Aeglea BioTherapeutics, Inc.
Form 424B5
February 13, 2019
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Filed Pursuant to Rule 424(b)(5)
Registration No. 333-228967

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 February 13, 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 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.

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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. 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

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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.

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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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 February 13, 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