having an aggregate offering price of up to $60,000,000 from time to time through Jefferies, acting as our agent.

Sales of our common stock, if any, under this prospectus supplement will be made by any method permitted that is deemed an at the market offering as defined in Rule 415(a)(4) under the Securities Act of 1933, as amended, or the Securities Act. Jefferies is not required to sell any specific amount, but will act as our sales agent using commercially reasonable efforts consistent with its normal trading and sales practices. There is no arrangement for funds to be received in any escrow, trust or similar arrangement.

Jefferies will be entitled to compensation at a commission rate of 3.0% of the gross sales price per share sold under the sales agreement. See Plan of Distribution beginning on page S-15 for additional information regarding the compensation to be paid to Jefferies. In connection with the sale of the common stock on our behalf, Jefferies will be deemed to be an underwriter within the meaning of the Securities Act and the compensation of Jefferies will be deemed to be underwriting commissions or discounts. We have also agreed to provide indemnification and contribution to Jefferies with respect to certain liabilities, including liabilities under the Securities Act.

Our common stock is listed on the Nasdaq Global Market under the symbol *AGLE*. On February 8, 2019, the last reported sale price of our common stock on the Nasdaq Global Market was $7.83 per share.

INVESTING IN OUR SECURITIES INVOLVES RISKS. SEE THE RISK FACTORS ON PAGE S-9 OF THIS PROSPECTUS SUPPLEMENT AND IN THE DOCUMENTS INCORPORATED BY REFERENCE IN THIS PROSPECTUS SUPPLEMENT CONCERNING FACTORS YOU SHOULD CONSIDER BEFORE INVESTING IN OUR COMMON STOCK.

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 supplement. Any representation to the contrary is a criminal offense.

Jefferies

The date of this prospectus supplement is , 2019.

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ABOUT THIS PROSPECTUS SUPPLEMENT

This prospectus supplement is part of a registration statement that we have filed with the Securities and Exchange Commission, or SEC, utilizing a shelf registration process, and relates to the offering of our common stock. Before buying any of the common stock that we are offering, we urge you to carefully read this prospectus supplement, the accompanying base prospectus and all of the information incorporated by reference herein and therein, as well as the additional information described under the heading Where You Can Find More Information; Incorporation by Reference. These documents contain important information that you should consider when making your investment decision.

We provide information to you about this offering of our common stock in two separate documents that are bound together: (1) this prospectus supplement, which describes the specific details regarding this offering; and (2) the accompanying base prospectus, which provides general information, some of which may not apply to this offering. Generally, when we refer to this prospectus, we are referring to both documents combined. If information in this prospectus supplement is inconsistent with the accompanying base prospectus, you should rely on this prospectus supplement. To the extent there is a conflict between the information contained in this prospectus supplement, on the one hand, and the information contained in any document incorporated by reference in this prospectus supplement, on the other hand, you should rely on the information in this prospectus supplement. If any statement in one of these documents is inconsistent with a statement in another document having a later date for example, a document incorporated by reference in this prospectus supplement the statement in the document having the later date modifies or supersedes the earlier statement.

You should rely only on the information contained in or incorporated by reference in this prospectus supplement, the accompanying base prospectus and any free writing prospectus that we may authorize for use in connection with this offering. We have not, and Jefferies has not, authorized anyone to provide you with different information. If anyone provides you with different or inconsistent information, you should not rely on it. We are not, and Jefferies is not, making an offer to sell these securities in any jurisdiction where the offer or sale is not permitted or in which the person making that offer or solicitation is not qualified to do so or to anyone to whom it is unlawful to make an offer or solicitation. You should assume that the information appearing in this prospectus supplement, the accompanying base prospectus, the documents incorporated by reference herein and therein and any free writing prospectus that we have authorized for use in connection with this offering, is accurate only as of the date of those respective documents. Our business, financial condition, results of operations and prospects may have changed since those dates. You should read this prospectus supplement, the accompanying base prospectus, the documents incorporated by reference herein and therein and any free writing prospectus that we have authorized for use in connection with this offering, in their entirety before making an investment decision.

When we refer to Aeglea, we, our, us, the Registrant, the Company and our company in this prospectus su we mean Aeglea BioTherapeutics, Inc., a Delaware corporation, and its subsidiaries taken as a whole, unless otherwise specified.

Aeglea and all product candidate names are our common law trademarks. This prospectus supplement also includes trademarks, tradenames and service marks that are the property of other organizations. Solely for convenience, trademarks and tradenames referred to in this prospectus supplement appear without the ® and symbols, but those references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights or that the applicable owner will not assert its rights, to these trademarks and tradenames.

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WHERE YOU CAN FIND MORE INFORMATION; INCORPORATION BY REFERENCE

Available Information

We file reports, proxy statements and other information with the SEC. The SEC maintains a web site that contains reports, proxy and information statements and other information about issuers, such as us, who file electronically with the SEC. The address of that website is *www.sec.gov*.

Our web site address is http://www.aegleabio.com. The information on our web site, however, is not, and should not be deemed to be, a part of this prospectus supplement.

This prospectus supplement and the accompanying base prospectus are part of a registration statement that we filed with the SEC and do not contain all of the information in the registration statement. The full registration statement may be obtained from the SEC or us, as provided below. Documents establishing the terms of the offered securities are or may be filed as exhibits to the registration statement. Statements in this prospectus supplement or the accompanying base prospectus about these documents are summaries and each statement is qualified in all respects by reference to the document to which it refers. You should refer to the actual documents for a more complete description of the relevant matters. You may inspect a copy of the registration statement through the SEC s website, as provided above, or at our principal executive offices, 901 S. MoPac Expressway, Barton Oaks Plaza One, Suite 250, Austin, TX 78746, during normal business hours.

Incorporation by Reference

The SEC allows us to incorporate by reference information that we file with the SEC, which means that we can disclose important information to you by referring you to those other documents. The information incorporated by reference is an important part of this prospectus supplement, and information we file later with the SEC will automatically update and supersede this information. A Current Report (or portion thereof) furnished, but not filed, on Form 8-K shall not be incorporated by reference into this prospectus supplement. We incorporate by reference the documents listed below and any future filings we make with the SEC under Section 13(a), 13(c), 14, or 15(d) of the Exchange Act prior to the termination of any offering of securities made by this prospectus supplement:

- Our Annual Report on Form 10-K for the year ended December 31, 2017, filed with the SEC on March 13, 2018, including certain information incorporated by reference therein from our Definitive Proxy Statement for our 2018 annual meeting of stockholders filed with the SEC on April 16, 2018;

- Our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2018, June 30, 2018 and September 30, 2018, filed with the SEC on May 8, 2018, August 9, 2018 and November 8, 2018, respectively;

- Our Current Reports on Form 8-K filed on March 26, 2018, April 16, 2018, April 19, 2018, June 8, 2018, July 16, 2018, July 23, 2018, October 10, 2018, November 29, 2018, December 21, 2018 and February 7, 2019 (in each case, except for information contained therein which is furnished rather than filed); and

The description of our Common Stock contained in our Registration Statement on Form 8-A, filed with the SEC on March 28, 2016, and any amendment or report filed with the SEC for the purpose of updating the description.

All reports and other documents we subsequently file pursuant to Section 13(a), 13(c), 14 or 15(d) of the Exchange Act prior to the termination of this offering, including all such documents we may file with the SEC after the date of the initial registration statement and prior to the effectiveness of the registration statement, but excluding any information furnished to, rather than filed with, the SEC, will also be incorporated by reference in this prospectus supplement and deemed to be part of this prospectus supplement from the date of the filing of such reports and documents.

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We will furnish without charge to you, on written or oral request, a copy of any or all of such documents that has been incorporated herein by reference (other than exhibits to such documents unless such exhibits are specifically incorporated by reference into the documents that this prospectus supplement incorporates). Written or oral requests for copies should be directed Aeglea BioTherapeutics, Inc., Attn: Investor Relations, 901 S. MoPac Expressway, Barton Oaks Plaza One, Suite 250, Austin, Texas 78746, telephone number (512) 942-2935.

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THE COMPANY

Company Overview

We are a biotechnology company that designs and develops innovative human enzyme therapeutics for patients with rare genetic diseases and cancer. We believe our novel approach of utilizing human enzymes offers advantages that provide a greater likelihood of clinical success and commercial adoption.

Our drug-hunting capabilities in enzyme engineering, preclinical disease modeling, and drug development in both rare genetic disease and cancer allow us to identify and advance innovative opportunities to address important unmet medical needs for the benefit of patients. Our programs and the decisions we make to progress assets into clinical studies are driven by the following considerations:

- Potential for enhancement of human enzymatic activity
- Ability to create novel human enzymatic activity
- Strong preclinical data and rationale
- Limited or no competition
- Meaningful commercial opportunities
- Worldwide commercial rights

We are a patient-focused organization conscious of the fact that people with a rare genetic disease or cancer have limited treatment options, and we recognize that their lives and well-being are highly dependent upon our efforts to develop improved therapies. For this reason, we are passionate about designing and developing novel therapeutics to address significant unmet medical need for rare genetic disease and cancer.

Our lead product candidate, pegzilarginase, is engineered to degrade the amino acid arginine and is being developed to exploit two aspects of arginine metabolism, including arginine excess in patients with Arginase 1 Deficiency, a rare genetic disease, as well as the arginine dependence of some cancers. We expect to start a single, global pivotal Phase 3 trial of pegzilarginase in patients with Arginase 1 Deficiency in the second quarter of 2019. We are currently evaluating pegzilarginase in multiple ongoing clinical trials, including a Phase 1/2 clinical trial for the treatment of Arginase 1 Deficiency, an open-label extension study for patients with Arginase 1 Deficiency, a Phase 1 clinical trial for the treatment of advanced solid tumors, and a Phase 1/2 combination clinical trial of pegzilarginase with pembrolizumab for the treatment of patients with small cell lung cancer (SCLC). We are also building a pipeline of additional product candidates targeting key amino acids and other metabolites, including AEB4104 for the treatment of homocystinuria, AEB5100 for the treatment of cystinuria, and AEB2109 for the treatment of cancer.

Rare Genetic Diseases

Pegzilarginase in Patients with Arginase 1 Deficiency

Arginase 1 Deficiency is a debilitating disease that progresses despite current medical management leading to severe complications and early death. Pegzilarginase is the first ever investigative therapy that addresses the elevated levels of arginine, which is the key driver of Arginase 1 Deficiency.

In December 2018, we announced the design of our single, global pivotal Phase 3 PEACE (Pegzilarginase Effect on Arginase 1 Deficiency Clinical Endpoints) trial with a primary endpoint of plasma arginine reduction and secondary endpoints which include assessments of clinical outcomes on mobility and adaptive behavior, safety and pharmacokinetics. The Phase 3 PEACE trial is designed to assess the effects of treatment with pegzilarginase versus placebo over 24 weeks, and we expect to enroll 30 patients with Arginase 1 Deficiency. We finalized the design of the Phase 3 PEACE trial to be a single, global pivotal trial based on the U.S. Food and

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Drug Administration (FDA) and the European Medicines Agency (EMA) feedback. Patients enrolled in the trial will be randomized on a two-to-one basis to receive weekly infusions of pegzilarginase, or placebo for the double-blind treatment period of 24 weeks. Patients will be considered eligible for the PEACE trial if they exhibit average plasma arginine of greater than 250 μM, are greater than two years of age and have a deficit of mobility or adaptive behavior. All assessments and dose adjustments will be conducted in a blinded fashion at pre-specified intervals. Patients will remain on current disease management for the duration of the Phase 3 PEACE trial. We expect to dose the first patient in the PEACE trial in the second quarter of 2019 and expect that data from the Phase 3 PEACE trial will be available in the first quarter of 2021. The FDA indicated that data from this Phase 3 PEACE trial showing plasma arginine reduction in conjunction with improvements in clinically meaningful aspects of the disease may be sufficient to support a marketing application for pegzilarginase in Arginine 1 Deficiency. Additional interim clinical data from our Phase 1/2 clinical trial reporting repeat dose administration of pegzilarginase is expected in the first half of 2019.

In October 2018, we announced new positive interim clinical data at the 2018 American Society of Human Genetics (ASHG) Conference from our ongoing Phase 1/2 trial of pegzilarginase in patients with Arginase 1 Deficiency. We reported clinical improvements with repeat dose administration of pegzilarginase after only eight weeks, including consistent reduction of arginine, and improvement in mobility or adaptive behavior. Pegzilarginase was generally well tolerated; most treatment-related adverse events were mild, and while investigators considered some of the hypersensitivity events as serious adverse events, the hypersensitivity reactions were generally manageable with standard measures and all patients continued study treatment. Additionally, we completed and exceeded our enrollment target with 16 patients in the Phase 1/2 clinical trial.

In addition, we announced in October 2018 that the FDA granted a rare pediatric disease designation to our lead product candidate, pegzilarginase, for the treatment of Arginase 1 Deficiency. This designation by the FDA confirms our eligibility to receive a rare pediatric disease priority review voucher upon approval of a biologics license application for pegzilarginase if completed before October 1, 2022.

AEB4104 in Patients with Homocystinuria

Homocystinuria is an inherited disorder of methionine metabolism caused by mutations in CBS and other genes leading to elevated levels of plasma and tissue homocysteine and homocystine, which affect multiple organ systems and cause early mortality. Current disease management, which includes dietary protein (methionine) restriction, vitamins, and betaine supplementation, is insufficient to effectively control the more severe forms of the disease. Given the severity of the disease, the limitations of current disease management approaches, and the data demonstrating improved survival in a preclinical model of the disease, we intend to advance AEB4104 into IND-enabling studies in the first half of 2019. The patent rights to AEB4104 were exclusively licensed to us from the Board of Regents of The University of Texas System, or the University, pursuant to the Amended and Restated License Agreement dated January 31, 2017, as amended, or the Restated License. For more information on the Restated License, see section titled Item 1. Business-Licensing in our Annual Report on Form 10-K for the fiscal year ended December 31, 2017.

In October 2018, we announced preclinical efficacy data on our AEB4104 homocystinuria program at the 2018 American Society of Human Genetics (ASHG) Conference, demonstrating that AEB4104 improved survival and important disease-related abnormalities in a preclinical model of homocystinuria. AEB4104 decreased homocysteine and homocystine levels in the plasma, including the CBS deficient model (CBS-/-) and the high methionine diet-induced model of homocystinuria. Treatment with AEB4104 prevented early mortality, stopped disease progression, and reversed liver pathology.

AEB5100 in Patients with Cystinuria

AEB5100 is a novel recombinant human enzyme that degrades plasma cystine and cysteine. We are developing AEB5100 for the treatment of patients with cystinuria, a rare genetic disease characterized by

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frequent and recurrent kidney stone formation requiring multiple procedural interventions and by an increased risk of chronic kidney disease. Cystinuria occurs due to genetic mutations in amino acid transporters that lead to increased amounts of cystine in the urine. This results in high cystine concentrations in the urine and formation of kidney stones.

In October 2018, we announced preclinical efficacy data on our AEB5100 cystinuria therapeutic program at the 2018 American Society of Nephrology (ASN) Conference, demonstrating that AEB5100 lowered blood levels of cystine and cysteine, decreased the amount of cystine in the urine and reduced kidney stone formation in a preclinical model of cystinuria. Given the compelling preclinical data and the limitations of current disease management approaches, we intend to advance AEB5100 into IND-enabling studies and we anticipate beginning GLP manufacturing for toxicology studies in the first half of 2019. The patent rights to AEB5100 were exclusively licensed to us from the University pursuant to the Restated License. For more information on the Restated License, see section titled Item 1. Business-Licensing in our Annual Report on Form 10-K for the fiscal year ended December 31, 2017.

Cancer

Pegzilarginase with Pembrolizumab in Patients with Small Cell Lung Cancer

In the first quarter of 2018, we initiated a Phase 1 clinical collaboration with Merck to evaluate the combination of pegzilarginase with Merck s anti-PD1 therapy, pembrolizumab, for the treatment of patients with SCLC, with the primary objectives of determining the safety and dose of pegzilarginase that can be combined with pembrolizumab to be used in Phase 2. The Phase 2 primary objective is objective response rate (ORR) and secondary objectives include safety, clinical benefit rate, time to response, duration of response, progression free survival (PFS), overall survival, pegzilarginase pharmacokinetics, and exploring the correlation of tumor expression of ASS1 and PD-L1 with clinical activity. We dosed the first patient in the first quarter of 2018, expect to initiate Phase 2 in the second quarter of 2019, and expect to report topline safety and clinical activity for Phase 1 in the first quarter of 2019.

Pegzilarginase in Patients with Advanced Solid Tumors

In October 2018, we presented interim clinical data at the European Society for Medical Oncology (ESMO) 2018 Congress, demonstrating that pegzilarginase monotherapy resulted in anti-tumor activity in heavily pre-treated patients with advanced melanoma. The investigator-assessed responses in 13 cutaneous melanoma patients and 15 uveal melanoma patients revealed that one patient achieved a confirmed partial response (PR) at week 20 and eight patients had stable disease (SD) at week 8 or later. These patients experienced treatment-related, serious Grade 3 adverse events, including asthenia and failure to thrive, vomiting and dehydration. Six patients remained on treatment at the time of the data cutoff. Anti-tumor activity appeared greater in tumors lacking argininosuccinate synthetase 1 (ASS1) expression, which is consistent with preclinical studies that suggest tumors lacking ASS1 expression are dependent on extracellular arginine for survival.

In addition, pegzilarginase was shown to rapidly and sustainably deplete plasma arginine with a manageable safety profile. The results, combined with preclinical evidence of synergy with immune checkpoint inhibitors, support further clinical evaluation of pegzilarginase in immunotherapy combinations.

Recent Developments

In May 2017, we entered into an at-the-market program and sales agreement with JonesTrading Institutional Services LLC, under which we may, from time to time, offer and sell common stock having an aggregate offering value of up to $20.0 million, referred to as our at-the-market offering. In October 2018, we sold 1,845,820 shares of our common stock under the at-the-market program for aggregate net proceeds of $16.4 million. On December 17, 2018, we

provided notice to JonesTrading Institutional Services LLC of our decision to terminate the sales agreement and at-the-market offering program, effective December 21, 2018.

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In February 2019, we sold 3,500,000 shares of our common stock and pre-funded warrants to purchase 4,000,000 shares of our common stock pursuant to a firm commitment underwritten public offering for aggregate net proceeds of approximately $56.1 million.

Company Information

We were formed as a limited liability company under the laws of the State of Delaware in December 2013 and converted to a Delaware corporation in March 2015. Our principal executive offices are located at 901 S. MoPac Expressway, Barton Oaks Plaza One, Suite 250, Austin, Texas 78746, and our telephone number is (512) 942-2935. Our website address is www.aegleabio.com. The information contained on, or that can be accessed through, our website is not part of this prospectus, and you should not consider information on our website to be part of this prospectus.

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THE OFFERING

Common stock offered by us	Shares of our common stock having an aggregate offering price of up to $60,000,000.
Common shares to be outstanding following the offering	Up to 29,761,053 shares (based on shares of common stock outstanding on September 30, 2018), assuming sales of 7,662,835 shares of our common stock in this offering at an offering price of $7.83 per share, which was the last reported sale price of our common shares on The Nasdaq Global Market on February 8, 2019. The actual number of shares issued will vary depending on the sales price under this offering.
Manner of offering	At the market offering that may be made from time to time on the Nasdaq Global Market or other existing trading market for our common stock through our agent, Jefferies LLC. See the section entitled Plan of Distribution on page S-15 of this prospectus supplement.
Use of proceeds	We intend to use the net proceeds of this offering primarily to fund research and development of our product candidates, working capital, capital expenditures and other general corporate purposes. See the section entitled Use of Proceeds on page S-12 of this prospectus supplement.
Risk factors	See Risk Factors beginning on page S-9 of this prospectus supplement and the other information included in, or incorporated by reference into, this prospectus supplement for a discussion of certain factors you should carefully consider before deciding to invest in shares of our common stock.
Nasdaq Global Market symbol	AGLE

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RISK FACTORS

Investment in any securities offered pursuant to this prospectus supplement and the accompanying base prospectus involves risks. You should carefully consider the risk factors described below and in our Quarterly Report on Form 10-Q for the quarterly period ended September 30, 2018, incorporated by reference in this prospectus supplement, any amendment or update thereto reflected in subsequent filings with the SEC, including in our Annual Reports on Form 10-K and Quarterly Reports on Form 10-Q, and all other information contained or incorporated by reference in this prospectus supplement, as updated by our subsequent filings under the Exchange Act. The occurrence of any of these risks might cause you to lose all or part of your investment in the offered securities.

Risks Relating to this Offering

If you purchase shares of our common stock sold in this offering, you will experience immediate and substantial dilution in the net tangible book value of your shares. In addition, we may issue additional equity or convertible debt securities in the future, which may result in additional dilution to you.

The price per share of our common stock being offered may be higher than the net tangible book value per share of our outstanding common stock prior to this offering. Assuming that an aggregate of 7,662,835 shares of our common stock are sold at a price of $7.83 per share, the last reported sale price of our common stock on the Nasdaq Global Market on February 8, 2019, for aggregate gross proceeds of approximately $60.0 million, and after deducting commissions and estimated offering expenses payable by us, new investors in this offering will incur immediate dilution of $3.74 per share. For a more detailed discussion of the foregoing, see the section entitled Dilution below. To the extent outstanding stock options or warrants are exercised, there will be further dilution to new investors. In addition, to the extent we need to raise additional capital in the future and we issue additional shares of common stock or securities convertible or exchangeable for our common stock, our then existing stockholders may experience dilution and the new securities may have rights senior to those of our common stock offered in this offering.

We have broad discretion in the use of the net proceeds from this offering and may not use them effectively.

Our management will have broad discretion in the application of the net proceeds from this offering, including for any of the purposes described in the section entitled Use of Proceeds, and you will not have the opportunity as part of your investment decision to assess whether the net proceeds are being used appropriately. Because of the number and variability of factors that will determine our use of the net proceeds from this offering, their ultimate use may vary substantially from their currently intended use. Our management might not apply our net proceeds in ways that ultimately increase the value of your investment. We expect to use the net proceeds from this offering to fund research and development of our product candidates, working capital, capital expenditures and other general corporate purposes. The failure by our management to apply these funds effectively could harm our business. Pending their use, we plan to invest the net proceeds from this offering in short-term and long-term, interest-bearing obligations, investment-grade instruments, certificates of deposit or guaranteed obligations of the U.S. government. These investments may not yield a favorable return to our stockholders. If we do not invest or apply the net proceeds from this offering in ways that enhance stockholder value, we may fail to achieve expected financial results, which could cause our stock price to decline.

The actual number of shares we will issue under the sales agreement, at any one time or in total, is uncertain.

Subject to certain limitations in the sales agreement and compliance with applicable law, we have the discretion to deliver a placement notice to Jefferies at any time throughout the term of the sales agreement. The number of shares that are sold by Jefferies after delivering a placement notice will fluctuate based on the market price of the common

shares during the sales period and limits we set with Jefferies. Because the price per share of each share sold will fluctuate based on the market price of our common stock during the sales period, it is not possible at this stage to predict the number of shares that will be ultimately issued.

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The common stock offered hereby will be sold in at the market offerings , and investors who buy shares at different times will likely pay different prices.

Investors who purchase shares in this offering at different times will likely pay different prices, and so may experience different outcomes in their investment results. We will have discretion, subject to market demand, to vary the timing, prices, and numbers of shares sold, and there is no minimum or maximum sales price. Investors may experience a decline in the value of their shares as a result of share sales made at prices lower than the prices they paid.

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CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus and documents incorporated herein by reference contain forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements involve a number of risks and uncertainties. We caution readers that any forward-looking statement is not a guarantee of future performance and that actual results could differ materially from those contained in the forward-looking statement. These statements are based on current expectations of future events.

Such statements include, but are not limited to, statements regarding expectations and intentions, costs and expenses, outcome of contingencies, financial condition, results of operations, liquidity, cost savings, objectives of management, debt financing, our future results of operations and financial position, business strategies, market size, potential growth opportunities, clinical development activities, efficacy and safety profile of our product candidates, our ability to maintain and recognize the benefits of certain designations received by product candidates, timing and results of our nonclinical studies and clinical trials, the receipt and timing of potential regulatory designations, the achievement of clinical and commercial milestones, the advancement of our technologies and our proprietary product candidates, approvals and commercialization of product candidates and other statements that are not historical facts. You can find many of these statements by looking for words like believes, expects, anticipates, estimates, may, might, sh could, plan, intend, project, seek or similar expressions in this prospectus, the documents incorporated by refere into this prospectus and any free writing prospectus. We intend that such forward-looking statements be subject to the safe harbors created thereby.

These forward-looking statements are based on the current beliefs and expectations of our management and are subject to significant risks and uncertainties. If underlying assumptions prove inaccurate or unknown risks or uncertainties materialize, actual results may differ materially from current expectations and projections. Factors that might cause such a difference include those discussed in Part II, Item 1A, Risk Factors, in our Quarterly Report on Form 10-Q for the quarter ended September 30, 2018, as well as those discussed in this prospectus, the documents incorporated by reference into this prospectus and any free writing prospectus. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date of this prospectus or, in the case of documents referred to or incorporated by reference, the date of those documents.

All subsequent written or oral forward-looking statements attributable to us or any person acting on our behalf are expressly qualified in their entirety by the cautionary statements contained or referred to in this section. We do not undertake any obligation to release publicly any revisions to these forward-looking statements to reflect events or circumstances after the date of this prospectus or to reflect the occurrence of unanticipated events, except as may be required under applicable U.S. securities law. If we do update one or more forward-looking statements, no inference should be drawn that we will make additional updates with respect to those or other forward-looking statements.

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USE OF PROCEEDS

We may issue and sell shares of our common stock having aggregate sales proceeds of up to $60,000,000 time to time. Because there is no minimum offering amount required as a condition to close this offering, the actual total public offering amount, commissions and proceeds to us, if any, are not determinable at this time.

We currently intend to use any net proceeds from the sale of securities under this prospectus primarily to fund research and development of our product candidates, working capital, capital expenditures and other general corporate purposes. Additionally, we may use a portion of the net proceeds from this offering to expand our current business by in-licensing or acquiring, as the case may be, commercial products, product candidates, technologies, compounds, other assets or complementary businesses, using cash or shares of our common stock. However, we have no current commitments or obligations to do so.

The amounts and timing of our actual expenditures will depend on numerous factors, including the progress of our clinical trials and other development efforts and other factors described under Risk Factors in this prospectus supplement, the accompanying base prospectus and the documents incorporated by reference herein and therein, as well as the amount of cash used in our operations. We may find it necessary or advisable to use the net proceeds for other purposes, and we will have broad discretion in the application of the net proceeds. Pending the uses described above, we plan to invest the net proceeds from this offering in short-term or long-term, interest-bearing obligations, investment-grade instruments, certificates of deposit or guaranteed obligations of the U.S. government.

DIVIDEND POLICY

We have never declared or paid any cash dividends on our capital stock. We intend to retain future earnings, if any, to finance the operation and expansion of our business and do not anticipate paying any cash dividends in the foreseeable future. Any future determination related to our dividend policy will be made at the discretion of our board of directors after considering our financial condition, results of operations, capital requirements, business prospects and other factors the board of directors deems relevant, and subject to the restrictions contained in any future financing instruments.

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DILUTION

If you invest in our common stock, your interest will be diluted to the extent of the difference between the price per share you pay in this offering and the net tangible book value per share of our common stock immediately after this offering. Our net tangible book value of our common stock as of September 30, 2018 was approximately $63.7 million, or approximately $2.88 per share of common stock based upon 22,098,218 shares outstanding. 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 as of September 30, 2018.

After giving effect to the sale of our common stock in the aggregate amount of $60.0 million at an assumed offering price of $7.83 per share, the last reported sale price of our common stock on the Nasdaq Global Market on February 8, 2019, and after deducting commissions and estimated offering expenses payable by us, our as adjusted net tangible book value as of September 30, 2018 would have been $121.6 million, or $4.09 per share of common stock. This represents an immediate increase in net tangible book value of $1.21 per share to our existing stockholders and an immediate dilution in net tangible book value of $3.74 per share to new investors in this offering.

The following table illustrates this calculation on a per share basis. The as adjusted information is illustrative only and will adjust based on the actual price to the public, the actual number of shares sold and other terms of the offering determined at the time shares of our common stock are sold pursuant to this prospectus supplement. The as adjusted information assumes that all of our common stock in the aggregate amount of $60.0 million is sold at the assumed offering price of $7.83 per share, the last reported sale price of our common stock on the Nasdaq Global Market on February 8, 2019. The shares sold in this offering, if any, will be sold from time to time at various prices.

Assumed public offering price per share		$ 7.83
Net tangible book value per share as of September 30, 2018	$ 2.88	
Increase in net tangible book value per share attributable to the offering	1.21	
As adjusted net tangible book value per share after giving effect to the offering		4.09
Dilution per share to new investors participating in the offering		$ 3.74

The number of shares of our common stock to be outstanding immediately after this offering is based on 22,098,218 shares of our common stock outstanding as of September 30, 2018. The number of shares outstanding as of September 30, 2018 excludes:

- 3,031,347 shares of common stock issuable upon exercise of options outstanding as of September 30, 2018, with a weighted average exercise price of $6.16 per share;

- 1,121,472 shares of common stock reserved and available for future issuance as of September 30, 2018, under our equity incentives plans, consisting of (1) 84,521 shares of common stock reserved and available for issuance under our 2016 Equity Incentive Plan as of September 30, 2018, (2) 50,851 shares of common stock reserved for issuance under our 2016 Employee Stock Purchase Plan as of September 30, 2018, (3) 986,100 shares of common stock reserved for issuance under our 2018 Equity Inducement Plan as of

September 30, 2018;

An increase in the number of shares of common stock approved by our stockholders pursuant to an amendment on October 8, 2018 to increase the number of shares available under the 2016 Equity Incentive Plan by 1,759,602 shares, which resulted in a total of 1,844,123 shares of common stock reserved and available for future issuance under the 2016 Equity Incentive Plan as of October 8, 2018. Of such 1,844,123 shares available for future issuance on October 8, 2018, options for an aggregate of 379,900 shares of common stock were granted after October 8, 2018, with a weighted average exercise price of $9.26 per share;

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1,845,820 shares of common stock sold under the at-the-market program with JonesTrading Institutional Services LLC in October 2018; and

3,500,000 shares of common stock and pre-funded warrants to purchase 4,000,000 shares of common stock, with an exercise price per share of $0.0001, sold pursuant to a firm commitment underwritten public offering in February 2019.

The foregoing table does not give effect to the exercise of any outstanding options or warrants. To the extent options and warrants are exercised, there may be further dilution to new investors.

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PLAN OF DISTRIBUTION

We have entered into a sales agreement with Jefferies under which we may issue and sell shares of our common stock from time to time up to an aggregate sales price of $60,000,000 through Jefferies. The sales agreement is filed as Exhibit 1.2 to our registration statement on Form S-3 of which this prospectus supplement forms a part, and is incorporated by reference in this prospectus supplement. Sales of our common stock, if any, under this prospectus supplement will be made by any method that is deemed an at the market offering as defined in Rule 415(a)(4) under the Securities Act, including sales made directly on or through the Nasdaq Global Market or any other existing trading market for our common stock.

When requested by us, Jefferies will offer the shares of common stock subject to the terms and conditions of the sales agreement, which may be on a daily basis for periods of time, or as we may otherwise agree with Jefferies. We will designate the maximum amount of shares of common stock to be sold through Jefferies when we request Jefferies to do so. Jefferies has agreed, subject to the terms and conditions of the sales agreement, to use its commercially reasonable efforts to execute our orders to sell, as our sales agent and on our behalf, shares of our common stock submitted to Jefferies from time to time by us, consistent with its normal sales and trading practices. We may instruct Jefferies not to place shares of common stock at or below a price designated by us. We or Jefferies may suspend the offering of shares of common stock under the sales agreement upon proper notice to the other party.

If we and Jefferies so agree, Jefferies may act as principal in connection with the placement of the securities offered hereby.

We will pay Jefferies a commission of 3.0% of the gross proceeds of any shares sold through it pursuant to this prospectus supplement, and reimburse Jefferies for up to $50,000 of its expenses, including fees and disbursements to its legal counsel. The estimated offering expenses payable by us, in addition to such commission and reimbursement of expenses, are approximately $270,000, which includes legal, accounting and printing costs and various other fees associated with registering the shares of common stock. The remaining sale proceeds, after deducting any other transaction fees, will equal our net proceeds from the sale of such shares.

Jefferies will provide written confirmation to us following the close of trading on the Nasdaq Global Market each day on which shares of common stock are sold under the sales agreement. Each confirmation will include the number of shares sold on that day, the aggregate gross proceeds of such sales and the commission payable by us to Jefferies. Settlement for sales of common stock will occur, unless otherwise agreed, on the second business day following the date on which such sales were made.

In connection with the sale of our common stock on our behalf, Jefferies will be deemed to be an underwriter within the meaning of the Securities Act and the compensation of Jefferies will be deemed to be underwriting commissions or discounts.

We have agreed to indemnify Jefferies against certain liabilities, including liabilities under the Securities Act. We have also agreed to contribute to payments Jefferies may be required to make in respect of such liabilities.

The offering of shares of common stock pursuant to the sales agreement will terminate upon the earliest of (i) the sale of all shares of common stock subject to the sales agreement and this prospectus supplement and (ii) the termination of the sales agreement according to its terms by either Jefferies or us.

Jefferies has provided, and may in the future provide, various investment banking, commercial banking, financial advisory and other services to us and our affiliates for which services it has received, and may in the future receive,

customary fees. In the course of its business, Jefferies may actively trade our securities for its own account or for the accounts of customers, and, accordingly, Jefferies may at any time hold long or short positions in such securities.

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LEGAL MATTERS

Fenwick & West LLP will pass upon certain legal matters relating to the issuance and sale of the securities offered hereby on behalf of Aeglea BioTherapeutics, Inc. Jefferies LLC is being represented in connection with this offering by Cooley LLP, New York, New York.

EXPERTS

The financial statements incorporated in this prospectus supplement by reference to the Annual Report on Form 10-K for the year ended December 31, 2017 have been so incorporated in reliance on the report of PricewaterhouseCoopers LLP, an independent registered public accounting firm, given on the authority of said firm as experts in auditing and accounting.

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Up to $60,000,000

Common Stock

PROSPECTUS SUPPLEMENT

Jefferies

, 2019

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PART II

INFORMATION NOT REQUIRED IN PROSPECTUS

Item 14. Other Expenses of Issuance and Distribution

The following table sets forth estimated expenses in connection with the issuance and distribution of the securities being registered:

SEC registration fee	$ 24,240
FINRA filing fee	30,500
Printing and engraving*	*
Legal fees and expenses*	*
Accounting fees and expenses*	*
Transfer agent and registrar fees and expenses*	*
Miscellaneous expenses*	*
Total*	$ *

* These fees are calculated based on the type of securities offered and the number of issuances and accordingly, cannot be estimated at this time.

Item 15. Indemnification of Officers and Directors

Section 145 of the Delaware General Corporation Law authorizes a court to award, or a corporation s board of directors to grant, indemnity to directors and officers under certain circumstances and subject to certain limitations. The terms of Section 145 of the Delaware General Corporation Law are sufficiently broad to permit indemnification under certain circumstances for liabilities, including reimbursement of expenses incurred, arising under the Securities Act of 1933, as amended, or the Securities Act.

As permitted by the Delaware General Corporation Law, the Registrant s restated certificate of incorporation contains provisions that eliminate the personal liability of its directors for monetary damages for any breach of fiduciary duties as a director, except liability for the following:

- any breach of the director s duty of loyalty to the Registrant or its stockholders;
- acts or omissions not in good faith or that involve intentional misconduct or a knowing violation of law;
- under Section 174 of the Delaware General Corporation Law (regarding unlawful dividends and stock purchases); or

any transaction from which the director derived an improper personal benefit.

As permitted by the Delaware General Corporation Law, the Registrant s restated bylaws provide that:

the Registrant is required to indemnify its directors and executive officers to the fullest extent permitted by the Delaware General Corporation Law, subject to very limited exceptions;

the Registrant may indemnify its other employees and agents as set forth in the Delaware General Corporation Law;

the Registrant is required to advance expenses, as incurred, to its directors and executive officers in connection with a legal proceeding to the fullest extent permitted by the Delaware General Corporation Law, subject to very limited exceptions; and

the rights conferred in the restated bylaws are not exclusive.

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The Registrant has entered, and intends to continue to enter, into separate indemnification agreements with its directors and executive officers to provide these directors and executive officers additional contractual assurances regarding the scope of the indemnification set forth in the Registrant s restated certificate of incorporation and restated bylaws and to provide additional procedural protections. At present, there is no pending litigation or proceeding involving a director or executive officer of the Registrant regarding which indemnification is sought. The indemnification provisions in the Registrant s restated certificate of incorporation, restated bylaws and the indemnification agreements entered into or to be entered into between the Registrant and each of its directors and executive officers may be sufficiently broad to permit indemnification of the Registrant s directors and executive officers for liabilities arising under the Securities Act.

The Registrant currently carries liability insurance for its directors and officers. One of the Registrant s directors, Armen Shanafelt, is also indemnified by his employer with regard to his service on the Registrant s board of directors.

Reference is made to the following documents filed as exhibits to this Registration Statement regarding relevant indemnification provisions described above and elsewhere herein:

Exhibit	Number
Restated Certificate of Incorporation	3.1
Restated Bylaws	3.2
Amended and Restated Investors Rights Agreement, dated March 10, 2015, by and among the Registrant and certain of its stockholders, as amended	4.2

Item 16. Exhibits

The exhibits listed in the accompanying Exhibit Index are filed (except where otherwise indicated) as part of this Registration Statement.

Item 17. Undertakings

(a) The undersigned Registrant hereby undertakes:

(1) To file, during any period in which offers or sales are being made, a post-effective amendment to this registration statement:

(i) to include any prospectus required by Section 10(a)(3) of the Securities Act of 1933;

(ii) to reflect in the prospectus any facts or events arising after the effective date of the registration statement (or the most recent post-effective amendment thereof) which, individually or in the aggregate, represent a fundamental change in the information set forth in the registration statement. Notwithstanding the foregoing, any increase or decrease in volume of securities offered (if the total dollar value of securities offered would not exceed that which was registered) and any deviation from the low or high end of the estimated maximum offering range may be reflected in the form of prospectus filed with the Securities and Commission pursuant to Rule 424(b) if, in the aggregate, the changes in volume and price represent no more than 20 percent change in the maximum aggregate offering price set forth in the Calculation of Registration Fee table in the effective registration statement; and

(iii) to include any material information with respect to the plan of distribution not previously disclosed in the registration statement or any material change to such information in the registration statement;

provided, however, that subparagraphs (i),(ii), and (iii) do not apply if the information required to be included in a post-effective amendment by those paragraphs is contained in reports filed with or furnished to the Securities and Commission by the Registrant pursuant to Section 13 or Section 15(d) of the Securities

Exchange Act of 1934 that are incorporated by reference in the registration statement, or is contained in a form of prospectus filed pursuant to Rule 424(b) that is part of the registration statement.

(2) That, for the purpose of determining any liability under the Securities Act of 1933, each such post-effective amendment shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial *bona fide* offering thereof.

(3) To remove from registration by means of a post-effective amendment any of the securities being registered which remain unsold at the termination of the offering.

(4) That, for the purpose of determining liability under the Securities Act of 1933 to any purchaser:

(i) Each prospectus filed by the Registrant pursuant to Rule 424(b)(3) shall be deemed to be part of the registration statement as of the date the filed prospectus was deemed part of and included in the registration statement; and

(ii) Each prospectus required to be filed pursuant to Rule 424(b)(2), (b)(5), or (b)(7) as part of a registration statement in reliance on Rule 430B relating to an offering made pursuant to Rule 415(a)(1)(i), (vii), or (x) for the purpose of providing the information required by Section 10(a) of the Securities Act of 1933 shall be deemed to be part of and included in the registration statement as of the earlier of the date such form of prospectus is first used after effectiveness or the date of the first contract of sale of securities in the offering described in the prospectus. As provided in Rule 430B, for liability purposes of the issuer and any person that is at that date an underwriter, such date shall be deemed to be a new effective date of the registration statement relating to the securities in the registration statement to which that prospectus relates, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof. *Provided, however*, that no statement made in a registration statement or prospectus that is part of the registration statement or made in a document incorporated or deemed incorporated by reference into the registration statement or prospectus that is part of the registration statement will, as to a purchaser with a time of contract of sale prior to such effective date, supersede or modify any statement that was made in the registration statement or prospectus that was part of the registration statement or made in any such document immediately prior to such effective date.

(5) That, for the purpose of determining liability of the Registrant under the Securities Act of 1933 to any purchaser in the initial distribution of the securities, the undersigned Registrant undertakes that in a primary offering of securities of the undersigned Registrant pursuant to this registration statement, regardless of the underwriting method used to sell the securities to the purchaser, if the securities are offered or sold to such purchaser by means of any of the following communications, the undersigned Registrant will be a seller to the purchaser and will be considered to offer or sell such securities to such purchaser:

(i) any preliminary prospectus or prospectus of the undersigned Registrant relating to the offering required to be filed pursuant to Rule 424;

(ii) any free writing prospectus relating to the offering prepared by or on behalf of the undersigned Registrant or used or referred to by the undersigned Registrant;

(iii) the portion of any other free writing prospectus relating to the offering containing material information about the undersigned Registrant or its securities provided by or on behalf of the undersigned Registrant; and

(iv) any other communication that is an offer in the offering made by the undersigned Registrant to the purchaser.

(b) The undersigned Registrant hereby undertakes that, for purposes of determining any liability under the Securities Act of 1933, each filing of the Registrant s annual report pursuant to Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934 (and, where applicable, each filing of an employee benefit plan s annual

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report pursuant to Section 15(d) of the Securities Exchange Act of 1934) that is incorporated by reference in the registration statement shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

(c) The undersigned Registrant hereby undertakes to deliver or cause to be delivered with the prospectus, to each person to whom the prospectus is sent or given, the latest annual report, to security holders that is incorporated by reference in the prospectus and furnished pursuant to and meeting the requirements of Rule 14a-3 or Rule 14c-3 under the Securities Exchange Act of 1934; and, where interim financial information required to be presented by Article 3 of Regulation S-X is not set forth in the prospectus, to deliver, or cause to be delivered to each person to whom the prospectus is sent or given, the latest quarterly report that is specifically incorporated by reference in the prospectus to provide such interim financial information.

(d) Insofar as indemnification for liabilities arising under the Securities Act of 1933 may be permitted to directors, officers, and controlling persons of the Registrant pursuant to the foregoing provisions, or otherwise, the Registrant has been advised that in the opinion of the Securities and Exchange Commission such indemnification is against public policy as expressed in the Securities Act of 1933 and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the Registrant of expenses incurred or paid by a director, officer, or controlling person of the Registrant in the successful defense of any action, suit, or proceeding) is asserted by such director, officer, or controlling person in connection with the securities being registered, the Registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act of 1933 and will be governed by the final adjudication of such issue.

(e) If and when applicable, the Registrant hereby further undertakes to file an application for the purpose of determining the eligibility of the trustee to act under subsection (a) of Section 310 of the Trust Indenture Act in accordance with the rules and regulations prescribed by the Securities and Exchange Commission under Section 305(b)(2) of the Trust Indenture Act.

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EXHIBIT INDEX

Exhibit Number	Exhibit Description	Incorporated by Reference				Filed Herewith
		Form	File No.	Exhibit	Filing Date	
1.1*	Form of Underwriting Agreement					
1.2	Open Market Sale Agreement℠, dated December 21, 2018, by and between the Registrant and Jefferies LLC	S-3	333-228967	1.2	12/21/18	
3.1	Restated Certificate of Incorporation	S-1/A	333-205001	3.2	9/14/2015	
3.2	Restated Bylaws	S-1/A	333-205001	3.4	9/14/2015	
4.1	Form of Common Stock Certificate	S-1/A	333-205001	4.1	9/14/2015	
4.2	Amended and Restated Investors Rights Agreement, dated March 10, 2015, by and among the Registrant and certain of its stockholders, as amended	S-1	333-205001	4.2	6/16/2015	
4.3	Form of Debt Security	S-3	333-228967	4.3	12/21/18	
4.4	Form of Indenture	S-3	333-228967	4.4	12/21/18	
4.5*	Form of Warrant					
4.6*	Form of Warrant Agreement					
4.7*	Form of Preferred Stock Certificate					
4.8*	Form of Subscription Rights Certificate					
4.9*	Form of Unit					
4.10*	Form of Unit Agreement					
5.1	Opinion of Fenwick & West LLP	S-3	333-228967	5.1	12/21/18	
23.1	Consent of PricewaterhouseCoopers LLP					X
23.2	Consent of Fenwick & West LLP (included in Exhibit 5.1)	S-3	333-228967	23.2	12/21/18	
24.1	Power of Attorney	S-3	333-228967	24.1	12/21/18	
25.1**	Form T-1 Statement of Eligibility of Trustee for Senior Indenture under the Trust Indenture Act of 1939.					
25.2**	Form T-1 Statement of Eligibility of Trustee for Subordinated Indenture under the Trust Indenture Act of 1939.					

* To be filed by amendment or as an exhibit to a report pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended and incorporated herein by reference.

** To be filed in accordance with the requirements of Section 305(b)(2) of the Trust Indenture Act of 1939 and Rule 5b-3 thereunder.

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SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, the Registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-3 and has duly caused this amendment to Registration Statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of Austin, State of Texas, on February 11, 2019.

AEGLEA BIOTHERAPEUTICS, INC.

By: /s/ Anthony G. Quinn, M.B Ch.B, Ph.D.
Anthony G. Quinn, M.B Ch.B, Ph.D.
Chief Executive Officer

Pursuant to the requirements of the Securities Act, this amendment to Registration Statement has been signed by the following persons in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Anthony G. Quinn, M.B Ch.B, Ph.D. Anthony G. Quinn, M.B Ch.B, Ph.D.	Chief Executive Officer and Director (Principal Executive Officer)	February 11, 2019
/s/ Charles N. York II Charles N. York II	Chief Financial Officer and Vice President (Principal Accounting Officer and Principal Financial Officer)	February 11, 2019
* Suzanne L. Bruhn, Ph.D.	Director	February 11, 2019
* Russell J. Cox	Director	February 11, 2019
* Ivana Magocevic-Liebisch, Ph.D.	Director	February 11, 2019
* Sandesh Mahatme, LLM	Director	February 11, 2019
*	Director	February 11, 2019

V. Bryan Lawlis, Ph.D.		
*	Director	February 11, 2019
Armen Shanafelt, Ph.D.		

* By: /s/ Charles N. York II
Charles N. York II

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