

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
 WASHINGTON, D.C. 20549

FORM S-3
REGISTRATION STATEMENT
 UNDER
THE SECURITIES ACT OF 1933

Aeglea BioTherapeutics, Inc.

(Exact name of registrant as specified in its charter)

Delaware
 (State or other jurisdiction of
 incorporation or organization)

46-4312787
 (I.R.S. Employer
 Identification No.)

805 Las Cimas Parkway
 Suite 100
 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.
 805 Las Cimas Parkway
 Suite 100
 Austin, TX 78746
 (512) 942-2935
 (Name, address, including zip code, and telephone number, including area code, of agent for service)

Copies to:

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Anthony G. Quinn
 Chief Executive Officer
 Aeglea BioTherapeutics, Inc.
 805 Las Cimas Parkway
 Suite 100
 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	<input type="checkbox"/>		Accelerated filer	<input type="checkbox"/>
Non-accelerated filer	<input checked="" type="checkbox"/>		Smaller reporting company	<input checked="" type="checkbox"/>
			Emerging growth company	<input checked="" type="checkbox"/>

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
Common stock, \$0.0001 par value per share	19,020,434	\$6.68	\$127,056,500	\$13,862

- (1) Pursuant to Rule 416 under the Securities Act, the shares being registered hereunder include such indeterminate number of additional shares of common stock as may be issuable as a result of stock splits, stock dividends or similar transactions with respect to the shares being registered hereunder.
- (2) Consists of an aggregate of 19,020,434 shares of the registrant's common stock, including 15,610,328 shares of common stock issuable upon the exercise of pre-funded warrants, of the registrant.
- (3) Estimated solely for the purpose of calculating the amount of the registration fee pursuant to Rule 457(c) under the Securities Act, based upon the average of the high and low prices for the common stock on May 25, 2021, as reported by the Nasdaq Global Market.

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.

The information in this prospectus is not complete and may be changed. These securities may not be sold 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 MAY 28, 2021

PROSPECTUS



Aeglea BioTherapeutics, Inc.

19,020,434 Shares

Common Stock

This prospectus relates to the sale or other disposition from time to time by the selling stockholder named in this prospectus of up to an aggregate of 19,020,434 shares of our common stock, par value \$0.0001 per share, which includes 15,610,328 shares of our common stock issuable upon the exercise of pre-funded warrants held by the Baker Funds (as defined below). We are not selling any shares of our common stock under this prospectus and will not receive any of the proceeds from the sale or other disposition of shares of common stock by the selling stockholder.

We are registering the shares for resale by the selling stockholder identified in this prospectus or its transferees, pledgees, donees, or successors. However, our registration of the shares of common stock covered by this prospectus does not mean that the selling stockholder will offer or sell any of the shares. The selling stockholder may sell or otherwise dispose of the shares of common stock covered by this prospectus in a number of different ways and at varying prices. We provide more information about how the selling stockholder may sell or otherwise dispose of its shares of common stock in the section entitled "Plan of Distribution." Discounts, concessions, commissions and similar selling expenses attributable to the sale of shares of common stock covered by this prospectus will be borne by the selling stockholder. We will pay all registration expenses incurred relating to the registration of the shares with the Securities and Exchange Commission and the selling stockholder will pay all selling expenses, including underwriting discounts and selling commissions, related to the sale of the shares registered under this registration statement. As of the date of this prospectus, no underwriter or other person has been engaged to facilitate the sale of the shares of common stock covered hereby.

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 5 of this prospectus before investing in our securities.

Our common stock is traded on The Nasdaq Global Market under the symbol "AGLE." On May 27, 2021 the last reported sales price for our common stock was \$6.76 per share.

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 _____, 2021.

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ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement on Form S-3 that we filed with the Securities and Exchange Commission, or SEC, using a “shelf” registration process. Under this shelf registration process, from time to time, the selling stockholder may sell up to 19,020,434 shares of our common stock in one or more offerings as described in this prospectus.

We have not authorized anyone to provide you with 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. We and the selling stockholder take no responsibility for, and can provide no assurances as to the reliability of, any other information that others may give you. The information contained in this prospectus (and in any supplement or amendment to this prospectus) or any related free writing prospectus, and the documents incorporated by reference herein and therein, are accurate only as of their respective dates, regardless of the time of delivery of this prospectus, any applicable prospectus supplement or any related free writing prospectus, or any sale of a security. We urge you to read carefully this prospectus (as supplemented and amended), together with the information incorporated herein by reference as described under the heading “Incorporation of Information by Reference” before deciding whether to invest in any of the shares of common stock being offered.

This prospectus contains summaries of certain provisions contained in some of the documents described herein, but reference is made to the actual documents for complete information. All of the summaries are qualified in their entirety by the actual documents. Copies of some of the documents referred to herein have been filed, will be filed or will be incorporated by reference as exhibits to the registration statement of which this prospectus is a part, and you may obtain copies of those documents as described below under the section entitled “Where You Can Find More Information.”

In this prospectus, unless the context otherwise requires, the terms “Aeglea,” the “Company,” “we,” “us,” and “our” refer to Aeglea BioTherapeutics, Inc., a Delaware corporation, and its consolidated subsidiaries. “Aeglea” and all product candidate names are our common law trademarks.

PROSPECTUS SUMMARY

This summary may not contain all the information that you should consider before investing in our common stock. 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 clinical-stage biotechnology company redefining the potential of human enzyme therapeutics to benefit people with rare metabolic diseases with limited treatment options. We believe our expertise in enzyme science, bioengineering and rare disease drug development coupled with an approach focused on diseases with unmet medical needs enables us to develop medicines with the potential to transform the lives of patients and families with rare metabolic diseases.

We employ a distinctive platform to fuel our innovative pipeline of human enzymes, which we believe reduces key risks throughout the development process and provides a greater likelihood of clinical success and commercial adoption.

Our mission is to provide transformative therapies to patient communities who have inadequate or no therapeutic options available to address these debilitating diseases. Driven by this purpose and urgent patient need, we have taken a focused approach to the selection and development of novel assets into clinical evaluation that is guided by defined strategic considerations:

- Clear, urgent unmet medical need
- Rigorous preclinical data and strong scientific rationale
- Mechanistic opportunity to create or enhance enzymatic activity through novel engineering
- Meaningful and sustainable commercial opportunities
- Potential to be first in class or best in class, with little competition

Pegzilarginase in Patients with Arginase 1 Deficiency

Our lead product candidate, pegzilarginase, is a recombinant human Arginase 1 that enzymatically degrades the amino acid arginine to lower arginine levels in patients with Arginase 1 Deficiency. We engineered pegzilarginase with modifications that enhance the stability and arginine-degrading activity of the enzyme in human plasma. For Arginase 1 Deficiency, which is a rare progressive disease, that presents in early childhood and results in severe complications and early mortality, we believe pegzilarginase may reduce the harmful metabolic effects caused by the accumulation of high levels of arginine and other arginine-derived metabolites. We are currently evaluating pegzilarginase in a global pivotal Phase 3 PEACE (Pegzilarginase Effect on Arginase 1 Deficiency Clinical Endpoints) trial and in a Phase 2 open-label extension study for patients with Arginase 1 Deficiency.

AGLE-177 in Homocystinuria

Our product candidate, AGLE-177, is a novel PEGylated, or polyethylene glycol modified, human enzyme engineered to degrade free homocysteine and homocystine in patients with Homocystinuria, a serious metabolic disorder characterized by elevated plasma homocysteine which leads to a wide range of life-altering complications and reduced life expectancy. We engineered AGLE-177 by directed mutagenesis of amino acid

residues within the active site of human cystathionine γ -lyase, resulting in a molecule that has high substrate specificity for homocysteine and homocystine but not for the native substrate, cystathionine. For Homocystinuria due to cystathionine β -synthase, or CBS, enzyme deficiency, which is the most common form of an inherited disorder of methionine metabolism that results in elevated homocysteine and homocystine, we believe AGL-177 may reduce the adverse impact of CBS enzyme deficiency in the transsulfuration pathway by providing an alternate pathway for enzymatic degradation of high plasma total homocysteine levels. We have initiated a Phase 1/2 clinical trial for the treatment of patients with Homocystinuria.

Cystinuria Program

Cystinuria is 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. As such, we engineered our Cystinuria program candidate to reduce plasma cystine and cysteine levels with accompanying reductions in urine cystine concentrations as an approach to inhibit both cystine crystal and kidney stone formation. Due to the impact of COVID-19, we have not provided a timeline for advancement of a therapeutic candidate into the clinic.

Corporate 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 805 Las Cimas Parkway, Suite 100, Austin, Texas 78746, and our telephone number is (512) 942-2935. We have research and development operations and corporate offices in Austin, TX.

The Offering

Common stock to be offered by the selling stockholder	19,020,434 shares, which includes 15,610,328 shares of common stock issuable upon the exercise of pre-funded warrants held by the Baker Funds (as defined below).
Use of proceeds	We will not receive any proceeds from the sale of the shares of common stock covered by this prospectus.
Risk factors	See “Risk Factors” beginning on page 5, for a discussion of factors you should carefully consider before deciding to invest in our common stock.
NASDAQ Global Market symbol	AGLE

The selling stockholder named in this prospectus may offer and sell up to an aggregate of 19,020,434 shares of our common stock, which includes 15,610,328 shares of common stock issuable upon the exercise of pre-funded warrants held by the Baker Funds (as defined below). Throughout this prospectus, when we refer to the shares of our common stock being registered on behalf of the selling stockholder, we are referring to all 19,020,434 shares of common stock, including 15,610,328 shares of common stock issuable upon the exercise of pre-funded warrants held by the Baker Funds (as defined below) as of May 15, 2021.

We agreed to file this prospectus pursuant to a registration rights agreement with 667, L.P. (“**667**”) and Baker Brothers Life Sciences, L.P. (“**Life Sciences**”), and together with 667, the “**Baker Funds**”) dated March 16, 2021 (the “**Registration Rights Agreement**”). Additional information with respect to the Registration Rights Agreement is contained in this prospectus under the heading “Selling Stockholder” and in our Annual Report on Form 10-K filed with the Securities and Exchange Commission on March 18, 2021.

When we refer to the selling stockholder, we are referring to the selling stockholder named herein and, as applicable, any donees, pledgees, transferees or other successors-in-interest selling shares received after the date of this prospectus from a selling stockholder as a gift, pledge, or other non-sale related transfer that may be identified in a supplement to this prospectus or, if required, a post-effective amendment to the registration statement of which this prospectus is a part.

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 March 31, 2021, 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 our future results of operations and financial position, business strategy, market size, potential growth opportunities, nonclinical and clinical development activities, efficacy and safety profile of our product candidates, potential therapeutic benefits and economic value of our product candidates, liquidity, debt financings, our ability to maintain and recognize the benefits of certain designations received by product candidates, the timing and results of nonclinical studies and clinical trials, commercial collaboration with third parties, our ability to obtain regulatory approval for, and commercialize, pegzilarginase, our ability to recognize milestone and royalty payments from commercialization agreements, the expected impact of the COVID-19 pandemic on our operations, and the receipt and timing of potential regulatory designations, 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,” “should,” “will,” “could,” “plan,” “intend,” “project,” “seek” or similar expressions in this prospectus, in documents incorporated by reference into 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 March 31, 2021, 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.

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, 805 Las Cimas Parkway, Suite 100, 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, 2020, filed with the SEC on March 18, 2021, including certain information incorporated by reference therein from our Definitive Proxy Statement for our 2021 annual meeting of stockholders filed with the SEC on April 22, 2021;
- our [Quarterly Report on Form 10-Q](#) for the quarter ended March 31, 2021, filed with the SEC on May 10, 2021;
- our Current Reports on Form 8-K filed on [January 5, 2021](#), [February 3, 2021](#), [February 24, 2021](#), and [March 22, 2021](#) (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, 805 Las Cimas Parkway, Suite 100, 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.

USE OF PROCEEDS

We will not receive any of the proceeds from the sale of our common stock by the selling stockholder pursuant to this prospectus. The selling stockholder and its affiliates will receive all the net proceeds from the sales of common stock pursuant to this prospectus.

SELLING STOCKHOLDER

The selling stockholder named in this prospectus may offer and sell up to an aggregate of 19,020,434 shares of our common stock, which includes 15,610,328 shares of common stock issuable upon the exercise of pre-funded warrants held by the Baker Funds.

On March 16, 2021, we entered into the Registration Rights Agreement with the Baker Funds, entities for which Baker Bros. Advisers LP (“**BBA**”) serves as investment adviser, pursuant to which the Baker Funds are entitled to certain resale registration rights with respect to shares of our common stock held by them (the “**Registrable Securities**”). Under the Registration Rights Agreement, following a request by the Baker Funds, we are obligated to file a resale registration statement on Form S-3, or other appropriate form, covering Registrable Securities. The registration statement of which this prospectus is a part is being filed pursuant to the Registration Rights Agreement.

In February 2019 and April 2020, we issued pre-funded warrants to the Baker Funds to purchase our common stock in underwritten public offerings at the offering price of the common stock, less the \$0.0001 per share exercise price of each pre-funded warrant. Per the terms of the pre-funded warrant agreements, the outstanding pre-funded warrants to purchase shares of our common stock may not be exercised if the holder of the pre-funded warrants, together with its affiliates and any persons who are members of a Section 13(d) group with the holder, would beneficially own more than 9.9% of the number of shares of common stock outstanding immediately after giving effect to such exercise (the “**Beneficial Ownership Limitation**”). By written notice to us, the holders of the pre-funded warrants purchased in February 2019 may increase or decrease the Beneficial Ownership Limitation, and the holders of the pre-funded warrants purchased in April 2020 may increase or decrease the Beneficial Ownership Limitation to any other percentage not in excess of 19.99%. Any increase in the Beneficial Ownership Limitation would not be effective until 61 days after written notice is received by us.

The following table sets forth, to our knowledge, certain information as of May 25, 2021 regarding the beneficial ownership of our common stock by the selling stockholder. Information with respect to beneficial ownership is based upon information obtained from the selling stockholder. The number of shares beneficially owned by the selling stockholder is determined under rules issued by the SEC, as qualified below. Under these rules, beneficial ownership includes any shares over which a selling stockholder has sole or shared voting power or investment power. In computing the beneficial ownership and percentage ownership of the selling stockholder, shares of common stock issuable upon the exercise of pre-funded warrants and shares of common stock underlying options held by the Baker Funds or for the benefit of the Funds that are currently exercisable or will become exercisable within 60 days following May 25, 2021 are considered outstanding, as qualified below. Percentage ownership is based on 49,024,331 shares of our common stock outstanding as of May 25, 2021. The selling stockholder may, from time to time, offer and sell some, all or none of its shares.

Solely for purposes of the table below, the information under the headings “Total ownership before the offering” and “Total ownership after the offering” disregards the Beneficial Ownership Limitation described above. The selling stockholder and its affiliates disclaim beneficial ownership of any shares of common stock, the issuance of which would violate such Beneficial Ownership Limitation.

The information set forth below is based upon information obtained from the selling stockholder and upon information known to us.

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Sara Brownstein is a member of our board of directors serving as a representative of the Baker Funds and their affiliates.

<u>Selling Stockholder</u>	<u>Total ownership before the offering(2)</u>		<u>Maximum number of shares to be sold pursuant to this prospectus</u>	<u>Total ownership after the offering(3)</u>	
	<u>Number of shares(2)</u>	<u>%</u>		<u>Number of shares</u>	<u>%</u>
Baker Bros. Advisors LP(1)	19,026,989	29	19,020,434	6,555	*

* Represents beneficial ownership of less than one percent.

- 1) Baker Bros. Advisors LP (“**BBA**”) is the investment adviser to 667, L.P. (“**667**”) and Baker Brothers Life Sciences, L.P. (“**Life Sciences**”, and together with 667, the “**Baker Funds**”) and has the sole voting and investment power with respect to the securities held by the Baker Funds and thus may be deemed to beneficially own such securities. Baker Bros. Advisors (GP) LLC (“**BBA GP**”) is the sole general partner of BBA and thus may be deemed to beneficially own the securities held by the Baker Funds. The principals of BBA GP are Julian C. Baker and Felix J. Baker, who may be deemed to beneficially own the securities held by the Baker Funds. Sara Brownstein is a member of our board of directors serving as a representative of the Baker Funds and their affiliates. Per the policy of BBA, employees of BBA are not allowed to receive compensation from the company for serving as a director. Therefore, Ms. Brownstein has no pecuniary interest in the options or common stock received from the exercise of options received as director compensation from the Company. The Baker Funds are instead entitled to the pecuniary interest in such options and common stock received from the exercise of such options. The address of BBA is 860 Washington Street, 3rd Floor, New York, NY 10014.
- 2) The beneficial ownership included in the table above consists of (i) 315,516 shares of common stock and 1,311,405 shares of common stock exercisable upon exercise of pre-funded warrants held by 667; (ii) 3,094,590 shares of common stock and 14,298,923 shares of common stock exercisable upon exercise of pre-funded warrants held by Life Sciences, and (iii) options exercisable for 6,555 shares of common stock within 60 days of May 25, 2021 held for the benefit of the Baker Funds. As noted above, the pre-funded warrants to purchase shares of our common stock may not be exercised if the holder of the pre-funded warrants, together with its affiliates and any persons who are members of a Section 13(d) group with the holder, would beneficially own more than 9.9% of the number of shares of common stock outstanding immediately after giving effect to such exercise (the “**Beneficial Ownership Limitation**”). By written notice to us, the holders of the pre-funded warrants purchased in February 2019 may increase or decrease the Beneficial Ownership Limitation, and the holders of the pre-funded warrants purchased in April 2020 may increase or decrease the Beneficial Ownership Limitation to any other percentage not in excess of 19.99%. Any increase in the Beneficial Ownership Limitation would not be effective until 61 days after written notice is received by us. The beneficial ownership amounts in the table above do not give effect to the Beneficial Ownership Limitation solely for illustrative purposes. BBA, BBA GP, Julian C. Baker and Felix J. Baker disclaim beneficial ownership of any shares disclosed above except to the extent of their pecuniary interest therein.
- 3) The selling stockholder may offer and sell all or part of the common stock covered by this prospectus, and no assumption can be made as to the actual number of shares of common stock that will be held by the selling stockholder after the completion of this offering.

PLAN OF DISTRIBUTION

The selling stockholder may, from time to time, sell any or all of their shares of common stock on any stock exchange, market or trading facility on which the shares are traded or in private transactions. These sales may be at fixed or negotiated prices. The selling stockholder may use any one or more of the following methods when selling shares:

- ordinary brokerage transactions and transactions in which a broker-dealer solicits purchasers;
- block trades in which a broker-dealer will attempt to sell the shares as agent, but may position and resell a portion of the block as principal to facilitate the transaction;
- purchases by a broker-dealer as principal and resale by the broker-dealer for its account under this prospectus;
- an exchange distribution in accordance with the rules of the applicable exchange;
- privately negotiated transactions;
- “at the market” or through market makers or into an existing market for the shares;
- delivery of securities in settlement of short sales after the date of this prospectus;
- through the writing or settlement of options or other hedging transactions, whether through an options exchange or otherwise;
- through the distribution of the common stock by any selling stockholder to its partners, members or stockholders;
- through broker-dealers that agree with the selling stockholder to sell a specified number of such shares at a stipulated price per share;
- through one or more underwritten offerings on a firm commitment or best efforts basis;
- a combination of any such methods of sale; and
- any other method permitted pursuant to applicable law.

The selling stockholder will act independently of us in making decisions with respect to the timing, manner and size of each sale. The selling stockholder also may resell all or a portion of the shares in open market transactions in reliance upon Rule 144, as permitted by that rule, or Section 4(a)(1) under the Securities Act, if available, rather than under this prospectus, provided that they meet the criteria and conform to the requirements of those provisions.

In connection with the sale of the shares, the selling stockholder may enter into hedging transactions with broker-dealers or other financial institutions, which may in turn engage in short sales of the common stock in the course of hedging the positions they assume. The selling stockholder may also sell shares of our common stock short and deliver these securities to close out their short positions, or loan or pledge the common stock to broker dealers that in turn may sell these securities. The selling stockholder may also enter into option or other transactions with broker-dealers or other financial institutions or the creation of one or more derivative securities which require the delivery to such broker-dealer or other financial institution of shares offered by this prospectus, which shares such broker-dealer or other financial institution may resell pursuant to this prospectus (as supplemented or amended to reflect such transaction).

The aggregate proceeds to the selling stockholder from the sale of the shares offered by them will be the purchase price of the common stock less discounts or commissions, if any. The selling stockholder reserves the right to accept and, together with their agents from time to time, to reject, in whole or in part, any proposed purchase of common stock to be made directly or through agents. We will not receive any of the proceeds from this offering.

The selling stockholder and any broker-dealers that act in connection with the sale of securities may be deemed to be “underwriters” within the meaning of Section 2(a)(11) of the Securities Act in connection with such sales, and

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any commissions received by such broker-dealers and any profit on the resale of the securities sold by them while acting as principals may be deemed to be underwriting discounts or commissions under the Securities Act. In the event that any selling stockholder is deemed to be an “underwriter” within the meaning of Section 2(a)(11) of the Securities Act, the selling stockholder will be subject to the prospectus delivery requirements of the Securities Act. The selling stockholder may indemnify any broker-dealer that participates in transactions involving the sale of the shares against certain liabilities, including liabilities arising under the Securities Act. To our knowledge, the selling stockholder has not received any shares as underwriting compensation.

The selling stockholder may from time to time pledge or grant a security interest in some or all of the shares of common stock beneficially owned by it and, if it defaults in the performance of its secured obligations, the pledgees or secured parties may offer and sell the shares of common stock from time to time under this prospectus after we have filed a supplement to this prospectus, or, if required, a post-effective amendment to the registration statement of which this prospectus is a part, supplementing or amending the list of selling stockholders to include the pledgee, transferee or other successors in interest as selling stockholders under this prospectus.

The selling stockholder also may transfer the shares of common stock in other circumstances, in which case the transferees or other successors in interest will be the selling beneficial owners for purposes of this prospectus and may sell the shares of common stock from time to time under this prospectus after we have filed a supplement to this prospectus or, if required, a post-effective amendment to the registration statement of which this prospectus is a part, supplementing or amending the list of selling stockholders to include the transferee or other successors in interest as selling stockholders under this prospectus.

To the extent required, the shares of our common stock to be sold, the names of the selling stockholders, the respective purchase prices and public offering prices, the names of any agents, dealer or underwriter, any applicable commissions or discounts with respect to a particular offer will be set forth in an amendment or supplement to this prospectus.

We will pay all registration expenses incurred relating to the registration of the shares with the SEC pursuant to the Registration Rights Agreement, and the selling stockholder will pay all selling expenses, including underwriting discounts and selling commissions, related to the sale of the shares registered under this registration statement. We have agreed to indemnify the selling stockholder against certain losses, claims, damages and liabilities, including liabilities under the Securities Act.

The selling stockholder has advised us that it has not entered into any agreements, understandings or arrangements with any underwriters or broker-dealers regarding the sale of their shares of common stock, nor is there an underwriter or coordinating broker acting in connection with a proposed sale of shares of common stock by the selling stockholder. If we are notified by the selling stockholder that any material arrangement has been entered into with a broker-dealer for the sale of shares of common stock, if required, we will file a supplement to this prospectus. If the selling stockholder uses this prospectus for any sale of the shares of common stock, it will be subject to the prospectus delivery requirements of the Securities Act.

We have advised the selling stockholder that the anti-manipulation rules of Regulation M under the Exchange Act may apply to sales of shares of our common stock in the market and to the activities of the selling stockholder and its affiliates. These rules may limit the timing of purchases and sales of the shares by such selling stockholder. Regulation M may also restrict the ability of any person engaged in the distribution of the shares of common stock to engage in market-making activities with respect to the shares of common stock. All of the foregoing may affect the marketability of the shares of common stock and the ability of any person or entity to engage in market-making activities with respect to the shares of common stock.

Our common stock is listed on The Nasdaq Global Market under the symbol “AGLE.” There can be no assurance that any selling stockholder will sell any or all of the shares of common stock registered pursuant to this prospectus.

LEGAL MATTERS

Fenwick & West LLP, San Francisco, California, will issue an opinion about certain legal matters with respect to the issuance and sale of the common stock offered by the selling stockholder.

EXPERTS

The financial statements incorporated in this Prospectus by reference to the Annual Report on Form 10-K for the year ended December 31, 2020 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.

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	\$ 13,862
Legal fees and expenses*	30,000
Accounting fees and expenses*	25,000
Printer fees and Miscellaneous expenses*	7,138
Total*	<u>\$ 76,000</u>

* Estimated

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.

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.

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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.

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 Exchange 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

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(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.

(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 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) 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.

EXHIBIT INDEX

Exhibit Number	Exhibit Description	Incorporated by Reference				Filed Herewith
		Form	File No.	Exhibit	Filing Date	
3.1	Restated Certificate of Incorporation	S-1/A	333-205001	3.2	9/14/2015	
3.2	Amended and Restated Bylaws	8-K	001-37722	3.1	4/03/2020	
4.1	Form of Common Stock Certificate	S-1/A	333-205001	4.1	9/14/2015	
4.2	Registration Rights Agreement, dated March 16, 2021, by and among the Registrant and Baker Brothers Life Sciences, L.P. and 667, L.P.	10-K	001-37722	4.5	3/18/2021	
5.1	Opinion of Fenwick & West LLP					X
23.1	Consent of PricewaterhouseCoopers LLP					X
23.2	Consent of Fenwick & West LLP (included in Exhibit 5.1)					X
24.1	Power of Attorney					X

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 May 28, 2021.

AEGLEA BIOTHERAPEUTICS, INC.

By: /s/ Anthony G. Quinn

Anthony G. Quinn, M.B Ch.B, Ph.D.
President, Chief Executive Officer and Director
(Principal Executive Officer and Principal Financial Officer)

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below hereby constitutes and appoints Anthony G. Quinn, M.B Ch.B, Ph.D. as his true and lawful attorney-in-fact, proxy and agent, with full power of substitution, for him in any and all capacities, to sign any and all amendments to this registration statement (including post-effective amendments or any abbreviated registration statement and any amendments thereto filed pursuant to Rule 462(b) increasing the number of securities for which registration is sought), and to file the same, with all exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorney-in-fact, proxy and agent full power and authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith, as fully for all intents and purposes as he might or could do in person, hereby ratifying and confirming all that said attorney-in-fact, proxy and agent, or his substitute or substitutes, may lawfully do or cause to be done by virtue hereof.

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

<u>Signature</u>	<u>Title</u>	<u>Date</u>
<u>/s/ Anthony G. Quinn</u> Anthony G. Quinn, M.B Ch.B, Ph.D.	Chief Executive Officer and Director (Principal Executive Officer)	May 28, 2021
<u>/s/ Steven Weber</u> Steven Weber	Vice President and Corporate Controller (Principal Accounting Officer)	May 28, 2021
<u>/s/ Russell J. Cox</u> Russell J. Cox	Director	May 28, 2021
<u>/s/ Ivana Magocevic-Liebisch</u> Ivana Magocevic-Liebisch, Ph.D.	Director	May 28, 2021
<u>/s/ Sandesh Mahatme</u> Sandesh Mahatme, LLM	Director	May 28, 2021

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<hr/> <i>/s/ Bryan Lawlis</i> Bryan Lawlis, Ph.D. <hr/>	Director	May 28, 2021
<hr/> <i>/s/ Armen B. Shanafelt</i> Armen B. Shanafelt, Ph.D. <hr/>	Director	May 28, 2021
<hr/> <i>/s/Alison Lawton</i> Alison Lawton <hr/>	Director	May 28, 2021
<hr/> <i>/s/ Sara Brownstein</i> Sara Brownstein <hr/>	Director	May 28, 2021



May 28, 2021

Aeglea BioTherapeutics, Inc.
805 Las Cimas Parkway
Suite 100
Austin, TX 78746

Ladies and Gentlemen:

At your request, we have examined the Registration Statement on Form S-3 filed by Aeglea BioTherapeutics, Inc. (the "**Company**") with the Securities and Exchange Commission (the "**Commission**") on May 28, 2021 (the "**Registration Statement**"), in connection with the registration for resale under the Securities Act of 1933, as amended (the "**Securities Act**"), of an aggregate of 19,020,434 shares of the Company's common stock, \$0.0001 par value per share (the "**Common Stock**"), which includes 3,410,106 shares of Common Stock (the "**Common Shares**") and 15,610,328 shares of Common Stock (the "**Warrant Shares**") issuable upon the exercise of pre-funded warrants (the "**Warrants**"), on behalf of the selling stockholder identified in the Registration Statement and the prospectus contained within the Registration Statement (the "**Prospectus**").

In connection with our opinion expressed below we have examined originals or copies of the Company's Restated Certificate of Incorporation, as amended (the "**Certificate**") and the Company's Restated Bylaws (the "**Bylaws**"), the Warrants, certain corporate proceedings of the Company's board of directors and stockholders relating to the Registration Statement, the Certificate and the Bylaws, and such other agreements, documents, certificates and statements of the Company, its transfer agent and public or government officials, as we have deemed advisable, and have examined such questions of law as we have considered necessary. We have assumed the authenticity of all documents submitted to us as originals, the genuineness of all signatures on documents submitted to us, the conformity to originals of all documents submitted to us as copies, and the absence of any undisclosed termination, waiver or amendment to any document reviewed by us. In giving our opinion, we have also relied upon a good standing certificate issued by the Delaware Secretary of State and representations made to us by the Company, including representations that the Company has available a sufficient number of authorized shares of Common Stock that are not currently outstanding or reserved for issuance under other outstanding securities or equity plans of the Company, to enable the Company to issue and deliver all of the shares of Common Stock to be sold by the Selling Stockholder pursuant to the Registration Statement and the Prospectus.

We render this opinion only with respect to, and express no opinion herein concerning the application or effect of the laws of any jurisdiction other than, the existing laws of the Delaware General Corporation Law.

Based upon the foregoing, we are of the opinion that, (i) the Common Shares and (ii) the Warrant Shares, when issued upon the exercise in accordance with the terms of the Warrants, to be sold by the Selling Stockholder pursuant to the Registration Statement and the Prospectus will be validly issued, nonassessable and fully paid.

We consent to the use of this opinion as an exhibit to the Registration Statement and further consent to all references to us, if any, in the Registration Statement, the Prospectus constituting a part thereof and any amendments thereto. We do not thereby admit that we are within the category of persons whose consent is required under Section 7 of the Securities Act or the rules and regulations of the Commission thereunder. This opinion is intended solely for use in connection with sale of the Common Stock to be sold by the Selling Stockholder pursuant to the Registration Statement and the Prospectus and is not to be relied upon for any other purpose. In providing this letter, we are opining only as to the specific legal issues expressly set forth above, and no opinion shall be inferred as to any other matter or matters. This opinion is rendered on, and speaks only as of, the date of this letter first written above, and does not address any potential change in facts or law that may occur after the date of this opinion letter. We assume no obligation to advise you of any fact, circumstance, event or change in the law or the facts that may hereafter be brought to our attention, whether or not such occurrence would affect or modify any of the opinions expressed herein.

Very Truly Yours,

/s/ Fenwick & West LLP

Fenwick & West LLP

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in this Registration Statement on Form S-3 of Aeglea BioTherapeutics, Inc. of our report dated March 18, 2021 relating to the financial statements, which appears in Aeglea BioTherapeutics, Inc.'s Annual Report on Form 10-K for the year ended December 31, 2020. We also consent to the reference to us under the heading "Experts" in such Registration Statement.

/s/ PricewaterhouseCoopers LLP
Austin, Texas
May 28, 2021