UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, DC 20549

FORM 10-Q

(Mark One)

☒ **QUARTERLY REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the quarterly period ended March 31, 2023

OR

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from to
Commission File Number: 001-37722

AEGLEA BIOTHERAPEUTICS, INC.

(Exact Name of Registrant as Specified in its Charter)

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

805 Las Cimas Parkway
Suite 100
Austin, TX 78746

(Address of principal executive offices including zip code)

Registrant's telephone number, including area code: (512) 942-2935

Former name, former address and former fiscal year, if changed since last report: N/A

Securities registered pursuant to Section 12(b) of the Exchange Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, $0.0001 Par Value Per Share	AGLE	The Nasdaq Stock Market LLC (Nasdaq Global Market)

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

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.

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

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☒

As of May 2, 2023, the registrant had 65,395,159 shares of common stock, $0.0001 par value per share, outstanding.

AEGLEA BIOTHERAPEUTICS, INC.

QUARTERLY REPORT ON FORM 10-Q
FOR THE QUARTER ENDED MARCH 31, 2023

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NOTE ABOUT FORWARD-LOOKING STATEMENTS

This Quarterly Report on Form 10-Q contains forward-looking statements within the meaning of Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act, and Section 27A of the Securities Act of 1933, as amended, or the Securities Act. All statements contained in this Quarterly Report other than statements of historical fact, including statements regarding our ability to identify, assess and execute a strategic transaction or realize any value from

our existing assets and the timing thereof, including updates concerning the process to explore strategic alternatives, our future results of operations and financial position, business strategy, the length of time that we believe our existing cash resources will fund operations, the costs we expect to incur in connection with our restructuring, 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, 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, and our ability to recognize milestone and royalty payments from commercialization agreements, the expected impact of macroeconomic conditions, including inflation, increasing interest rates and volatile market conditions, current or potential bank failures, as well as global events, including the COVID-19 pandemic and the ongoing military conflict in Ukraine on our operations, and the receipt and timing of potential regulatory designations, approvals and commercialization of product candidates, are forward-looking statements. The words “believe,” “may,” “will,” “potentially,” “estimate,” “continue,” “anticipate,” “predict,” “target,” “intend,” “could,” “would,” “should,” “project,” “plan,” “expect,” and similar expressions that convey uncertainty of future events or outcomes are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

These forward-looking statements are subject to a number of risks, uncertainties and assumptions, including those described in Item 1A, “Risk Factors” and elsewhere in this Quarterly Report. Moreover, we operate in a very competitive and rapidly changing environment, and new risks emerge from time to time. It is not possible for our management to predict all risks, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements we may make. In light of these risks, uncertainties, and assumptions, the forward-looking events and circumstances discussed in this Quarterly Report may not occur and actual results could differ materially and adversely from those anticipated or implied in the forward-looking statements.

You should not rely upon forward-looking statements as predictions of future events. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee that the future results, levels of activity, performance or events and circumstances reflected in the forward-looking statements will be achieved or occur. We undertake no obligation to update publicly any forward-looking statements for any reason after the date of this report to conform these statements to actual results or to changes in our expectations, except as required by law. You should read this Quarterly Report with the understanding that our actual future results, levels of activity, performance and events and circumstances may be materially different from what we expect.

Unless the context indicates otherwise, as used in this Quarterly Report, the terms “Aeglea,” “the Company,” “we,” “us,” and “our” refer to Aeglea BioTherapeutics, Inc., a Delaware corporation, and its consolidated subsidiaries taken as a whole. “Aeglea” and all product candidate names are our common law trademarks. This Quarterly Report contains additional trade names, trademarks and service marks of other companies, which are the property of their respective owners. We do not intend our use or display of other companies’ trade names, trademarks or service marks to imply a relationship with, or endorsement or sponsorship of us by, these other companies.

PART I. – FINANCIAL INFORMATION

Item 1. Financial Statements

Aeglea BioTherapeutics, Inc.
Condensed Consolidated Balance Sheets
(Unaudited)

(In thousands, except share and per share amounts)

	March 31, 2023	December 31, 2022
ASSETS		
CURRENT ASSETS		
Cash and cash equivalents	$ 35,243	$ 34,863
Marketable securities	3,235	20,848
Development receivables	330	375
Prepaid expenses and other current assets	5,567	6,172
Total current assets	44,375	62,258
Restricted cash	1,310	1,553
Property and equipment, net	3,424	3,220
Operating lease right-of-use assets	3,266	3,430
Other non-current assets	78	683
TOTAL ASSETS	$ 52,453	$ 71,144
LIABILITIES AND STOCKHOLDERS' EQUITY		
CURRENT LIABILITIES		
Accounts payable	$ 2,062	$ 677
Operating lease liabilities	608	625
Deferred revenue	302	517
Accrued and other current liabilities	9,665	12,837
Total current liabilities	12,637	14,656
Non-current operating lease liabilities	3,823	4,004
Deferred revenue, net of current portion	2,341	2,179
TOTAL LIABILITIES	18,801	20,839
Commitments and Contingencies (Note 7)		
STOCKHOLDERS' EQUITY		
Preferred stock, $0.0001 par value; 10,000,000 shares authorized as of March 31, 2023 and December 31, 2022; no shares issued and outstanding as of March 31, 2023 and December 31, 2022	—	—
Common stock, $0.0001 par value; 500,000,000 shares authorized as of March 31, 2023 and December 31, 2022; 65,395,159 shares and 65,350,343 shares issued and outstanding as of March 31, 2023 and December 31, 2022, respectively	6	6
Additional paid-in capital	477,698	475,971
Accumulated other comprehensive loss	(6)	(48)
Accumulated deficit	(444,046)	(425,624)
TOTAL STOCKHOLDERS' EQUITY	33,652	50,305
TOTAL LIABILITIES AND STOCKHOLDERS' EQUITY	$ 52,453	$ 71,144

The accompanying notes are an integral part of these condensed consolidated financial statements.

Aeglea BioTherapeutics, Inc.
Condensed Consolidated Statements of Operations
(Unaudited)

(In thousands, except share and per share amounts)

	Three Months Ended March 31,	
	2023	**2022**
Revenue:		
Development fee and royalty	$ 198	$ 1,362
Total revenue	198	1,362
Operating expenses:		
Research and development	13,776	16,978
General and administrative	5,228	8,825
Total operating expenses	19,004	25,803
Loss from operations	(18,806)	(24,441)
Other income (expense):		
Interest income	420	35
Other income (expense), net	(72)	(30)
Total other income (expense)	348	5
Loss before income tax expense	(18,458)	(24,436)
Income tax benefit (expense)	36	—
Net loss	$ (18,422)	$ (24,436)
Net loss per share, basic and diluted	$ (0.20)	$ (0.37)
Weighted-average common shares outstanding, basic and diluted	94,262,660	65,996,161

The accompanying notes are an integral part of these condensed consolidated financial statements.

Aeglea BioTherapeutics, Inc.
Condensed Consolidated Statements of Comprehensive Loss
(Unaudited)

(In thousands)

	Three Months Ended March 31,	
	2023	**2022**
Net loss	$ (18,422)	$ (24,436)
Other comprehensive income (loss):		
Foreign currency translation adjustment	10	(13)
Unrealized gain (loss) on marketable securities	32	(120)
Total comprehensive loss	$ (18,380)	$ (24,569)

The accompanying notes are an integral part of these condensed consolidated financial statements.

Aeglea BioTherapeutics, Inc.
Condensed Consolidated Statements of Changes in Stockholders' Equity
(Unaudited)

(In thousands)

	Three Months Ended March 31, 2023					
	Common Stock		Additional Paid-In Capital	Accumulated Other Comprehensive Income (Loss)	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount				
Balances - December 31, 2022	65,350	$ 6	$ 475,971	$ (48)	$ (425,624)	$ 50,305
Issuance of common stock in connection with employee stock purchase plan	45	—	18	—	—	18
Stock-based compensation expense	—	—	1,709	—	—	1,709
Foreign currency translation adjustment	—	—	—	10	—	10
Unrealized gain on marketable securities	—	—	—	32	—	32
Net loss	—	—	—	—	(18,422)	(18,422)
Balances - March 31, 2023	65,395	$ 6	$ 477,698	$ (6)	$ (444,046)	$ 33,652

	Three Months Ended March 31, 2022					
	Common Stock		Additional Paid-In Capital	Accumulated Other Comprehensive Income (Loss)	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount				
Balances - December 31, 2021	49,355	$ 5	$ 425,765	$ (20)	$ (341,809)	$ 83,941
Issuance of common stock in connection with employee stock purchase plan	65	—	184	—	—	184
Stock-based compensation expense	—	—	2,101	—	—	2,101
Foreign currency translation adjustment	—	—	—	(13)	—	(13)
Unrealized loss on marketable securities	—	—	—	(120)	—	(120)
Net loss	—	—	—	—	(24,436)	(24,436)
Balances - March 31, 2022	49,420	$ 5	$ 428,050	$ (153)	$ (366,245)	$ 61,657

The accompanying notes are an integral part of these condensed consolidated financial statements.

Aeglea BioTherapeutics, Inc.
Condensed Consolidated Statements of Cash Flows
(Unaudited)

(In thousands)

	Three Months Ended March 31,	
	2023	**2022**
CASH FLOWS FROM OPERATING ACTIVITIES		
Net loss	$ (18,422)	$ (24,436)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	384	403
Stock-based compensation	1,709	2,101
Amortization of operating lease assets	164	94
Purchase net premium on marketable securities	—	(33)
Net amortization of premium (accretion of discount) on marketable securities	(107)	15
Other	2	2
Changes in operating assets and liabilities:		
Accounts payable	1,384	(338)
Prepaid expenses and other assets	622	150
Development receivables	45	(197)
Operating lease liabilities	(198)	(119)
Deferred revenue	(53)	(767)
Accrued and other liabilities	(3,164)	(3,138)
Net cash used in operating activities	(17,634)	(26,263)
CASH FLOWS FROM INVESTING ACTIVITIES		
Purchases of property and equipment	—	(37)
Purchases of marketable securities	—	(3,500)
Proceeds from maturities and sales of marketable securities	17,750	29,296
Net cash provided by investing activities	17,750	25,759
CASH FLOWS FROM FINANCING ACTIVITIES		
Proceeds from employee stock plan purchases and stock option exercises	18	184
Principal payments on finance lease obligation	(8)	(172)
Net cash provided by financing activities	10	12
Effect of exchange rate on cash, cash equivalents, and restricted cash	11	(23)
NET INCREASE (DECREASE) IN CASH, CASH EQUIVALENTS, AND RESTRICTED CASH	137	(515)
CASH, CASH EQUIVALENTS, AND RESTRICTED CASH		
Beginning of period	36,416	16,980
End of period	$ 36,553	$ 16,465

The accompanying notes are an integral part of these condensed consolidated financial statements.

1. The Company and Basis of Presentation

Aeglea BioTherapeutics, Inc. (“Aeglea” or the “Company”) is a clinical-stage biotechnology company developing human enzyme therapeutics to benefit people with rare metabolic diseases. The Company was formed as a Limited Liability Company ("LLC") in Delaware on December 16, 2013 under the name Aeglea BioTherapeutics Holdings, LLC and was converted from a Delaware LLC to a Delaware corporation on March 10, 2015. The Company operates in one segment and has its principal offices in Austin, Texas.

On April 12, 2023, based on the review of the inconclusive interim results from our Phase 1/2 clinical trial of pegtarviliase for the treatment of Classical Homocystinuria and business considerations, the Company announced that it had initiated a process to explore strategic alternatives to maximize stockholder value and engaged an independent exclusive financial advisor to support this process (See Note 9).

Liquidity

As of March 31, 2023, the Company had working capital of $31.7 million, an accumulated deficit of $444.0 million, and cash and cash equivalents, marketable securities, and restricted cash of $39.8 million. The Company has not generated any product revenues and has not achieved profitable operations. There is no assurance that profitable operations will ever be achieved, and, if achieved, could be sustained on a continuing basis. In addition, development activities, clinical and nonclinical testing, and commercialization of the Company’s products will require significant additional financing before a commercial drug can be produced and marketed.

The Company is subject to a number of risks similar to other life science companies, including, but not limited to, risks related to the successful discovery, development, and commercialization of product candidates, raising additional capital, development of competing drugs and therapies, protection of proprietary technology and market acceptance of the Company’s products. As a result of these and other factors and the related uncertainties, there can be no assurance of the Company’s future success.

On April 8, 2023 the Board of Directors approved a restructuring of the Company’s workforce pursuant to which the Company’s workforce will be reduced by approximately 83% of the Company’s existing headcount, retaining approximately 10 employees. On April 12, 2023, the Company announced interim results from its ongoing Phase 1/2 clinical trial of pegtarviliase for the treatment of classical homocystinuria. Following a review of the interim results and business considerations, the Company is exploring strategic alternatives with the goal of maximizing stockholder value, including possible business combinations and/or a divestiture of the Company’s clinical programs. There can be no assurance that this strategic review will result in the Company pursuing a transaction or that any transaction, if pursued, will be completed on attractive terms. The Company will continue to pay existing obligations and payroll for critical personnel while exploring strategic alternatives.

In accordance with Accounting Standard Codification ("ASC") 205-40, Going Concern, the Company has evaluated whether there are conditions and events, considered in the aggregate, that raise substantial doubt about the Company’s ability to continue as a going concern within one year after the date the financial statements are issued. After considering various alternatives, the Company determined that there is substantial doubt about the Company’s ability to continue as a going concern within twelve months of the issuance date of these financial statements. The accompanying condensed consolidated financial statements do not include any adjustments that might result from the outcome of this uncertainty and assumes the Company will continue as a going concern through the realization of assets and satisfaction of liabilities and commitments in the ordinary course of business. The Company plans to address this condition through the exploration of strategic alternatives, including possible business combinations and/or a divestiture of the Company's clinical programs.

Unaudited Interim Financial Information

The interim condensed consolidated financial statements included in this document are unaudited. The unaudited interim financial statements have been prepared on the same basis as the annual financial statements and reflect, in the opinion of management, all adjustments of a normal and recurring nature that are necessary for a fair statement of the Company’s financial position as of March 31, 2023, and its results of operations for the three months ended March 31, 2023 and 2022, changes in stockholders’ equity for the three months ended March 31, 2023 and 2022, and cash flows for the three months ended March 31, 2023 and 2022. The results of operations for the three months ended March 31, 2023, are not necessarily indicative of the results to be expected for the year ending December 31, 2023 or for any other future annual or interim period. The December 31, 2022 balance sheet was derived from audited financial statements, but does not include

all disclosures required by accounting principles generally accepted in the United States (“U.S. GAAP”). These financial statements should be read in conjunction with the audited financial statements included in the Company’s Form 10-K for the year ended December 31, 2022 as filed with the Securities and Exchange Commission ("SEC").

2. Summary of Significant Accounting Policies

Summary of Significant Accounting Policies

These interim condensed consolidated financial statements have been prepared in accordance with U.S. GAAP and SEC instructions for interim financial information, and should be read in conjunction with the Company's Annual Report on Form 10-K for the year ended December 31, 2022 (“Annual Report”). Significant accounting policies and other disclosures normally provided have been omitted since such items are disclosed in the Company's Annual Report. The Company uses the same accounting policies in preparing quarterly and annual financial statements.

Use of Estimates

The preparation of financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the amounts reported in the condensed consolidated financial statements and accompanying notes. Management bases its estimates on historical experience and on various other market-specific and relevant assumptions that management believes to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets, liabilities, and equity and the amount of revenues and expenses. Actual results could differ significantly from those estimates. The most significant estimates and assumptions that management considers in the preparation of the Company's financial statements relate to accrued research and development costs, stock-based compensation expense and revenue recognition.

3. Fair Value Measurements

The Company measures and reports certain financial instruments as assets and liabilities at fair value on a recurring basis. The following tables sets forth the fair value of the Company’s financial assets and liabilities at fair value on a recurring basis based on the three-tier fair value hierarchy (in thousands):

	March 31, 2023			
	Level 1	Level 2	Level 3	Total
Financial Assets:				
Money market funds	$ 29,544	$ —	$ —	$ 29,544
Commercial paper	—	5,226	—	5,226
Corporate bonds	—	750	—	750
Total financial assets	$ 29,544	$ 5,976	$ —	$ 35,520

	December 31, 2022			
	Level 1	Level 2	Level 3	Total
Financial Assets:				
Money market funds	$ 15,250	$ —	$ —	$ 15,250
Commercial paper	—	23,641	—	23,641
U.S. government securities	—	4,230	—	4,230
Corporate bonds	—	3,732	—	3,732
Total financial assets	$ 15,250	$ 31,603	$ —	$ 46,853

The Company measures the fair value of money market funds on quoted prices in active markets for identical asset or liabilities. The Level 2 assets include commercial paper, U.S. government securities and corporate bonds and are valued based on quoted prices for similar assets in active markets and inputs other than quoted prices that are derived from observable market data. The Company evaluates transfers between levels at the end of each reporting period.

4. Cash Equivalents and Marketable Securities

The following tables summarize the estimated fair value of the Company's cash equivalents and marketable securities and the gross unrealized gains and losses (in thousands):

	March 31, 2023			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Cash equivalents:				
Money market funds	$ 29,544	$ —	$ —	$ 29,544
Commercial paper	2,740	1	—	2,741
Total cash equivalents	32,284	1	—	32,285
Marketable securities:				
Commercial paper	2,484	1	—	2,485
Corporate bonds	749	1	—	750
Total marketable securities	$ 3,233	$ 2	$ —	$ 3,235

	December 31, 2022			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Cash equivalents:				
Money market funds	$ 15,250	$ —	$ —	$ 15,250
Commercial paper	7,021	1	(2)	7,020
U.S. government securities	3,736	—	(1)	3,735
Total cash equivalents	26,007	1	(3)	26,005
Marketable securities:				
Commercial paper	16,644	2	(25)	16,621
Corporate bonds	3,738	—	(6)	3,732
U.S. government securities	495	—	—	495
Total marketable securities	$ 20,877	$ 2	$ (31)	$ 20,848

The following table summarizes the available-for-sale securities in an unrealized loss position for which an allowance for credit losses has not been recorded as of March 31, 2023 and December 31, 2022, aggregated by major security type and length of time in a continuous unrealized loss position:

	March 31, 2023					
	Less Than 12 Months		12 Months or Longer		Total	
	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses
Commercial paper	$ 993	$ (1)	$ —	$ —	$ 993	$ (1)
Total marketable securities	$ 993	$ (1)	$ —	$ —	$ 993	$ (1)

	December 31, 2022					
	Less Than 12 Months		12 Months or Longer		Total	
	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses
Commercial paper	$ 17,699	$ (27)	$ —	$ —	$ 17,699	$ (27)
U.S. government securities	3,735	(1)	-	-	3,735	$ (1)
Corporate bonds	3,732	(6)	—	—	3,732	(6)
Total marketable securities	$ 25,166	$ (34)	$ —	$ —	$ 25,166	$ (34)

The Company evaluated its securities for credit losses and considered the decline in market value to be primarily attributable to current economic and market conditions and not to a credit loss or other factors. Additionally, the Company does not intend to sell the securities in an unrealized loss position and does not expect they will be required to sell the securities before recovery of the unamortized cost basis. As of March 31, 2023 and December 31, 2022, an allowance for

credit losses had not been recognized. Given the Company's intent and ability to hold such securities until recovery, and the lack of significant change in credit risk of these investments, the Company does not consider these marketable securities to be impaired as of March 31, 2023 and December 31, 2022.

The financial instruments that potentially subject the Company to a concentration of credit risk consist principally of cash deposits. Accounts at each U.S. banking institution are insured by the Federal Deposit Insurance Corporation ("FDIC") up to $250,000 per depositor. At March 31, 2023 and December 31, 2022, the Company had $31.8 million and $23.5 million, respectively, of U.S. cash deposits in excess of the FDIC insured limit. Uninsured foreign cash deposits were immaterial for both periods.

There were no realized gains or losses on marketable securities for the three months ended March 31, 2023 and 2022. Interest on marketable securities is included in interest income. Accrued interest receivable on available-for-sale debt securities was $0.1 million at March 31, 2023 and December 31, 2022, respectively, and is excluded from the estimate of credit losses.

The following table summarizes the contractual maturities of the Company's marketable securities at estimated fair value (in thousands):

	March 31, 2023	December 31, 2022
Due in one year or less	$ 3,235	$ 20,848
Due thereafter	—	—
Total marketable securities	$ 3,235	$ 20,848

The Company may sell investments at any time for use in current operations even if they have not yet reached maturity. As a result, the Company classifies marketable securities, including securities with maturities beyond twelve months as current assets.

5. Accrued and Other Current Liabilities

Accrued and other current liabilities consist of the following (in thousands):

	March 31, 2023	December 31, 2022
Accrued contracted research and development costs	$ 5,938	$ 6,972
Accrued compensation	2,857	4,589
Accrued professional and consulting fees	591	946
Other	279	330
Total accrued and other current liabilities	$ 9,665	$ 12,837

6. Stockholders' Equity

Registered Direct Offering

In May 2022, the Company issued and sold 10,752,688 shares of common stock at an offering price of $1.60 per share and pre-funded warrants to purchase up to 17,372,312 shares of common stock at an offering price of $1.5999 per warrant (representing the price per share of common stock sold in the offering minus the $0.0001 exercise price per warrant) in a registered direct offering pursuant to a shelf registration statement on Form S-3. The net proceeds to the Company from this offering were approximately $42.9 million, after deducting placement agent fees and offering costs of $2.1 million.

Pre-Funded Warrants

In February 2019, April 2020 and May 2022, the Company issued pre-funded warrants to purchase the Company's common stock in underwritten public offerings at the offering price of the common stock, less the $0.0001 per share exercise price of each warrant. The warrants were recorded as a component of stockholders' equity within additional paid-in capital and have no expiration date. Per the terms of the warrant agreements, the outstanding warrants to purchase shares of common stock may not be exercised if the holder's ownership of the Company's common stock would exceed 4.99% ("Maximum Ownership Percentage"), or 9.99% for certain holders. By written notice to the Company, each holder may increase or decrease the Maximum Ownership Percentage to any other percentage (not in excess of 19.99% for the majority of such warrants). The revised Maximum Ownership Percentage would be effective 61 days after the notice is received by the Company.

As of March 31, 2023, the following pre-funded warrants for common stock were issued and outstanding:

Issue Date	Expiration Date	Exercise Price	Number of Warrants Outstanding
February 8, 2019	None	$ 0.0001	3,750,000
April 30, 2020	None	$ 0.0001	11,860,328
May 20, 2022	None	$ 0.0001	13,281,250
Total pre-funded warrants			28,891,578

Stock-Based Compensation

The 2016 Equity Incentive Plan ("2016 Plan") provides for an automatic increase in the number of shares reserved for issuance thereunder on January 1 of each year for the remaining term of the plan (through 2028) equal to (a) 4.0% of the number of issued and outstanding shares of common stock on December 31 of the immediately preceding year, or (b) a lesser amount as approved by the Company's board of directors each year. As a result of this provision, on January 1, 2023 and January 1, 2022, an additional 2,614,013 and 1,974,205 shares, respectively, became available for issuance under the 2016 Plan.

As of March 31, 2023, the 2016 Plan had 797,690 shares available for future issuance.

The following table summarizes the Company's stock awards granted for each of the periods indicated:

	Three Months Ended March 31,			
	2023		2022	
	Grants	Weighted Average Grant Date Fair Value	Grants	Weighted Average Grant Date Fair Value
Stock options	4,440,500	$ 0.44	2,143,000	$ 3.18

In July 2020, the Company granted 228,200 RSUs to certain employees, with vesting terms subject to regulatory, commercial, and clinical milestones, in addition to a service condition. As of March 31, 2023, none of these RSUs have vested and all RSUs were forfeited since the performance milestones were not met within the required time frame. No stock-based compensation expense was recognized on these awards.

Under the Company's 2016 Employee Stock Purchase Plan ("2016 ESPP"), the Company issued and sold 44,816 shares for aggregate cash proceeds of less than $0.1 million during the three months ended March 31, 2023. There were 64,743 shares issued and sold under the 2016 ESPP for aggregate cash proceeds of $0.2 million during the three months ended March 31, 2022.

Total stock-based compensation expense related to the 2016 Plan and 2016 ESPP was as follows (in thousands):

	Three Months Ended March 31,	
	2023	2022
Research and development	$ 777	$ 701
General and administrative	932	1,400
Total stock-based compensation expense	$ 1,709	$ 2,101

The following table summarizes the weighted-average Black-Scholes option pricing model assumptions used to estimate the fair value of stock options granted under the Company's 2016 Plan, and the shares purchasable under the 2016 ESPP during the periods presented:

	Three Months Ended March 31,	
	2023	2022
2016 Plan		
Expected term (in years)	6.02	6.02
Expected volatility	99 %	82 %
Risk-free interest	4.06 %	0.19 %
Dividend yield	—	—
2016 ESPP		
Expected term (in years)	0.49	0.49
Expected volatility	181 %	76 %
Risk-free interest	4.99	1.09 %
Dividend yield	—	—

7. Strategic License Agreements

On March 21, 2021, the Company entered into an exclusive license and supply agreement with Immedica Pharma AB ("Immedica"). By entering into this agreement, the Company agreed to provide Immedica the following goods and services:

i. Deliver an exclusive, sublicensable, license and know-how (the "License") to develop and commercialize pegzilarginase (the "Product") in the territory comprising the members states of the European Economic Area, United Kingdom, Switzerland, Andorra, Monaco, San Marino, Vatican City, Turkey, Saudi Arabia, United Arab Emirates, Qatar, Kuwait, Bahrain, and Oman (the "Territory");

ii. Complete the global pivotal PEACE (Pegzilarginase Effect on Arginase 1 Deficiency Clinical Endpoints) Phase 3 trial ("PEACE Trial") and related Biologics License Application ("BLA") package to file with the United States Food and Drug Administration ("FDA"), which will be leveraged by Immedica in obtaining the necessary regulatory approvals in the Territory; and

iii. Perform a Pediatric Investigation Plan trial ("PIP Trial") in order for Immedica to be able to receive certain regulatory approvals within the Territory.

In addition, the Company and Immedica formed a Joint Steering Committee ("JSC") to provide oversight to the activities performed under the agreement; however, the substance of the Company's participation in the JSC does not represent an additional promised service, but rather, a right of the Company to protect its own interests in the arrangement.

Further, the Company agreed to supply to Immedica, and Immedica agreed to purchase from the Company, substantially all commercial requirements of the Product. The terms of the agreement do not provide for either (i) an option to Immedica to purchase the Product from the Company at a discount from the standalone selling price or (ii) minimum purchase quantities. Finally, Immedica will bear (i) all costs and expenses for any development or commercialization of the Product in the Territory subject to the License exclusive of the Company's promised goods and services summarized above and (ii) all costs and fees associated with applying for regulatory approval of the Product in the Territory.

The Company received a non-refundable payment of $21.5 million and Immedica agreed to provide payment of 50% of the Company's costs incurred in performing the PIP Trial up to a maximum of $1.8 million. In addition, the Company has the ability to receive additional payments under the agreement of up to approximately $122.1 million in regulatory and commercial milestone payments, assuming an exchange rate of $1.09 to €1.00. The Company is also entitled to receive royalties in the mid-20 percent range on net sales of the Product in the Territory. In July 2021, the Company modified the agreement with Immedica to provide certain additional services in relation to the PEACE Trial and BLA package performance obligation in exchange for the reimbursement of up to $3.0 million of the actual costs incurred in relation to such incremental services.

The Company concluded that Immedica meets the definition to be accounted for as a customer because the Company is delivering intellectual property and other services within the Company's normal course of business, in which the parties are not jointly sharing the risks and rewards. Therefore, the Company concluded that the promises summarized above represent transactions with a customer within the scope of ASC 606. The Company determined that the following promises

represent distinct promised services, and therefore, performance obligations: (i) the License, (ii) the PEACE Trial and BLA package, and (iii) the PIP Trial.

Specifically, in making these determinations, the Company considered the following factors:

- As of inception of the agreement, the Company had completed the Phase 1/2 clinical trial related to the Product and were conducting the PEACE Trial. Accordingly, the Company is not promising, nor expecting, to perform additional research and development activities pursuant to the agreement that would either significantly modify, customize or be considered highly interdependent or interrelated with pegzilarginase.
- The License represents functional intellectual property given the functionality of the License is not expected to change substantially as a result of the company's ongoing activities.
- The services necessary to complete the PEACE Trial, BLA package and PIP Trial could be performed by other parties.

Given that Immedica is not obligated to purchase any minimum amount or quantities of Product, the supply of Product for commercial use to Immedica was determined to be an option for Immedica, rather than a performance obligation of the Company at contract inception and will be accounted for if and when exercised. The Company also determined that Immedica's option to purchase the Product does not create a material right as the expected pricing is not at a discount.

The Company determined that the upfront fixed payment amount of $21.5 million must be included in the transaction price. Additionally, the Company determined at inception of the arrangement that 50% of the probable estimated costs to be incurred in relation to the PIP Trial exceeded $1.8 million and included the full reimbursement amount of $1.8 million in the transaction price. Upon subsequent re-evaluation due to changing facts and circumstances, the Company determined the probable estimated costs are now less than the maximum allowable reimbursement and a portion of the variable consideration was constrained, which did not materially impact the revenue recognized to date. Additionally, upon the modification of the agreement in July 2021, the Company determined that the probable estimated costs to perform the additional services related to the PEACE Trial and BLA package exceeds the maximum allowable reimbursement of $3.0 million. Therefore, the Company included an estimated total of $3.6 million that will be due in relation to the PIP Trial, PEACE Trial, and BLA package in the transaction price and it is probable that a significant reversal will not occur in the future. In total, the modified transaction price was determined to be $25.1 million.

The Company has allocated $9.6 million and $3.5 million of the modified transaction price to the PEACE Trial and BLA package and PIP Trial performance obligations, respectively, based on the stand-alone selling prices ("SSP"), which was based on the estimated costs that a third-party would charge in performing such services on a stand-alone basis. The SSP for the License was established at inception of the arrangement using a residual value approach due to the uniqueness of and lack of observable data related to the License, and without a specific analog from which to make reliable estimates, resulting in an allocation of $12.0 million.

The potential regulatory milestone payments that the Company is eligible to receive were excluded from the transaction price, as the milestone amounts were fully constrained based on the probability of achievement, since the milestones relate to successful achievement of certain regulatory approvals, which might not be achieved. The Company determined that the royalties and commercial milestone payments relate predominantly to the license of intellectual property and are therefore excluded from the transaction price under the sales- or usage-based royalty exception of Topic 606. The Company will reevaluate the transaction price, including all constrained amounts, at the end of each reporting period and as uncertain events are resolved or other changes in circumstances occur, the Company will adjust its estimate of the transaction price as necessary. The Company will recognize the royalties and commercial milestone payments as revenue when the associated sales occur, and relevant sales-based thresholds are met. The Company assessed the arrangement with Immedica and concluded that a significant financing component does not exist.

The Company recognized revenue allocated to the License performance obligation at a point in time and upon transfer of the License. The Company completed the transfer of the know-how necessary for Immedica to benefit from the License in June 2021 and recognized $12.0 million of revenue at that time. The development fee allocated to the PEACE Trial, BLA package and PIP Trial performance obligations is recognized over time using an input method of costs incurred related to the performance obligations.

For the three months ended March 31, 2023, the Company recognized revenue of $0.1 million under the Immedica Agreement related to the progress in the PEACE Trial and BLA package performance. For the three and ended March 31, 2022, the Company recognized revenue of $1.4 million related to the PEACE Trial and BLA package performance obligation. As of March 31, 2023, and 2022, the Company has recorded deferred revenue of $2.6 million and $2.8 million, respectively, associated with the license and supply agreement with Immedica, of which $0.3 million and $2.1 million, respectively, is classified as current.

Contract Balances from Customer Contract

The timing of revenue recognition, billings and cash collections results in contract assets and contract liabilities on the balance sheets. The Company recognizes license and development receivables based on billed services, which are derecognized upon reimbursement. When consideration is received, or such consideration is unconditionally due, from a customer prior to transferring goods or services to the customer under the terms of a contract, a contract liability is recorded. Contract liabilities are recognized as revenue after control of the goods or services is transferred to the customer and all revenue recognition criteria have been met.

The following table presents changes in the Company's contract liabilities for the periods presented (in thousands):

Three Months Ended March 31, 2023	December 31, 2022	Additions	Deductions	March 31, 2023
Contract liabilities:				
Deferred revenue	$ 2,696	$ —	$ (53)	$ 2,643

The Company had no contract assets during the three months ended March 31, 2023 and 2022.

8. Net Loss Per Share

Basic and diluted net loss per share is computed by dividing net loss by the weighted-average number of common stock and pre-funded warrants outstanding during the period. The pre-funded warrants are included in the computation of basic net loss per share as the exercise price is negligible and they are fully vested and exercisable. For periods in which the Company generated a net loss, the Company does not include the potential impact of dilutive securities in diluted net loss per share, as the impact of these items is anti-dilutive.

The following weighted-average equity instruments were excluded from the calculation of diluted net loss per share because their effect would have been anti-dilutive for the periods presented:

	Three Months Ended March 31,	
	2023	2022
Options to purchase common stock	11,485,631	7,694,512
Unvested restricted stock units	19,144	190,000

9. Subsequent Events

On April 12, 2023, based on the review of the inconclusive interim results from its Phase 1/2 clinical trial of pegtarviliase for the treatment of Classical Homocystinuria and business considerations, the Company announced that it had initiated a process to explore strategic alternatives to maximize stockholder value and engaged an independent exclusive financial advisor to support this process. As a result, the Company implemented a restructuring plan resulting in an approximate 83% reduction of the Company's existing headcount. The Company estimates that it will incur $6.2 million in employee-related restructuring charges in connection with the restructuring, consisting of (i) approximately $5.6 million in cash-based expenses related to employee severance and notice period payments, benefits and related costs, and (ii) approximately $0.6 million in non-cash stock-based compensation expense related to the vesting of stock-based awards. The Company expects that the majority of the restructuring charges will be incurred in the second quarter of 2023 and that the execution of the restructuring, including cash payments, will be substantially complete by the end of the second quarter of 2023.

The estimates of the charges and cash expenditures that the Company expects to incur in connection with the restructuring, and the timing thereof, are subject to a number of assumptions and actual amounts may differ materially from estimates. In addition, the Company may incur other charges or cash expenditures not currently contemplated due to unanticipated events that may occur, including in connection with the implementation of the restructuring.

Item 2. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

You should read the following discussion and analysis of our financial condition and results of operations in conjunction with our unaudited condensed consolidated financial statements and related notes included in Part I, Item 1 of this Quarterly Report as well as the audited consolidated financial statements and notes and Management's Discussion and Analysis of Financial Condition and Results of Operations, included in our Annual Report on Form 10-K for the year ended December 31, 2022 filed with the Securities and Exchange Commission, or the SEC, on March 2, 2023. This discussion and other parts of this Quarterly Report contain forward-looking statements that involve risks and uncertainties, such as statements of our plans, objectives, expectations and intentions. Our actual results could differ materially from those discussed in these forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in the section of this report entitled "Risk Factors." As used in this report, unless the context suggests otherwise, "we", "us", "our", "the Company" or "Aeglea" refers to Aeglea BioTherapeutics, Inc.

Overview

We are a clinical-stage biotechnology company developing human enzyme therapeutics to benefit people with rare metabolic diseases. Our two clinical programs are pegtarviliase for Homocystinuria and pegzilarginase for Arginase 1 Deficiency. Both clinical programs are focused on the underlying key metabolites that drive the clinical manifestations of these devastating rare metabolic diseases. Our current focus is to explore strategic alternatives with the goal of maximizing stockholder value, including possible business combinations and/or a divestiture of our clinical programs.

Pegtarviliase is being investigated for the treatment of Classical Homocystinuria. The drug is an investigational PEGylated, or polyethylene glycol modified, human enzyme engineered to reduce elevated levels of total homocysteine, or tHcy, circulating in the plasma. Homocystinuria is a rare genetic disease characterized by elevated plasma homocysteine levels, which can result in debilitating, often irreversible, neurologic, psychiatric, ocular and skeletal complications, and life-threatening vascular events. There are various etiologies leading to Homocystinuria and Classical Homocystinuria is specifically characterized by a deficiency in the cystathionine β-synthase (CBS) enzyme. Currently available treatments for Classical Homocystinuria are burdensome and have limited effectiveness in reducing tHcy for most patients, resulting in a significant unmet need for patients.

Pegzilarginase is a recombinant human arginase 1 that is engineered to enzymatically degrade the amino acid arginine to reduce elevated levels of arginine in patients with Arginase 1 Deficiency. Arginase 1 Deficiency is a rare, inherited metabolic disorder with progressive, debilitating neurologic manifestations driven by persistently high arginine levels. There are currently no approved therapies that address the underlying driver of the disease, and most patients experience long-term clinical deterioration, including neuromuscular and cognitive decline, with current standard of care.

On April 12, 2023, based on our review of the inconclusive interim results from our Phase 1/2 clinical trial of pegtarviliase for the treatment of Classical Homocystinuria and business considerations, we announced that we have initiated a process to explore strategic alternatives to maximize stockholder value and engaged an independent exclusive financial advisor to support this process. As we pursue strategic alternatives, we established a restructuring plan, which included an approximate 83% reduction in workforce to be completed in the second quarter of 2023. As part of the restructuring, we are in the process of reducing all clinical trial spend while assessing strategic alternatives to maximize stockholder value.

Our Strategy

We believe there is significant potential to address rare metabolic diseases through human enzyme therapies. Our strategy has been to develop treatments for rare metabolic diseases where we believe there is a causal link between disease development and progression, and levels of key metabolites that drive the clinical manifestations of the diseases. For our two clinical programs, we have engineered and modified enzymes to have specific characteristics needed to address the underlying metabolic drivers of the diseases. For example, pegtarviliase was modified to have specificity for both the monomer and dimer forms of homocysteine and pegzilarginase was modified to have increased arginine-degrading activity. We selected therapeutic candidates for clinical development based on strong biological rationale and robust preclinical evidence to support a potential therapy that can transform patient outcomes.

Pegtarviliase has been studied in a Phase 1/2 clinical trial to assess safety and efficacy in patients with Classical Homocystinuria, also known as Homocystinuria due to cystathionine β-synthase deficiency. In April 2023, we announced interim results from the first three cohorts of the Phase 1/2 clinical trial. These results indicated that additional dose exploration and data from longer duration treatment may be needed to support dialog with regulators on a pivotal trial design. While we believe that additional exploration of pegtarviliase may be warranted, due to business considerations we are not

currently enrolling additional cohorts. We estimate that there are approximately 30,000 Classical Homocystinuria patients in global addressable markets, or the 38 countries with a combination of sufficient census data and other commercial elements (e.g., IP protection, access and reimbursement framework), and we estimate about 80% of these patients are unable to control their tHcy levels to targeted clinical thresholds with the currently available treatments. With significantly elevated homocysteine levels, these patients are continuing to experience irreversible progression and remain at risk for catastrophic thromboembolic events resulting in death.

Our other clinical program is pegzilarginase for the treatment of Arginase 1 Deficiency. We reported positive topline data for pegzilarginase for our global pivotal PEACE (Pegzilarginase Effect on Arginase 1 Deficiency Clinical Endpoints) Phase 3 trial in December 2021. Based on the results from PEACE and a previous Phase 1/2 clinical trial, a Marketing Authorization Application, or MAA, was submitted to the European Medicines Agency, or EMA, by Immedica Pharma AB, or Immedica, our commercial partner in Europe and several countries in the Middle East. A potential decision on approval of the MAA is expected in late 2023. We are also continuing to determine potential paths forward regarding the potential resubmission of the pegzilarginase BLA after receiving a Refusal to File, or RTF, letter from the Food and Drug Administration, or FDA. Based on a published genetic prevalence analysis, we estimate that the Arginase 1 Deficiency population is greater than 2,500 patients in the global addressable markets. Because the manifestations of Arginase 1 Deficiency may overlap with other disorders such as hereditary spastic paraplegia, cerebral palsy or epilepsy, the prevalence of Arginase 1 Deficiency may be underestimated.

In addition to our clinical programs, we have leveraged enzyme engineering to create additional pipeline candidates for the treatment of Cystinuria and other undisclosed diseases. These programs represent innovative solutions for diseases that previously were not believed to be addressable with enzyme therapies. For example, Cystinuria is a rare genetic disease characterized by frequent and recurrent kidney stone formation due to increased amounts of cystine in the urine. We engineered and optimized AGLE-325 to reduce plasma cystine and cysteine levels and therefore reduce urine cystine concentrations as an approach to inhibit cystine crystal and kidney stone formation.

We retain worldwide intellectual property rights for pegtarviliase and all other preclinical product candidates. We retain all intellectual property rights for pegzilarginase in the United States and other regions outside of our commercial partnership with Immedica in Europe and several countries in the Middle East.

We have incurred net losses in each year since inception. Our net losses were $18.4 million and $24.4 million for the three months ended March 31, 2023 and 2022, respectively, and have resulted from costs incurred in connection with our research and development programs and from general and administrative expenses associated with our operations. As of March 31, 2023, we had an accumulated deficit of $444.0 million.

We anticipate that our expenses will decrease as we limit activities related to our clinical programs and have decided to voluntarily pause our clinical programs. After considering various alternatives, the Company determined that there is substantial doubt about the Company's ability to continue as a going concern within twelve months of the issuance date of these financial statements.

Recent Developments

Corporate

In April 2023, we began exploring strategic alternatives with the goal of maximizing stockholder value. We engaged Wedbush Securities Inc. as an exclusive financial advisor to assist in the process of exploring strategic alternatives, which may include, but are not limited to, an acquisition, merger, reverse merger, other business combination, sales of assets or other strategic transactions. There can be no assurance that the exploration of strategic alternatives will result in any agreements or transactions, or that, if completed, any agreements will be reached or transactions will be successfully consummated or on attractive terms. We have not set a timetable for completion of this strategic review and do not intend to comment further on the status of this process unless or until our board of directors has approved a definitive course of action, or it is determined that other disclosure is appropriate or required.

Additionally, we have reduced our workforce and will retain approximately 10 employees required to support the evaluation of strategic alternatives and ongoing business activities. We also announced the departures of Michael C. Hanley, MBA, chief business officer, and Linda Neuman, MD, MBA, chief medical officer.

Our Pipeline of Product Candidates

Pegtarviliase in Homocystinuria

We have completed three cohorts of a Phase 1/2 clinical trial for the treatment of patients with Classical Homocystinuria to assess the safety and clinical activity of pegtarviliase. The primary objective of the trial is to evaluate the safety and tolerability of pegtarviliase in participants with Classical Homocystinuria. A secondary objective of the trial is to characterize the pharmacokinetics and pharmacodynamics, as measured as the magnitude of change in plasma tHcy, of pegtarviliase after multiple doses following intravenous and subcutaneous administration. In cohorts 1 through 3, we enrolled 13 patients diagnosed with Classical Homocystinuria, aged 12 years or older (18 or older in the U.S.) with plasma homocysteine levels of 50 µM or greater at screening, and with a history of tHcy greater than or equal to 80 µM. Patients were dosed once weekly for four weeks, with three to four patients in each of the dosing cohorts.

In April 2023, we announced interim results from the first three cohorts of the Phase 1/2 clinical trial. Results from the first two cohorts (0.15 mg/kg and 0.45 mg/kg, respectively) showed that treatment with pegtarviliase lowered total homocysteine levels in participants when compared to baseline values. Results from the third cohort (1.35 mg/kg) did not show a consistent reduction in total homocysteine levels compared to baseline. Further analysis of the results indicated that participants in the third cohort developed anti-drug antibodies, which may have impacted the pharmacokinetics and reduced the effect of pegtarviliase in reducing total homocysteine levels. While we have paused clinical development for this program, we believe that the data indicates that exploration of higher doses or dosing of longer duration may be warranted in order to better determine the potential efficacy of pegtarviliase in lowering total homocysteine.

Percent Change of Total Homocysteine from Baseline After 4 Weeks of Pegtarviliase Treatment

	3 Days Post Dose (SD)	7 Days Post Dose (SD)
Cohort 1 (n=3, 0.15 mg/kg)	-26.3% (12.3)	-8.0% (7.9)
Cohort 2 (n=4, 0.45 mg/kg)	-33.0% (19.0)	-26.8% (4.9)
Cohort 3 (n=4, 1.35 mg/kg)	-11.3% (22.1)	+15.0% (57.9)*

*n=3, due to missing data point from one of four evaluable patients. SD = standard deviation

Pegtarviliase was well tolerated with the majority of adverse events being Grade 1 or Grade 2 injection site reactions and hypersensitivity reactions, which were managed with antihistamine and/or steroid treatment. There was one serious adverse event that was assessed as unrelated to treatment. No participants withdrew from the trial or had a dose reduction due to an adverse event. The below table summarizes the current safety results:

Adverse Events (AE)	Participants N=13
Any treatment-emergent AE	13 (100%)
AE leading to discontinuation	0
AE leading to dose reduction	0
AE of special interest: HSR ISR	2 (15.3%) 10 (76.9%)
Serious AEs Fatal Related	1 (7.7%) 0 0

Regulatory: We have obtained Orphan Drug Designation from the FDA and EMA for pegtarviliase for the treatment of patients with Homocystinuria. In addition, the FDA granted Fast Track and Rare Pediatric Disease designations for pegtarviliase for the treatment of Homocystinuria. These designations do not necessarily lead to faster development or regulatory review of pegtarviliase, or increase the likelihood that it will receive marketing approval. The Rare Pediatric Disease designation by the FDA provides the potential to receive a Priority Review Voucher if a qualifying BLA for pegtarviliase is approved before October 1, 2026.

In October 2022, we received a letter from the FDA regarding our protocol amendment for the Phase 1/2 clinical trial of pegtarviliase for the treatment of Classical Homocystinuria. The protocol amendment, among other things, allowed the inclusion of adolescent patients at clinical trial sites in the United States. The FDA stated the protocol did not provide adequate justification and evidence to support the prospect of direct clinical benefit for pediatric patients and placed the trial on partial clinical hold for the enrollment of patients less than 18 years of age under this investigational new drug application, or IND, at this time. A local Australian ethics committee, responsible for two clinical trial sites, recently stated that it would like to align with the FDA and place a hold on the enrollment of pediatric participants at those sites. Neither site has pediatric patients currently enrolled and no pediatric patients are pending enrollment at those sites. Both sites can continue to enroll adult patients.

Pegzilarginase in Arginase 1 Deficiency

We announced topline results from the double-blind placebo-controlled portion of our PEACE Phase 3 trial in December 2021. The trial is believed to be the first-ever investigative therapy that directly addresses the high arginine levels that are believed to be the key drivers of this devastating disease for patients with Arginase 1 Deficiency.

PEACE was a global, randomized, double-blind, placebo-controlled trial designed to assess the effects of treatment with pegzilarginase versus placebo over 24 weeks with a primary endpoint of statistically significant plasma arginine reduction from baseline. The primary endpoint assessed the effectiveness of pegzilarginase in lowering plasma arginine levels. Secondary endpoints included clinical outcome assessments focused primarily on measuring the impact on functional mobility, including the key secondary endpoints consisting of Gross Motor Function Measure Part E, or GMFM-E, and 2 Minute Walk Test, or 2MWT, in addition to safety and pharmacokinetics.

The pivotal trial enrolled 32 patients aged two years and older, who had plasma arginine levels greater than 250 μM and a baseline deficit in at least one clinical response assessment. Patients enrolled in the trial were randomized on a two-to-one basis to receive weekly infusions of pegzilarginase (0.1 mg/kg starting dose), or placebo for the double-blind treatment period. Dose adjustments during this period were allowed in order to optimize plasma arginine control. Patients remained on current disease management for the duration of the PEACE Phase 3 trial. Upon completion of the 24-week treatment period, patients were eligible to participate in a long-term extension study of pegzilarginase, with all 31 patients who completed the double-blind period continuing into the long-term extension study and switching to subcutaneous administration.

In December 2021, we announced the topline results for the PEACE Phase 3 trial. In April 2022 and August 2022, we presented data from our PEACE Phase 3 trial at the Society for Inherited Metabolic Disorders, or SIMD, and at the Society for the Study of Inborn Errors of Metabolism, or SSIEM, respectively. Highlights from the PEACE Phase 3 trial to date are summarized as follows:

- Primary endpoint was achieved with a highly statistically significant 76.7% reduction in mean plasma arginine in pegzilarginase treated patients ($p<0.0001$) compared to the placebo arm.
- Normal plasma arginine levels (40-115μM) were achieved in 90.5% of pegzilarginase treated patients compared to no patients in the placebo arm.
- Accompanying improvements in the key secondary mobility assessment endpoint in pegzilarginase treated patients compared to the placebo arm.
    - Gross Motor Function Measure Part E (GMFM-E): The least squares mean score improved by 4.2 units for pegzilarginase treated patients and worsened by 0.4 units in the placebo arm ($p=0.1087$), establishing a positive trend.
    - 2-minute walk test (2MWT): The least squares mean distance increased 7.4 meters in pegzilarginase treated patients and 1.9 meters in the placebo arm ($p=0.5961$).
- Pegzilarginase was well-tolerated and safety data were consistent with results from previous clinical trials. Adverse events were generally mild to moderate in severity. There were no study discontinuations due to adverse events.

*Regulato*ry: In August 2022, we announced that the EMA had validated the MAA, for pegzilarginase for the treatment of Arginase 1 Deficiency that was submitted by Immedica our commercialization partner in Europe and several countries in the Middle East. Review of the MAA is underway, and a decision from the EMA with respect to approval of pegzilarginase may occur in late 2023.

In April 2022, we announced that we submitted a BLA to the FDA in order to provide all the study results for the FDA to review in detail. In June 2022, we announced that we received a RTF letter from the FDA for the BLA for pegzilarginase for the treatment of Arginase 1 Deficiency. In the RTF letter, the FDA requested additional data to support effectiveness, such as evidence showing that plasma arginine and metabolite reduction predicts clinical benefit in patients with ARG1-D or clinical data demonstrating a treatment effect on clinically meaningful outcomes. The FDA also requested additional information relating to Chemistry Manufacturing and Controls, or CMC. There were no issues related to safety raised in the letter. Upon receipt of the RTF letter, we had 30 days in which to request a Type A meeting with the FDA to clarify and respond to items identified in the RTF letter. The Type A meeting with the FDA was held in July 2022.

We have obtained Orphan Drug designation from the FDA and the EMA, as well as Fast Track and Breakthrough Therapy designations from the FDA, for pegzilarginase for the treatment of patients with Arginase 1 Deficiency. In addition, the FDA granted a Rare Pediatric Disease designation for pegzilarginase for the treatment of Arginase 1 Deficiency. These designations do not necessarily lead to faster development or regulatory review of pegzilarginase, or increase the likelihood that it will receive marketing approval. The Rare Pediatric Disease designation by the FDA confirms our eligibility to receive a Rare Pediatric Disease priority review voucher if a qualifying BLA for pegzilarginase is approved before October 1, 2026.

Licensing: We licensed to Immedica the rights to the commercialization of pegzilarginase in the European Economic Area, United Kingdom, Switzerland, Andorra, Monaco, San Marino, Vatican City, Turkey, Saudi Arabia, United Arab Emirates, Qatar, Kuwait, Bahrain, and Oman. The license and supply agreement, or Immedica Agreement, we entered into with Immedica includes a non-refundable upfront payment of $21.5 million from Immedica and development services provided to Immedica, up to $3.0 million. Under the terms of the Immedica Agreement, we are eligible to receive additional payments of up to approximately $122.1 million in regulatory and commercial milestone payments, assuming an exchange rate of $1.09 to €1.00. Additionally, we are entitled to receive royalties in the mid-20 percent range on net sales of the product in countries included in the Immedica Agreement. We will continue to be responsible for certain clinical development activities and the manufacturing of pegzilarginase and we retain commercialization rights in the United States and the rest of the world.

For the three months ended March 31, 2023, we recognized revenue of $0.2 million under the Immedica Agreement related to the progress in satisfying our obligations relating to the PEACE Phase 3 trial and BLA package performance. For the three months ended March 31, 2022, we recognized $1.4 million relating to the PEACE Phase 3 trial and BLA package performance.

AGLE-325 in Cystinuria and other research programs

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 and optimized AGLE-325 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. We presented preclinical data on a precursor molecule to AGLE-325 demonstrating reduced kidney stone formation in a preclinical model of Cystinuria.

Critical Accounting Policies and Estimates

Our condensed consolidated financial statements are prepared in accordance with generally accepted accounting principles in the United States. The preparation of these condensed consolidated financial statements requires us to make estimates and assumptions that affect the reported amounts of assets, liabilities, revenue, costs and expenses, and related disclosures. These estimates form the basis for judgments we make about the carrying values of our assets, liabilities and equity and the amount of revenues and expenses, which are not readily apparent from other sources. We base our estimates on historical experience and on various other assumptions that we believe are reasonable under the circumstances. On an ongoing basis, we evaluate our estimates and assumptions. Our actual results may differ materially from these estimates under different assumptions or conditions.

Our critical accounting policies are those policies which require the most significant judgments and estimates in the preparation of our condensed consolidated financial statements. As such, we believe that the assumptions and estimates associated with our most critical accounting policies are those relating to accrued research and development costs and revenue recognition. Our significant accounting policies are more fully described in Note 2 to our condensed consolidated financial statements appearing elsewhere in this quarterly report.

There have been no significant changes in our critical accounting policies and estimates as compared to the critical accounting policies and estimates disclosed in Management's Discussion and Analysis of Financial Condition and Operations included in our Annual Report on Form 10-K for the year ended December 31, 2022.

Results of Operations

Comparison of the Three Months Ended March 31, 2023 and 2022

The following table summarizes our results of operations for the three months ended March 31, 2023, and 2022, together with the changes in those items in dollars and as a percentage:

	Three Months Ended March 31,		Dollar Change	% Change
	2023	2022		
	(dollars in thousands)			
Revenue:				
Development fee and royalty	$ 198	$ 1,362	$ (1,164)	85 %
Total revenue	198	1,362	(1,164)	85 %
Operating expenses:				
Research and development	13,776	16,978	(3,202)	19 %
General and administrative	5,228	8,825	(3,597)	41 %
Total operating expenses	19,004	25,803	(6,799)	26 %
Loss from operations	(18,806)	(24,441)	5,635	23 %
Interest income	420	35	385	*
Other (expense) income, net	(72)	(30)	(42)	*
Loss before income tax expense	(18,458)	(24,436)	5,978	24 %
Income tax benefit (expense)	36	—	36	*
Net loss	$ (18,422)	$ (24,436)	$ 6,014	25 %

* Percentage not meaningful

Development Fee and Royalty Revenue. For the three months ended March 31, 2023, we recognized $0.2 million of revenue in connection with the Immedica Agreement. The total revenue generated was attributable to the PEACE Phase 3 trial and royalties from an early access program in France. For the three months ended March 31, 2022, we recognized $1.4 million of development fee revenue in connection with the Immedica Agreement, which was attributable to the PEACE Phase 3 trial and BLA package.

Research and Development Expenses. Research and development expenses decreased by $3.2 million, or 19%, to $13.8 million for the three months ended March 31, 2023, from $17.0 million for the three months ended March 31, 2022. The change in research and development expenses was primarily due to:

- a $1.6 million decrease in expense associated with the PEACE Phase 3 trial of pegzilarginase for the treatment of patients with Arginase 1 Deficiency;
- a $1.3 million decrease related to BLA submission expenses for Arginase 1 Deficiency; and
- a $0.3 million decrease in expense associated with the pause of the pegzilarginase Phase 1/2 trial.

General and Administrative Expenses. General and administrative expenses decreased by $3.6 million, or 41%, to $5.2 million for the three months ended March 31, 2023, from $8.8 million for the three months ended March 31, 2022. The decrease in general and administrative expenses was due to a $1.5 million decrease in compensation and other personnel expenses associated with a decrease in headcount, a $0.9 million decrease related to our Arginase 1 Deficiency commercial expenses, and a $0.9 million decrease in general support activities primarily driven by financing expenditures.

Liquidity and Capital Resources

Sources of liquidity

We are a clinical-stage biotechnology company with a limited operating history, and due to our significant research and development expenditures, we have generated operating losses since our inception and have not generated any revenue from the sale of any products. Since our inception and through March 31, 2023, we have funded our operations primarily by raising an aggregate of approximately $506.2 million of gross proceeds from the sale and issuance of convertible

preferred and common equity securities, pre-funded warrants, the collection of grant proceeds, and the licensing of our product rights for commercialization of pegzilarginase in Europe and certain countries in the Middle East.

In March 2021, we entered into the Immedica Agreement, pursuant to which Immedica licensed the product rights for commercialization of pegzilarginase in the European Economic Area, United Kingdom, Switzerland, Andorra, Monaco, San Marino, Vatican City, Turkey, Saudi Arabia, United Arab Emirates, Qatar, Kuwait, Bahrain, and Oman. In April 2021, we received an upfront payment of $21.5 million from Immedica. Under the terms of the Immedica Agreement, we are also eligible to receive additional payments of up to approximately $122.1 million in regulatory and commercial milestone payments, assuming an exchange rate of $1.09 to €1.00. Additionally, we are entitled to receive royalties in the mid-20 percent range on the net sales of the product in countries included in the Immedica Agreement. In July 2021, the Immedica Agreement was modified to include additional development services, up to $3.0 million, to support the PEACE Phase 3 trial and BLA package performance obligation.

In July 2020, we filed and the SEC declared effective a shelf registration statement on Form S-3, or the 2020 Registration Statement, for the potential offering, issuance and sale by us of up to $400.0 million of our common stock, preferred stock, debt securities, warrants to purchase common stock, preferred stock and debt securities, subscription rights to purchase common stock and units consisting of all or some of these securities.

In May 2022, we sold 10,752,688 shares of common stock and pre-funded warrants to purchase up to 17,372,312 shares of common stock in a registered direct offering, or the 2022 RDO, for gross proceeds of $45.0 million, resulting in net proceeds of $42.9 million after deducting placement agent fees and offering costs. The shares of common stock and pre-funded warrants sold in the 2022 RDO were offered pursuant to the 2020 Registration Statement.

Also in May 2022, we entered into a sales agreement, or the 2022 Sales Agreement, with JonesTrading Institutional Services LLC, as sales agent, to issue and sell shares of our common stock for an aggregate offering price of $60.0 million under an at-the-market offering program with JonesTrading Institutional Services LLC. As of the date of the filing of this report, $60.0 million of our common stock remained available for sale pursuant to the 2022 Sales Agreement. Any sales of common stock to be sold under the 2022 Sales Agreement will be made pursuant to the 2020 Registration Statement.

Since we are a clinical-stage biotechnology company, we have incurred significant operating losses since our inception and anticipate we will continue to incur operating losses related to our future restructured operations. Our current primary use of cash is to fund business operations while we evaluate strategic alternatives.

Future funding requirements and operational plan

Our operational plan for the near future is to identify, assess and execute a strategic transaction to maximize stockholder value. As such, we have reduced or eliminated our research and development expenditures and general and administrative expenditures on nonclinical studies, clinical trials, manufacturing, and commercial development. We intend to maintain a level of general and administrative expenses to support our business as we explore our options for strategic alternatives. We expect our principal expenditures during this time period to include expenses for the following:

- funding business development-related activities, including any strategic alternatives; and
- funding working capital, including general operating expenses.

Due to our significant research and development expenditures, we have generated substantial losses in each period since inception. We have an accumulated deficit of $444.0 million as of March 31, 2023. We anticipate that we will continue to incur operating losses related to our future restructured operations. We currently have no debt, credit facility or additional committed capital.

On April 8, 2023 the Board of Directors approved a restructuring of the Company's workforce pursuant to which the Company's workforce will be reduced by approximately 83% of the Company's existing headcount, retaining approximately 10 employees. On April 12, 2023, the Company announced interim results from its ongoing Phase 1/2 clinical trial of pegtarviliase for the treatment of classical homocystinuria. Following a review of the interim results and business considerations, the Company is exploring strategic alternatives with the goal of maximizing stockholder value, including possible business combinations and/or a divestiture of the Company's clinical programs. The Company will continue to pay existing obligations and payroll for critical personnel while exploring strategic alternatives. We estimate that we have sufficient cash and cash equivalents, marketable securities, and restricted cash for us to identify, assess and execute a strategic transaction. There can be no assurance that this strategic review will result in the Company pursuing a transaction or that any transaction, if pursued, will be completed on attractive terms.

After considering various alternatives, the Company determined that there is substantial doubt about the Company's ability to continue as a going concern within twelve months of the issuance date of these financial statements. The Company

plans to address this condition through the exploration of strategic alternatives, including possible business combinations and/or a divestiture of the Company's clinical programs.

Cash flows

The following table summarizes our cash flows for the periods indicated (in thousands):

	Three Months Ended March 31,	
	2023	2022
Net cash, cash equivalents, and restricted cash (used in) provided by:		
Operating activities	$ (17,634)	$ (26,263)
Investing activities	17,750	25,759
Financing activities	10	12
Effect of exchange rate on cash, cash equivalents, and restricted cash	11	(23)
Net increase (decrease) in cash, cash equivalents, and restricted cash	$ 137	$ (515)

Cash used in operating activities

Cash used in operating activities for the three months ended March 31, 2023, was $17.6 million and reflected a net loss of $18.4 million. Our net loss was offset in part by non-cash expenses of $1.7 million for stock-based compensation, and $0.6 million for depreciation and amortization. The net change in operating assets and liabilities of $1.4 million was primarily related to a $3.2 million decrease in accrued and other liabilities and $0.2 million decrease in operating lease liabilities, offset by a $1.4 million increase in accounts payable and a $0.6 million increase in prepaid and other current assets.

Cash used in operating activities for the three months ended March 31, 2022 was $26.3 million and reflected a net loss of $24.4 million. Our net loss was offset in part by a non-cash expense of $2.1 million for stock-based compensation, and $0.5 million for depreciation and amortization. The net change in operating assets and liabilities of $4.4 million was primarily related to a $2.8 million decrease in accrued compensation costs and a $0.8 million decrease in deferred revenue.

Cash provided by investing activities

Cash provided by investing activities for the three months ended March 31, 2023 was $17.8 million from maturities and sales of marketable securities.

Cash provided by investing activities for the three months ended March 31, 2022, was $25.8 million and consisted of $29.3 million in maturities and sales of marketable securities, offset by $3.5 million in purchases of marketable securities.

Cash provided by financing activities

Cash provided by financing activities for the three months ended March 31, 2023, was $0.1 million, which primarily consisted of the sale of common stock under our 2016 Employee Stock Purchase Plan.

Cash provided by financing activities for the three months ended March 31, 2022, was $12 thousand, which consisted of $0.2 million in the sale of common stock under our 2016 Employee Stock Purchase Plan, offset by $0.2 million in principal payments made on our finance lease obligations.

Contractual Obligations and Other Commitments

In April 2019, the Company entered into a lease agreement for its corporate headquarters and laboratory space located in Austin, TX. Future minimum lease commitments under this lease through April 2028 are $5.8 million. See Note 7, “Leases,” included in our Annual Report on Form 10-K for the year ended December 31, 2022, for additional information.

We have entered into agreements in the normal course of business with contract research organizations for clinical trials and contract manufacturing organizations, and with vendors for nonclinical research studies and other services and products for operating purposes. These contractual obligations are cancelable at any time by us, generally upon 30 to 60 days’ prior written notice to the vendor.

Recently Adopted Accounting Pronouncements

None.

Item 3. Quantitative and Qualitative Disclosures About Market Risk.

We are exposed to market risks in the ordinary course of our business. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates, particularly because our investments are in marketable securities. Our marketable securities are subject to interest rate risk and could fall in value if market interest rates increase. However, we believe that our exposure to interest rate risk is not significant as the majority of our investments are short-term in duration and due to the low risk profile of our investments, a 10% change in interest rates would not have a material effect on the total market value of our investment portfolio. We have the ability to hold our marketable securities until maturity, and therefore we would not expect our operating results or cash flows to be affected to any significant degree by the effect of a change in market interest rates on our investments.

As of March 31, 2023, we held $39.8 million in cash and cash equivalents, marketable securities, and restricted cash, all of which was denominated in U.S. dollar assets, and consisting primarily of investments in money market funds, commercial paper, and corporate bonds.

We are also exposed to market risk related to changes in foreign currency exchange rates, as a result of entering into transactions denominated in currencies other than U.S. dollars. Due to the uncertain timing of expected payments in foreign currencies, we do not utilize any forward exchange contracts. All foreign transactions settle on the applicable spot exchange basis at the time such payments are made. For the three months ended March 31, 2023, a majority of our expenditures were denominated in U.S. dollars. A hypothetical 10% change in foreign exchange rates during any of the periods presented would not have had a material impact on our consolidated financial statements.

Item 4. Controls and Procedures.

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our principal executive officer and principal financial officer, evaluated, as of the end of the period covered by this Quarterly Report on Form 10-Q, the effectiveness of our disclosure controls and procedures. Based on that evaluation of our disclosure controls and procedures as of March 31, 2023, our principal executive officer and principal financial officer concluded that our disclosure controls and procedures as of such date are effective at the reasonable assurance level. The term “disclosure controls and procedures,” as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, or the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act are recorded, processed, summarized and reported within the time periods specified in the SEC’s rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by us in the reports we file or submit under the Exchange Act is accumulated and communicated to our management, including our principal executive officer and principal financial officer, as appropriate to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and our management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures.

Changes in Internal Control over Financial Reporting

There were no changes in our internal control over financial reporting during the quarter ended March 31, 2023, that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

PART II. – OTHER INFORMATION

Item 1. Legal Proceedings

From time to time, we may become involved in legal proceedings relating to claims arising from the ordinary course of business. Our management believes that there are currently no claims or actions pending against us, the ultimate disposition of which could have a material adverse effect on our results of operations, financial condition or cash flows.

Item 1A. Risk Factors

Investing in our common stock involves a high degree of risk. The risks and uncertainties described below are not the only ones we face. Additional risks and uncertainties that we are unaware of, or that we currently believe are not material, may also become important factors that affect us. If any of the following risks occur, our business, operating results and prospects could be materially harmed. In that event, the price of our common stock could decline, and you could lose part or all of your investment.

There have been no material changes from the risk factors set forth in our Annual Report on Form 10-K for the year ended December 31, 2022, except for the following:

Risks Related to Strategic Alternative Process and Potential Strategic Transaction

We may not be successful in identifying, assessing and executing any strategic business combination or other transaction, and any strategic transaction that we may consummate in the future could have negative consequences. If a strategic transaction is not consummated, our board of directors may decide to pursue a dissolution and liquidation. In the event of such liquidation or other wind-down event, holders of our securities will likely suffer a total loss of their investment.

In addition to our efforts, if any, to pursue clinical development of our product candidates, we also continue to evaluate all potential strategic options for the Company, including a merger, reverse merger, sale, wind-down, liquidation and dissolution or other strategic transaction. However, there can be no assurance that we will be able to successfully consummate any particular strategic transaction. No decision has been made with respect to any transaction, and there can be no assurance that the exploration of strategic alternatives will result in the identification or consummation of any transaction, or that any strategic alternative identified, evaluated and consummated will provide the anticipated benefits or otherwise preserve or enhance stockholder value.

The process of continuing to evaluate these strategic options may be very costly, time-consuming and complex and we expect to incur significant costs related to this continued evaluation, such as legal and accounting fees and expenses and other related charges. We may also incur additional unanticipated expenses in connection with this process. A considerable portion of these costs will be incurred regardless of whether any such course of action is implemented or transaction is completed. Any such expenses will decrease the remaining cash available for use in our business.

There can be no assurances that any particular course of action, business arrangement or transaction, or series of transactions, will be pursued, successfully consummated, lead to increased stockholder value, or achieve the anticipated results. In addition, there can be no assurance that our current strategic direction, or the board's evaluation of strategic alternatives, will result in any initiatives, agreements, transactions or plans that will enhance stockholder value. If we are unable to consummate a strategic transaction, our board of directors may decide to pursue a dissolution and liquidation. In the event of such liquidation or other wind-down event, holders of our securities will likely suffer a total loss of their investment.

We may not realize any additional value in a strategic transaction.

Potential counterparties in a strategic transaction involving us may place minimal or no value on our assets. Further, the development and any potential commercialization of our product candidates will require substantial additional cash. Consequently, any potential counterparty in a strategic transaction involving our company may choose not to spend additional resources and continue development of our product candidates and may attribute little or no value, in such a transaction, to those product candidates.

If we are successful in completing a strategic transaction, we may be exposed to other operational and financial risks.

Although there can be no assurance that a strategic transaction will result from the process we have undertaken or will undertake to identify and evaluate strategic alternatives, the negotiation and consummation of any such transaction will require significant time on the part of our management, and the diversion of management's attention may disrupt our business.

The negotiation and consummation of any such transaction may also require more time or greater cash resources than we anticipate and expose us to other operational and financial risks, including:

- increased near-term and long-term expenditures;
- exposure to unknown liabilities;
- higher than expected acquisition or integration costs;
- incurrence of substantial debt or dilutive issuances of equity securities to fund future operations;
- write-downs of assets or goodwill or incurrence of non-recurring, impairment or other charges;
- increased amortization expenses;
- difficulty and cost in combining the operations and personnel of any acquired business with our operations and personnel;
- impairment of relationships with key suppliers or customers of any acquired business due to changes in management and ownership;
- inability to retain key employees of our company or any acquired business; and
- possibility of future litigation.

Any of the following risks could have a material adverse effect on our business, financial condition and prospects.

We may not fully realize the expected cost savings and/or operating efficiencies from our restructuring activities and our ability to consummate a strategic transaction depends on our ability to retain our employees required to consummate such transaction.

On April 12, 2023, we announced a restructuring plan of our operations to narrow our near-term business focus and reduce our workforce by approximately 83%. We believe these changes were needed to streamline our organization and reallocate our resources to better align with our current strategic goals, including our current focus on pursuing strategic alternatives. However, these expense reduction measures have and may continue to yield unintended consequences and costs, such as the loss of institutional knowledge and expertise, attrition beyond our intended reductions in workforce, a reduction in morale among our remaining employees, and the risk that we may not achieve the anticipated benefits, all of which may have an adverse effect on our results of operations or financial condition.

In connection with the restructuring, two executive officers departed the Company, Michael Hanley, the Company's Chief Business Officer, and Linda Neuman, the Company's Chief Medical Officer on April 14, 2023. Our ability to successfully complete a strategic transaction depends in large part on our ability to retain certain of our remaining personnel. If we are unable to successfully retain our remaining personnel, we are at risk of a disruption to our exploration and consummation of a strategic transaction as well as business operations.

We may become involved in securities litigation that could divert management's attention and harm our business, and insurance coverage may not be sufficient to cover all costs and damages.

In the past, securities litigation has often followed certain significant business transactions, such as the sale of a company or announcement of any other strategic transaction, or the announcement of negative events, such as negative results from clinical trials. We may be exposed to such litigation even if no wrongdoing occurred. Litigation is usually expensive and diverts management's attention and resources, which could adversely affect our business and cash resources and our ability to consummate a potential strategic transaction or the ultimate value our stockholders receive in any such transaction.

Risks Related to Our Financial Position and Need for Additional Capital

We have expressed substantial doubt about our ability to continue as a going concern.

We have evaluated whether there are conditions and events, considered in the aggregate, that raise substantial doubt about our ability to continue as a going concern within one year after the date the unaudited condensed consolidated financial statements included in this Quarterly Report on Form 10-Q were issued. After considering various alternatives, the Company determined that there is substantial doubt about the Company's ability to continue as a going concern within twelve months of this filing on Form 10-Q.

In view of these matters, our ability to continue as a going concern is dependent upon our ability to raise additional capital through outside sources. We have commenced a process to explore strategic alternatives, however, there can be no assurance that the exploration of strategic alternatives will result in any agreements or transactions, or that, if completed, any agreements will be reached or transactions will be successfully consummated or on attractive terms. If we are unable to consummate a strategic transaction, we may seek to obtain funding through the sale of common stock in public offerings and/or private placements, debt financings, or through other capital sources, including collaborations with other companies or other strategic transactions. The failure to obtain sufficient financing or strategic transactions could adversely affect our ability to achieve our business objectives and continue as a going concern.

We have no source of product revenue and we have incurred significant losses since inception. We expect to incur losses for the foreseeable future and may never achieve or maintain profitability.

We have a limited operating history and no approved products. Our ability to generate revenue and become profitable depends upon our ability to successfully complete the development of any of our product candidates, including pegtarviliase and pegzilarginase, for any of our target indications and to obtain necessary regulatory approvals. To date, we have recognized revenue from a license and supply agreement and a fully utilized government grant and have not generated any product revenue. Even if we receive regulatory approval for any of our product candidates, we do not know when these product candidates will generate revenue for us, if at all.

In addition, since inception, we have incurred significant operating losses. For the three months ended March 31, 2023, we reported a net loss of $18.4 million. For the years ended December 31, 2022 and 2021, we reported a net loss of $83.8 million and $65.8 million, respectively. As of March 31, 2023, we had an accumulated deficit of $444.0 million. After considering various alternatives, the Company determined that there is substantial doubt about the Company's ability to continue as a going concern within twelve months of the issuance date of the unaudited condensed consolidated financial statements included in this Quarterly Report on Form 10-Q. We have commenced a process to explore strategic alternatives, however, there can be no assurance that the exploration of strategic alternatives will result in any agreements or transactions, or that, if completed, any agreements will be reached or transactions will be successfully consummated or on attractive terms. If we are unable to consummate a strategic transaction, we may seek to fund our operations through the sale of common stock in public offerings and/or private placements, debt financings, or through other capital sources, including collaborations with other companies or other strategic transactions. In the past, we have financed our operations primarily through private placements of our preferred stock, the initial public offering of our common stock, follow-on public offerings of our common stock and pre-funded warrants, collection of a research grant, and the licensing of our product rights for commercialization of pegzilarginase in Europe and several countries in the Middle East. We have devoted substantially all of our efforts to research and development. Other than our work pursuing clinical development of pegtarviliase for the treatment of Homocystinuria and pegzilarginase for the treatment of Arginase 1 Deficiency, we have not initiated clinical development of our other product candidates and none of our product candidates are ready for commercialization.

We are unable to predict the timing or amount of increased expenses, or when, or if, we will be able to achieve or maintain profitability because of the numerous risks and uncertainties associated with product development. In addition, our expenses could increase significantly beyond expectations if we are required by the FDA, EMA, MHRA, or other relevant regulatory authorities, or collectively the Health Authorities, to modify protocols of our clinical trials or perform studies in addition to those that we currently anticipate. Even if pegzilarginase, or any of our other product candidates, is approved for commercial sale, we anticipate incurring significant costs associated with the commercial launch of any product candidate.

To become and remain profitable, we must develop and eventually commercialize a product candidate or product candidates with significant market potential. This will require us to be successful in a range of challenging activities, including completing nonclinical testing, initiating and completing clinical trials of one or more of our product candidates, obtaining marketing approval for these product candidates, manufacturing, marketing and selling those product candidates for which we obtain marketing approval and satisfying any post-marketing requirements. We may never succeed in these activities and, even if we do, we may never generate revenues that are significant or large enough to achieve profitability. We previously reported that we received a Refuse to File letter, or RTF Letter, from the FDA regarding our BLA submission for pegzilarginase for the treatment of Arginase 1 Deficiency. In the RTF Letter, the FDA requested additional data to support effectiveness and additional information relating to Chemistry Manufacturing and Controls. We are continuing to engage with FDA to identify a potential path to BLA resubmission. We also previously reported that we received a letter from the FDA regarding a protocol amendment for our Phase 1/2 clinical trial of pegtarviliase for the treatment of Classical Homocystinuria in which the FDA stated the protocol did not provide adequate justification and evidence to support the prospect of direct clinical benefit for pediatric patients and placed the trial on partial clinical hold for the enrollment of patients less than 18 years of age. A local Australian ethics committee, responsible for two clinical trial sites, subsequently stated that it would like to align with the FDA and place a hold on the enrollment of pediatric participants at those sites. In April

2023, we announced that the interim results of our Phase 1/2 trial of pegtarviliase for the treatment of Classical Homocystinuria showed the development of anti-drug antibodies in the third cohort. We are in the nonclinical development stages for our remaining product candidates. If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of the company and could impair our ability to raise capital, maintain or expand our research and development efforts, expand our business or continue our operations.

We will need substantial additional funding. If we are unable to raise capital when needed, our business will be adversely affected.

We expect our expenses to increase in parallel with our ongoing activities, particularly as we explore strategic transactions. Furthermore, we expect to continue to incur additional costs associated with operating as a public company. Accordingly, we will need to obtain substantial additional funding to support our continuing operations. If we are unable to raise capital when needed for any reason, including but not limited to inflation, increasing interest rates, volatile market conditions and global events, or on acceptable terms, our business would be adversely impacted.

Even if successful in raising new capital, we could be limited in the amount of capital we raise due to investor demand restrictions placed on the amount of capital we raise or other reasons. For example, as of the filing of this Quarterly Report, we are subject to the limitations set forth in Instruction I.B.6 of Form S-3 (the "baby shelf restrictions") or other reasons.

Risks Related to Our Product Development and Regulatory Approval

We depend heavily on the success of our most advanced product candidates, pegtarviliase and pegzilarginase. Existing and future clinical trials of our product candidates, including pegtarviliase and pegzilarginase, may not be successful.

We have invested a significant portion of our efforts and financial resources in the nonclinical and clinical development and testing of pegzilarginase for the treatment of patients with Arginase 1 Deficiency and in certain oncology trials and pegtarviliase for the treatment of Homocystinuria. Our ability to generate product revenues, if ever, has depended heavily on the successful development and commercialization of pegtarviliase and pegzilarginase. The success of pegtarviliase, pegzilarginase, and our other product candidates has depended on many factors, including the following:

- receiving required regulatory approvals for the development and commercialization of our product candidates as monotherapy or in combination with other products;
- establishing commercial manufacturing capabilities or making arrangements with third-party manufacturers;
- obtaining and maintaining patent and trade secret protection and non-patent exclusivity for our product candidates and their components;
- enforcing and defending intellectual property rights and claims;
- achieving desirable therapeutic properties for our product candidates' intended indications;
- launching commercial sales of our product candidates, if and when approved, whether alone or in collaboration with third parties;
- acceptance of our product candidates, if and when approved, by patients, the medical community and third-party payors;
- effectively competing with other therapies; and
- maintaining an acceptable safety profile of our product candidates through clinical trials and following regulatory approval.

If we do not achieve one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize our product candidates, which would materially harm our business. We have experienced challenges in advancing our product candidates through clinical trials and seeking regulatory approval. In June 2022, we reported that we received a RTF Letter from the FDA regarding our BLA submission for pegzilarginase. In the RTF Letter, the FDA requested additional data to support effectiveness and additional information relating to Chemistry Manufacturing and Controls. Although we have engaged in subsequent discussions with the FDA concerning pegzilarginase, we have not been successful in coming to an agreement concerning our BLA resubmission. Furthermore, in April 2023, based on the review of the inconclusive interim results from its Phase 1/2 clinical trial of pegtarviliase for the

treatment of Classical Homocystinuria and business considerations, the Company announced that it had initiated a process to explore strategic alternatives to maximize stockholder value. Since the announcement of our plan to explore strategic alternatives in April 2023, we have decided to voluntarily pause our clinical programs.

Clinical drug development involves a lengthy and expensive process with an uncertain outcome. We may experience delays in completing, or ultimately be unable to complete, the development and commercialization of any of our product candidates.

As announced on April 12, 2023, the interim results of our Phase 1/2 trial of pegtarviliase for the treatment of Classical Homocystinuria showed the development of anti-drug antibodies in the third cohort. We may be unable to find, through a strategic transaction or otherwise, a third-party entity willing to continue development of pegtarviliase. The risk of failure for all of our product candidates is high. Before obtaining marketing approval from regulatory authorities for the sale of any product candidate, we or successor sponsors must complete nonclinical development and then conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans for the respective target indications. Clinical testing is expensive, difficult to design and implement, can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process.

The results of nonclinical studies and early clinical trials of our product candidates may not be predictive of the results of later-stage clinical trials that will likely differ in design and size from early-stage clinical trials, and interim results of a clinical trial do not necessarily predict final results. For example, while we have observed a reduction in blood arginine and arginine metabolite levels due to administration of pegzilarginase in patients with Arginase 1 Deficiency, and a reduction in blood arginine levels due to pegzilarginase in patients with advanced solid tumors, these data may not necessarily be predictive of the final results of all patients treated with pegzilarginase, and may also not be predictive of pegzilarginase's ability to reduce arginine or arginine metabolite levels for these patients over a longer term nor predictive of positive clinical outcomes. In addition, while we intend to announce interim data from our clinical trials from time to time, such reports may be based on unaudited data provided by our clinical trial investigators. An audit or subsequent review of this data may change the conclusions drawn from this unaudited data provided by our clinical trial investigators indicating less promising results than we anticipate. In addition, our observations of clinical improvements, through clinician and assessor feedback or assessment tools in the Phase 1/2 clinical trial, the Phase 2 open-label study, the PEACE Phase 3 clinical trial and its open-label extension of pegzilarginase in patients with Arginase 1 Deficiency after cumulative doses, may not be representative of our observations with subsequently dosed patients out to a similar or longer duration of cumulative dosing.

It is impossible to predict when or if any of our product candidates will prove effective or safe in humans or will receive regulatory approval.

We may experience delays in our clinical trials and we do not know whether planned clinical trials will begin or enroll subjects on time, whether enrolled subjects will complete trials on time or at all, whether such trials will need to be redesigned or whether they will be able to be completed on schedule, if at all. There can be no assurance that the Health Authorities will allow us to begin clinical trials or that they will not put any of the trials for any of our product candidates that enter or have entered clinical development on clinical hold in the future. We may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent our ability to receive marketing approval or commercialize our product candidates. Clinical trials may be delayed, suspended or prematurely terminated because costs are greater than we anticipate or for a variety of reasons, such as:

- delay or failure in reaching agreement with the Health Authorities on a trial design that we are able to execute;
- delay or failure in obtaining authorization to commence a trial or inability to comply with conditions imposed by a regulatory authority regarding the scope or design of a clinical trial;
- delays in reaching, or failure to reach, agreement on acceptable clinical trial contracts or clinical trial protocols with planned trial sites;
- modifications to our clinical trial protocols due to regulatory requirements or decisions made by regulatory authorities;
- geographic complexities of managing the design and completion of clinical trials across different Health Authorities in the United States, Canada, Europe, Australia, and other jurisdictions where we currently or may in the future conduct clinical trials;
- reports of safety issues, side effects or dose-limiting toxicities, or any additional or more severe safety issues in addition to those observed to date;

- inability, delay, or failure in identifying and maintaining a sufficient number of trial sites, many of which may already be engaged in other clinical programs;
- delay or failure in recruiting and enrolling suitable subjects to participate in one or more clinical trials;
- delay or failure in having subjects complete a trial or return for post-treatment follow-up. For instance, one patient withdrew from the Phase 1/2 clinical trial of pegtarviliase for Classical Homocystinuria and two patients previously dosed in our Phase 1/2 clinical trial of pegzilarginase for the treatment of Arginase 1 Deficiency withdrew from the trial due to personal reasons;
- clinical sites and investigators deviating from the trial protocol, failing to conduct the trial in accordance with regulatory requirements, or dropping out of a trial;
- a clinical hold for any of our clinical trials, including for pegtarviliase or pegzilarginase, where a clinical hold in a trial in one indication could result in a clinical hold for clinical trials in other indications;
- failure of the Company, third party manufacturers, or sites participating in our clinical trials to pass regulatory inspections under applicable standards, including Good Clinical Practice and Good Manufacturing Practice;
- clinical trials of our product candidates may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct more clinical trials than we anticipate or abandon product development programs;
- the number of patients required for clinical trials of our product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate or insufficient or participants may drop out of these clinical trials at a higher rate than we anticipate;
- we may experience delays or difficulties in the enrollment of patients, including the identification of patients with Classical Homocystinuria or Arginase 1 Deficiency;
- our third-party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;
- we may have difficulty partnering with experienced CROs that can run our clinical trials effectively, adhere to the trial protocols and follow policies and procedures;
- regulators may require that we or our investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks or privacy concerns;
- the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate; or
- there may be changes in governmental regulations or administrative actions.

If we are required to modify our ongoing clinical trial protocols, conduct additional clinical trials or other testing of our product candidates beyond those that we currently contemplate, if we are unable to successfully initiate or complete clinical trials of our product candidates or other testing, if the results of these trials or tests do not demonstrate sufficient clinical benefit or if our product candidates do not have an acceptable safety profile, we may:

- be delayed in obtaining marketing approval for our product candidates;
- not obtain marketing approval at all;
- cease development of our product candidates;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with labeling that includes significant use or distribution restrictions or safety warnings that would reduce the potential market for our product candidates or inhibit our ability to successfully commercialize our product candidates;
- be subject to additional post-marketing restrictions, requirements, and/or testing requirements; or
- have the product removed from the market after obtaining marketing approval.

For example, in June 2017, we delayed enrollment of pediatric patients in our Phase 1/2 clinical trial of pegzilarginase for the treatment of Arginase 1 Deficiency due to a difference in opinion with the FDA on data required to support inclusion

of pediatric patients. Although we reached an agreement with the FDA in November 2017 and began dosing pediatric patients, the FDA may require additional information or studies to be conducted, or impose conditions that could further delay or restrict our other planned clinical activities in the future. Similarly, in October 2022, we received a letter from the FDA regarding a protocol amendment for our Phase 1/2 clinical rial of pegtarviliase in which the FDA stated the protocol did not provide adequate justification and evidence to support the prospect of direct clinical benefit for pediatric patients and placed the trial on partial clinical hold for the enrollment of patients less an 18 years of age. A local Australian ethics committee, responsible for two clinical trial sites, recently stated that it would like to align with the FDA and place a hold on the enrollment of pediatric participants at those sites. We began our global pivotal PEACE Phase 3 clinical trial in which we are studying plasma arginine reduction from baseline over 24 weeks as our primary endpoint. However, evidence of stabilization or improvement of clinical signs and symptoms of Arginase 1 Deficiency, such as our secondary endpoints, consisting of clinical outcome assessments focused primarily on mobility, as well as clinician and caregiver global impressions of effectiveness, may be required in addition to the primary endpoint to support approval. Certain of our clinical outcome secondary endpoints are being measured using motor assessments that have not been previously validated for Arginase 1 Deficiency, including the gross motor function classification system. Such motor assessments have only been validated in ambulatory children with cerebral palsy. We believe these motor functional assessments are translatable to Arginase 1 Deficiency patients given the similarities in symptoms of children with cerebral palsy and the Arginase 1 Deficiency populations, however the FDA or other Health Authorities may disagree. For example, on June 2, 2022, we reported that we received a RTF Letter from the FDA regarding our BLA submission for pegzilarginase. In the RTF Letter, the FDA requested additional data to support effectiveness and additional information relating to Chemistry Manufacturing and Controls.

Significant nonclinical or clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do and impair our ability to successfully commercialize our product candidates and may materially harm our business and results of operations.

Risks Related to Our Reliance on Third Parties

We may not be successful in finding strategic partners for continuing development or commercialization of certain of our product candidates.

We may seek to develop strategic partnerships for developing certain of our product candidates, due to capital costs required to develop the product candidates or manufacturing constraints. We also have entered into and may enter into future partnership agreements to commercialize pegzilarginase outside the United States, including through our licensing agreement with Immedica. We may not be successful in our efforts to establish such a strategic partnership or other alternative arrangements for our product candidates because our research and development pipeline may be insufficient, our product candidates may be deemed to be at too early of a stage of development for collaborative effort or third parties may not view our product candidates as having the requisite potential to demonstrate safety and efficacy. In addition, we may be restricted under existing collaboration or license and development agreements from entering into future agreements with potential strategic partners. We cannot be certain that, following a strategic transaction or license, we will achieve an economic benefit that justifies such a transaction.

If we are unable to reach agreements with suitable strategic partners on a timely basis, on acceptable terms or at all, we may have to curtail the development of a product candidate, reduce or delay its development program, delay its potential commercialization, reduce the scope of any sales or marketing activities or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to fund development or commercialization activities on our own, or our existing or future partners are not able to adequately fund their development or commercialization activities pursuant to our arrangements, we may need to obtain additional expertise and additional capital, which may not be available to us on acceptable terms or at all. If we fail to enter into collaborations and do not have sufficient funds or expertise to undertake the necessary development and commercialization activities, we may not be able to further develop our product candidates and our business, financial condition, results of operations and prospects may be materially and adversely affected.

Risks Related to Government Regulation

Recently enacted and future legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates and affect the prices we may obtain.

In the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any product candidates for which we obtain marketing approval.

The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively the ACA, is a sweeping law intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add transparency requirements for the healthcare and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms. The ACA, among other things, also expanded manufacturers' rebate liability under the Medicaid Drug Rebate Program and imposed a significant annual, nondeductible fee on companies that manufacture or import certain branded prescription drug products.

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. These changes included aggregate reductions to Medicare payments to providers of up to 2% per fiscal year. These reductions went into effect in 2013 and, due to subsequent legislative amendments to the statute, will remain in effect through 2023. In January 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, reduced Medicare payments to several providers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. On January 20, 2017, federal agencies with authorities and responsibilities under the ACA were directed to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal burden on states or a cost, fee, tax, penalty or regulatory burden on individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. More recently, the Tax Cuts and Jobs Act was signed into law, which eliminated certain requirements of the ACA, including the individual mandate. On June 17, 2021, the United States Supreme Court held that plaintiffs do not have standing to challenge the constitutionality of the individual mandate. It is unclear whether there will be additional challenges to the ACA. Additionally, on January 28, 2021, the President of the United States issued an executive order that initiated a special enrollment period from February 15, 2021 through May 15, 2021 for purposes of obtaining health insurance coverage through the ACA marketplace. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA. It is uncertain how other such litigation or the healthcare measures of the United States administration will impact the ACA and our business.

We expect that the ACA, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any approved product. For example, on September 9, 2021, the Biden administration published a wide-ranging list of policy proposals to lower prescription drug prices, including by allowing Medicare to negotiate prices and disincentivizing price increases, and to support market changes that strengthen supply chains, promote biosimilars and generic drugs, and increase price transparency. These initiatives recently culminated in the enactment of the Inflation Reduction Act, or IRA, in August 2022, which will, among other things, allow the U.S. Department of Health and Human Services, or HHS, to negotiate the selling price of certain drugs and biologics that CMS reimburses under Medicare Part B and Part D, although this will only apply to high-expenditure single-source drugs that have been approved for at least 7 years (11 years for biologics). The negotiated prices, will first become effective in 2026, and will be capped at a statutory ceiling price. The IRA will also, beginning in October 2023, penalize drug manufacturers that increase prices of Medicare Part B and Part D drugs at a rate greater than the rate of inflation. In addition, the law eliminates the "donut hole" under Medicare Part D beginning in 2025 by significantly lowering the beneficiary maximum out-of-pocket cost and requiring manufacturers to subsidize, through a newly established manufacturer discount program, 10% of Part D enrollees' prescription costs for brand drugs below the out-of-pocket maximum and 20% once the out-of-pocket maximum has been reached. The IRA permits the Secretary of HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years. HHS has and will continue to issue and update guidance as these programs are implemented. Manufacturers that fail to comply with the IRA may be subject to various penalties, including civil monetary penalties. The IRA also extends enhanced subsidies for individuals purchasing health insurance coverage in ACA marketplaces through plan year 2025. These provisions will take effect progressively starting in 2023, although they may be subject to legal challenges. Further, in response to the Biden administration's October 2022 executive order, on February 14, 2023, HHS released a report outlining three new models for testing by the CMS Innovation Center which will be evaluated on their ability to lower the cost of drugs, promote

accessibility, and improve quality of care. It is unclear whether the models will be utilized in any health reform measures in the future. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our product candidates.

Legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. We cannot be sure whether additional legislative changes will be enacted, or whether FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our product candidates, if any, may be. In addition, increased scrutiny by the U.S. Congress of the FDA's approval process may significantly delay or prevent marketing approval, as well as subject us to more stringent product labeling and post-marketing testing and other requirements.

Risks Related to Employee Matters, Managing Growth and Other Risks Related to Our Business

Our future success depends on our ability to retain key executives and to attract, retain and motivate qualified personnel.

We are a clinical-stage biotechnology company with a limited operating history, and, as of March 31, 2023, had 61 employees. On April 12, 2023, we announced a restructuring plan of our operations to narrow our near-term business focus and reduce our workforce by approximately 83%. In connection with the restructuring, two executive officers departed the Company, Michael Hanley, the Company's Chief Business Officer, and Linda Neuman, the Company's Chief Medical Officer on April 14, 2023. We have been highly dependent on the research and development, clinical and business development expertise of our executive officers, as well as the other principal members of our management, scientific and clinical team. Any of our management team members may terminate their employment with us at any time. We do not maintain "key person" insurance for any of our executives or other employees.

Retaining qualified personnel will also be critical to our success, including with respect to any strategic transaction that we may pursue. The loss of the services of our executive officers or other key employees could impede the achievement of our research, development and commercialization objectives and seriously harm our ability to successfully implement our business strategy. Furthermore, replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully develop, facilitate regulatory approval of and commercialize product candidates. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these key personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions.

In addition, we rely on consultants and advisors, including scientific and clinical advisors such as our scientific advisory board, to assist us in formulating our discovery and nonclinical and clinical development and commercialization strategy. Our consultants and advisors, including members of our scientific advisory board, may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us. If we are unable to continue to attract and retain high quality personnel, our ability to pursue our growth strategy will be limited.

Risks Related to Our Common Stock

The price of our common stock has been and may be volatile and fluctuate substantially, which could result in substantial losses for purchasers of our common stock.

Our stock price is volatile. The stock market in general and the market for smaller biotechnology companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. The market price for our common stock may be influenced by many factors, including:

- the success or failure of our ability to identify, assess and execute a strategic transaction or realize any value from our existing assets and the timing thereof;
- the success or failure of competitive products or technologies;
- results of clinical trials of our product candidates or those of our competitors;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;

- the recruitment or departure of key personnel;
- the level of expenses related to any of our product candidates or clinical development programs;
- the results of our efforts to discover, develop, acquire or in-license additional product candidates or products;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- operating results that fail to meet expectations of securities analysts that cover our company;
- variations in our financial results or those of companies that are perceived to be similar to us;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic and market conditions, including rising interest rates and inflation, as well as the possibility of a recession or further economic downturn, and the economic impact of the war in Ukraine and its potential suppler chain impacts and the ongoing COVID-19 pandemic;
- recent and potential future disruptions in access to bank deposits or lending commitments due to bank failures and any negative consequences that may result therefrom; and
- the other factors described in this “Risk Factors” section.

We will not receive a significant amount, or potentially any, additional funds upon the exercise of our pre-funded warrants; however, any exercise would increase the number of shares eligible for future resale in the public market and result in substantial dilution to our stockholders.

As of March 31, 2023, we have issued pre-funded warrants to purchase a total of 34,982,640 shares of our common stock, of which 6,091,062 have been exercised and 28,891,578 are currently outstanding. Each pre-funded warrant is exercisable for $0.0001 per share of common stock underlying such pre-funded warrant, which may be paid by way of a cashless exercise, meaning that the holder may not pay a cash purchase price upon exercise, but instead would receive upon such exercise the net number of shares of common stock determined according to the formula set forth in the pre-funded warrant. Accordingly, we will not receive a significant amount, or potentially any, additional funds upon the exercise of the pre-funded warrants. To the extent such pre-funded warrants are exercised, additional shares of common stock will be issued for nominal or no additional consideration, which will result in substantial dilution to the then existing holders of our common stock and will increase the number of shares eligible for resale in the public market. Sales of substantial numbers of such shares in the public market could adversely affect the market price of the common stock, causing our stock price to decline.

Item 2. Unregistered Sales of Equity Securities and Use of Proceeds.

None.

Item 3. Defaults Upon Senior Securities.

Not applicable.

Item 4. Mine Safety Disclosure.

Not applicable.

Item 5. Other Information.

Not applicable.

Item 6. Exhibits.

The exhibits filed or furnished as part of this Quarterly Report on Form 10-Q are set forth below.

Exhibit Number	Description	Form	File No	Incorporate by Date of Filing	Exhibit No.	Filed Herewith
3.1	Restated Certificate of Incorporation	S-1/A	333-205001	9/14/2015	3.2	
3.2	Amended and Restated Bylaws	8-K	001-37722	12/19/2022	3.1	
31.1	Certification of the Principal Executive Officer pursuant to Rule 13a-14(a) or 15d-14(a) of the Securities Exchange Act of 1934.					X
31.2	Certification of the Principal Financial Officer pursuant to Rule 13a-14(a) or 15d-14(a) of the Securities Exchange Act of 1934.					X
32.1(1)	Certification of the Principal Executive Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.					X
32.2(1)	Certification of the Principal Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.					X
101.INS	Inline XBRL Instance Document – the instance document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document.					X
101.SCH	Inline XBRL Taxonomy Extension Schema Document					X
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document					X
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document					X
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document					X
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document					X
104	The cover page from this Quarterly Report on Form 10-Q for the quarter ended March 31, 2023, formatted in Inline XBRL and contained in Exhibit 101					

(1) The certifications on Exhibit 32 hereto are deemed not “filed” for purposes of Section 18 of the Exchange Act or otherwise subject to the liability of that Section. Such certifications will not be deemed incorporated by reference into any filing under the Securities Act or the Exchange Act.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Date: May 11, 2023

AEGLEA BIOTHERAPEUTICS, INC.

By: /s/ Jeffrey Goldberg
Jeffrey Goldberg
Chief Executive Officer
(Principal Executive Officer)

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Date: May 11, 2023

AEGLEA BIOTHERAPEUTICS, INC.

By: /s/ Jonathan Alspaugh
Jonathan Alspaugh
Chief Financial Officer
(Principal Financial Officer and duly Authorized Signatory)

Exhibit 31.1

Certification of Periodic Report under Section 302 of the Sarbanes-Oxley Act of 2002

I, Jeffrey Goldberg, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Aeglea BioTherapeutics, Inc.;
2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;
3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;
4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a 15(f) and 15d 15(f)) for the registrant and have:
    a. Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant is made known to us by others within those entities, particularly during the period in which this report is being prepared;
    b. Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;
    c. Evaluated the effectiveness of the registrant's disclosure controls and procedures, and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and
    d. Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting.
5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):
    a. All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and
    b. Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: May 11, 2023

/s/ Jeffrey Goldberg
Jeffrey Goldberg
Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

Certification of Periodic Report under Section 302 of the Sarbanes-Oxley Act of 2002

I, Jonathan Alspaugh, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Aeglea BioTherapeutics, Inc.;
2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;
3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;
4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a 15(f) and 15d 15(f)) for the registrant and have:
    a. Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant is made known to us by others within those entities, particularly during the period in which this report is being prepared;
    b. Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;
    c. Evaluated the effectiveness of the registrant's disclosure controls and procedures, and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and
    d. Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting.
5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):
    a. All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and
    b. Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: May 11, 2023

/s/ Jonathan Alspaugh

Jonathan Alspaugh

Chief Financial Officer

(Principal Financial Officer and Principal Accounting Officer)

Exhibit 32.1

Certification Of
Principal Executive Officer and Principal Financial Officer
Pursuant To 18 U.S.C. Section 1350,
As Adopted Pursuant To
Section 906 of The Sarbanes-Oxley Act Of 2002

In connection with the Quarterly Report of Aeglea BioTherapeutics, Inc. (the "Company") on Form 10-Q for the period ended March 31, 2023, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, Jeffrey Goldberg, Chief Executive Officer of the Company, certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to my knowledge:

1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

2) The information contained in the Report fairly presents, in all material respects, the financial condition of the Company at the end of the period covered by the Report and results of operations of the Company for the period covered by the Report.

Date: May 11, 2023

/s/ Jeffrey Goldberg
Jeffrey Goldberg
Chief Executive Officer
(Principal Executive Officer)

Exhibit 32.2

Certification Of
Principal Executive Officer and Principal Financial Officer
Pursuant To 18 U.S.C. Section 1350,
As Adopted Pursuant To
Section 906 of The Sarbanes-Oxley Act Of 2002

In connection with the Quarterly Report of Aeglea BioTherapeutics, Inc. (the "Company") on Form 10-Q for the period ended March 31, 2023 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, Jonathan Alspaugh, Chief Financial Officer of the Company, certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to my knowledge:

1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

2) The information contained in the Report fairly presents, in all material respects, the financial condition of the Company at the end of the period covered by the Report and results of operations of the Company for the period covered by the Report.

Date: May 11, 2023

/s/ Jonathan Alspaugh
Jonathan Alspaugh
Chief Financial Officer
(Principal Financial Officer and Principal Accounting Officer)