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 September 30, 2022

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 October 28, 2022, the registrant had 61,511,078 shares of common stock, $0.0001 par value per share, outstanding.

AEGLEA BIOTHERAPEUTICS, INC.

QUARTERLY REPORT ON FORM 10-Q
FOR THE QUARTER ENDED SEPTEMBER 30, 2022

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NOTE ABOUT FORWARD-LOOKING STATEMENTS

This Quarterly Report 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 future results of operations and financial position, business strategy, the length of time that we believe our existing cash resources will fund operations, 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, use of net proceeds from our public offerings, 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 the COVID-19 pandemic 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 on Form 10-Q, 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, unless otherwise noted. “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)

	September 30, 2022	December 31, 2021
ASSETS		
CURRENT ASSETS		
Cash and cash equivalents	$ 38,989	$ 15,142
Marketable securities	34,687	77,986
License and development receivables	669	815
Prepaid expenses and other current assets	7,874	4,948
Total current assets	82,219	98,891
Restricted cash	1,529	1,838
Property and equipment, net	3,555	4,549
Operating lease right-of-use assets	3,514	3,806
Other non-current assets	749	842
TOTAL ASSETS	$ 91,566	$ 109,926
LIABILITIES AND STOCKHOLDERS' EQUITY		
CURRENT LIABILITIES		
Accounts payable	$ 4,178	$ 3,319
Operating lease liabilities	587	436
Deferred revenue	505	2,359
Accrued and other current liabilities	12,408	14,030
Total current liabilities	17,678	20,144
Non-current operating lease liabilities	4,159	4,608
Deferred revenue, net of current portion	2,174	1,217
Other non-current liabilities	—	16
TOTAL LIABILITIES	24,011	25,985
Commitments and Contingencies (Note 7)		
STOCKHOLDERS' EQUITY		
Preferred stock, $0.0001 par value; 10,000,000 shares authorized as of September 30, 2022 and December 31, 2021; no shares issued and outstanding as of September 30, 2022 and December 31, 2021	—	—
Common stock, $0.0001 par value; 500,000,000 shares authorized as of September 30, 2022 and December 31, 2021; 61,511,078 shares and 49,355,130 shares issued and outstanding as of September 30, 2022 and December 31, 2021, respectively	6	5
Additional paid-in capital	474,535	425,765
Accumulated other comprehensive loss	(184)	(20)
Accumulated deficit	(406,802)	(341,809)
TOTAL STOCKHOLDERS' EQUITY	67,555	83,941
TOTAL LIABILITIES AND STOCKHOLDERS' EQUITY	$ 91,566	$ 109,926

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 September 30,		Nine Months Ended September 30,	
	2022	2021	2022	2021
Revenue:				
License	$ —	$ —	$ —	$ 12,000
Development fee	174	1,399	2,161	3,095
Total revenue	174	1,399	2,161	15,095
Operating expenses:				
Research and development	11,977	14,853	44,328	40,287
General and administrative	6,952	6,839	23,452	20,015
Total operating expenses	18,929	21,692	67,780	60,302
Loss from operations	(18,755)	(20,293)	(65,619)	(45,207)
Other income (expense):				
Interest income	288	36	427	77
Other income (expense), net	24	(24)	25	(107)
Total other income (expense)	312	12	452	(30)
Loss before income tax expense	(18,443)	(20,281)	(65,167)	(45,237)
Income tax benefit (expense)	209	(26)	174	(118)
Net loss	$ (18,234)	$ (20,307)	$ (64,993)	$ (45,355)
Net loss per share, basic and diluted	$ (0.19)	$ (0.31)	$ (0.81)	$ (0.69)
Weighted-average common shares outstanding, basic and diluted	94,197,958	65,789,449	80,574,683	65,675,915

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 September 30,		Nine Months Ended September 30,	
	2022	2021	2022	2021
Net loss	$ (18,234)	$ (20,307)	$ (64,993)	$ (45,355)
Other comprehensive income (loss):				
Foreign currency translation adjustment	(38)	(10)	(87)	(4)
Unrealized gain (loss) on marketable securities	74	1	(77)	(5)
Total comprehensive loss	$ (18,198)	$ (20,316)	$ (65,157)	$ (45,364)

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 and Nine Months Ended September 30, 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
Issuance of common stock and pre-funded warrants in connection with registered direct offering, net of offering costs	10,753	1	42,872	—	—	42,873
Issuance of common stock in connection with exercise of pre-funded warrants	1,000	—	—	—	—	—
Stock-based compensation expense	—	—	2,017	—	—	2,017
Foreign currency translation adjustment	—	—	—	(36)	—	(36)
Unrealized loss on marketable securities	—	—	—	(31)	—	(31)
Net loss	—	—	—	—	(22,323)	(22,323)
Balances - June 30, 2022	61,173	$ 6	$ 472,939	$ (220)	$ (388,568)	$ 84,157
Issuance of common stock in connection with exercise of pre-funded warrants	251	—	—	—	—	—
Issuance of common stock in connection with registered direct offering, net of offering costs	—	—	(8)	—	—	(8)
Issuance of common stock in connection with employee stock purchase plan	87		38			38
Stock-based compensation expense	—	—	1,566	—	—	1,566
Foreign currency translation adjustment	—	—	—	(38)	—	(38)
Unrealized gain on marketable securities	—	—	—	74	—	74
Net loss	—	—	—	—	(18,234)	(18,234)
Balances - September 30, 2022	61,511	$ 6	$ 474,535	$ (184)	$ (406,802)	$ 67,555

	Three and Nine Months Ended September 30, 2021					
	Common Stock		Additional Paid-In Capital	Accumulated Other Comprehensive Income (Loss)	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount				
Balances - December 31, 2020	47,959	$ 5	$ 415,824	$ 11	$ (276,008)	$ 139,832
Issuance of common stock in connection with employee stock purchase plan	38	—	224	—	—	224
Issuance of common stock in connection with exercise of stock options	23	—	146	—	—	146
Issuance of common stock in connection with exercise of pre-funded warrants	1,000	—	—	—	—	—
Stock-based compensation expense	—	—	1,757	—	—	1,757
Foreign currency translation adjustment	—	—	—	4	—	4
Unrealized gain on marketable securities	—	—	—	10	—	10
Net loss	—	—	—	—	(18,218)	(18,218)
Balances - March 31, 2021	49,020	$ 5	$ 417,951	$ 25	$ (294,226)	$ 123,755
Issuance of common stock in connection with exercise of stock options	6	—	33	—	—	33
Stock-based compensation expense	—	—	2,080	—	—	2,080
Foreign currency translation adjustment	—	—	—	2	—	2
Unrealized loss on marketable securities	—	—	—	(16)	—	(16)
Net loss	—	—	—	—	(6,830)	(6,830)
Balances - June 30, 2021	49,026	$ 5	$ 420,064	$ 11	$ (301,056)	$ 119,024
Issuance of common stock in connection with employee stock purchase plan	45	—	230	—	—	230
Issuance of common stock in connection with exercise of stock options	235	—	1,036	—	—	1,036
Stock-based compensation expense	—	—	2,107	—	—	2,107
Foreign currency translation adjustment	—	—	—	(10)	—	(10)
Unrealized gain on marketable securities	—	—	—	1	—	1
Net loss	—	—	—	—	(20,307)	(20,307)
Balances - September 30, 2021	49,306	$ 5	$ 423,437	$ 2	$ (321,363)	$ 102,081

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)

	Nine Months Ended September 30,	
	2022	**2021**
CASH FLOWS FROM OPERATING ACTIVITIES		
Net loss	$ (64,993)	$ (45,355)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	1,182	1,165
Stock-based compensation	5,684	5,944
Purchase net premium on marketable securities	351	(374)
Non-cash operating lease expense	292	334
Net amortization of premium (accretion of discount) on marketable securities	(175)	490
Other	—	2
Changes in operating assets and liabilities:		
Accounts payable	859	(390)
License and development receivables	146	—
Prepaid expenses and other assets	(2,863)	(1,555)
Accrued and other liabilities	(1,293)	(828)
Deferred revenue	(897)	6,405
Operating lease liabilities	(297)	(286)
Net cash used in operating activities	(62,004)	(34,448)
CASH FLOWS FROM INVESTING ACTIVITIES		
Purchases of property and equipment	(38)	(573)
Purchases of marketable securities	(35,000)	(119,829)
Proceeds from maturities and sales of marketable securities	78,046	88,120
Net cash provided by (used in) investing activities	43,008	(32,282)
CASH FLOWS FROM FINANCING ACTIVITIES		
Proceeds from issuance of common stock and pre-funded warrants in registered direct offering, net of offering costs	42,874	—
Proceeds from employee stock plan purchases and stock option exercises	222	1,654
Principal payments on finance lease obligation	(410)	(341)
Net cash provided by financing activities	42,686	1,313
Effect of exchange rate on cash, cash equivalents, and restricted cash	(152)	(18)
NET INCREASE (DECREASE) IN CASH, CASH EQUIVALENTS, AND RESTRICTED CASH	23,538	(65,435)
CASH, CASH EQUIVALENTS, AND RESTRICTED CASH		
Beginning of period	16,980	91,937
End of period	$ 40,518	$ 26,502
Supplemental Disclosure of Non-Cash Investing and Financing Information:		
Leased assets obtained in exchange for lease obligations	$ —	$ 872

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 redefining the potential of human enzyme therapeutics to benefit people with rare metabolic diseases with limited treatment options. 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.

Liquidity

As of September 30, 2022, the Company had working capital of $64.5 million, an accumulated deficit of $406.8 million, and cash, cash equivalents, marketable securities, and restricted cash of $75.2 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.

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.

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. Based upon the Company’s current operating plans, the Company believes that it has sufficient resources to fund operations into the fourth quarter of 2023 with its existing cash, cash equivalents, and marketable securities. Accordingly, based on its recurring losses from operations incurred since inception, the expectation of continued operating losses, and the need to raise additional capital to finance its future operations, 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 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.

Although the Company has been successful in raising capital in the past, there is no assurance that it will be successful in obtaining such additional financing on terms acceptable to the Company, if at all, nor is it considered probable under the accounting standards. If the Company is unable to obtain sufficient funding on acceptable terms, it could be forced to delay, reduce or eliminate some or all of its research and development programs or commercialization activities, which could materially adversely affect its business prospects or its ability to continue operations.

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 September 30, 2022, and its results of operations for the three and nine months ended September 30, 2022 and 2021, changes in stockholders’ equity for the three and nine months ended September 30, 2022 and 2021, and cash flows for the nine months ended September 30, 2022 and 2021. The results of operations for the three and nine months ended September 30, 2022, are not necessarily indicative of the results to be expected for the year ending December 31, 2022 or for any other future annual or interim period. The December 31, 2021 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, 2021 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, 2021 (“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 judgements 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 our 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):

	September 30, 2022			
	Level 1	Level 2	Level 3	Total
Financial Assets:				
Money market funds	$ 13,554	$ —	$ —	$ 13,554
U.S. treasury securities	999	—	—	999
Commercial paper	—	35,206	—	35,206
U.S. government securities	—	6,974	—	6,974
Corporate bonds	—	3,974	—	3,974
Total financial assets	$ 14,553	$ 46,154	$ —	$ 60,707

	December 31, 2021			
	Level 1	Level 2	Level 3	Total
Financial Assets:				
Money market funds	$ 8,888	$ —	$ —	$ 8,888
Commercial paper	—	65,412	—	65,412
Corporate bonds	—	12,574	—	12,574
Total financial assets	$ 8,888	$ 77,986	$ —	$ 86,874

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):

	September 30, 2022			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Cash equivalents:				
Money market funds	$ 13,554	$ —	$ —	$ 13,554
U.S. government securities	6,974	—	—	6,974
Commercial paper	5,492	—	—	5,492
Total cash equivalents	26,020	—	—	26,020
Marketable securities:				
Commercial paper	29,809	—	(95)	29,714
Corporate bonds	3,993	—	(19)	3,974
U.S. treasury securities	1,001	—	(2)	999
Total marketable securities	$ 34,803	$ —	$ (116)	$ 34,687

	December 31, 2021			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Cash equivalents:				
Money market funds	$ 8,888	$ —	$ —	$ 8,888
Commercial paper	—	—	—	—
Total cash equivalents	8,888	—	—	8,888
Marketable securities:				
Commercial paper	65,443	3	(34)	65,412
Corporate bonds	12,581	—	(7)	12,574
Total marketable securities	$ 78,024	$ 3	$ (41)	$ 77,986

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 September 30, 2022 and December 31, 2021, aggregated by major security type and length of time in a continuous unrealized loss position:

	September 30, 2022					
	Less Than 12 Months		12 Months or Longer		Total	
	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses
Commercial paper	$ 30,960	$ (95)	$ —	$ —	$30,960	$ (95)
Corporate bonds	3,974	(19)	—	—	3,974	(19)
U.S. treasury securities	999	(2)	—	—	999	(2)
Total marketable securities	$ 35,933	$ (116)	$ —	$ —	$35,933	$ (116)

	December 31, 2021					
	Less Than 12 Months		12 Months or Longer		Total	
	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses
Commercial paper	$ 47,425	$ (34)	$ —	$ —	$47,425	$ (34)
Corporate bonds	12,573	(7)	—	—	12,573	(7)
Total marketable securities	$ 59,998	$ (41)	$ —	$ —	$59,998	$ (41)

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 September 30, 2022 and December 31, 2021, an allowance for credit losses had not been recognized. Given our intent and ability to hold such securities until recovery, and the lack of significant change in credit risk of these investments, we do not consider these marketable securities to be impaired as of September 30, 2022 and December 31, 2021.

There were no realized gains or losses on marketable securities for the three and nine months ended September 30, 2022 and 2021. Interest on marketable securities is included in interest income. Accrued interest receivable on available-for-sale debt securities was immaterial at September 30, 2022. Accrued interest totaled $0.1 million at December 31, 2021 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):

	September 30, 2022	December 31, 2021
Due in one year or less	$ 34,687	$ 77,986
Due thereafter	—	—
Total marketable securities	$ 34,687	$ 77,986

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):

	September 30, 2022	December 31, 2021
Accrued compensation	$ 4,690	$ 4,988
Accrued contracted research and development costs	5,842	5,995
Accrued professional and consulting fees	1,514	2,264
Other	362	783
Total accrued and other current liabilities	$ 12,408	$ 14,030

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 September 30, 2022, 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	17,120,800
Total pre-funded warrants			32,731,128

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, 2022 and January 1, 2021, an additional 1,974,205 and 1,918,363 shares, respectively, became available for issuance under the 2016 Plan.

As of September 30, 2022, the 2016 Plan had 1,182,245 shares available for future issuance.

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

	Three Months Ended September 30,				Nine Months Ended September 30, 2022			
	2022		2021		2022		2021	
	Grants	Weighted Average Grant Date Fair Value	Grants	Weighted Average Grant Date Fair Value	Grants	Weighted Average Grant Date Fair Value	Grants	Weighted Average Grant Date Fair Value
Stock options	1,270,153	$ 0.67	396,200	$ 4.91	3,842,153	$ 2.10	2,557,600	$ 5.05

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 September 30, 2022, 150,000 of these RSUs are outstanding. As of September 30, 2022 and 2021, respectively, the performance conditions of these RSUs were not probable of being achieved. If and when the performance milestones are deemed probable of being achieved within the required time frame, the Company may recognize up to $1.2 million of stock-based compensation.

Under the Company's 2016 Employee Stock Purchase Plan ("2016 ESPP"), the Company issued and sold 87,087 shares for aggregate cash proceeds of less than $0.1 million during the three months ended September 30, 2022 and 151,827 shares for aggregate cash proceeds of $0.2 million during the nine months ended September 30, 2022. There were 44,957 shares issued and sold under the 2016 ESPP for aggregate cash proceeds of $0.2 million during the three months ended September 30, 2021 and 82,965 shares for aggregate cash proceeds of $0.4 million during the nine months ended September 30, 2021.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2022	2021	2022	2021
Research and development	$ 639	$ 703	$ 2,031	$ 2,057
General and administrative	926	1,404	3,653	3,887
Total stock-based compensation expense	$ 1,565	$ 2,107	$ 5,684	$ 5,944

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 September 30,		Nine Months Ended September 30,	
	2022	2021	2022	2021
2016 Plan				
Expected term (in years)	6.02	6.08	5.96	5.99
Expected volatility	85%	82%	83%	83%
Risk-free interest	3.16%	0.95%	2.43%	0.84%
Dividend yield	—	—	—	—
2016 ESPP				
Expected term (in years)	0.50	0.50	0.49	0.50
Expected volatility	95%	77%	84%	86%
Risk-free interest	3.26	0.08%	1.95%	0.08%
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 $113.4 million in regulatory and commercial milestone payments, assuming an exchange rate of $0.98 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 ongoing 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 and nine months ended September 30, 2022, the Company recognized revenue of $0.2 million and $2.2 million, under the Immedica Agreement related to the progress in the PEACE Trial and BLA package performance. For the three and nine months ended September 30, 2021, the Company recognized revenue of $1.4 million and $3.1 million, respectively, related to the PEACE Trial and BLA package performance obligation. For the three and nine months ended September 30, 2021, the Company recognized no revenue and $12.0 million, respectively, related to the transfer of

the License. As of September 30, 2022, and 2021, the Company has recorded deferred revenue of $2.7 million and $6.4 million, respectively, associated with the license and supply agreement with Immedica, of which $0.5 million and $4.8 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):

Nine Months Ended September 30, 2022	December 31, 2021	Additions	Deductions	September 30, 2022
Contract liabilities:				
Deferred revenue	$ 3,576	$ 1,264	$ (2,161)	$ 2,679

The Company had no contract liabilities during the nine months ended September 30, 2021 and no contract assets during the nine months ended September 30, 2022 and 2021.

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 September 30,		Nine Months Ended September 30,	
	2022	2021	2022	2021
Options to purchase common stock	8,788,325	7,066,486	8,384,866	6,650,758
Unvested restricted stock units	150,000	194,435	182,879	202,540

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, 2021 filed with the Securities and Exchange Commission, or the SEC, on March 8, 2022. 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 redefining the potential of human enzyme therapeutics to benefit people with rare metabolic diseases with limited treatment options. We believe our expertise in enzyme science, bioengineering and rare disease drug development coupled with an approach focused on diseases with unmet medical needs enables us to develop medicines with the potential to transform the lives of patients and families with rare metabolic diseases.

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

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

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

Our product candidate, pegtarviliase, previously referred to as AGLE-177, is a novel PEGylated, or polyethylene glycol modified, human enzyme engineered to degrade free homocysteine and homocystine in patients with Homocystinuria, a serious rare metabolic disorder characterized by elevated plasma homocysteine which leads to a wide range of life-altering complications and reduced life expectancy. We engineered pegtarviliase by directed mutagenesis of amino acids within cystathionine γ-lyase, resulting in a molecule that has high substrate specificity for homocysteine and homocystine but not for the native substrate, cystathionine. Classical Homocystinuria, or Homocystinuria due to cystathionine β-synthase, or CBS, enzyme deficiency is the most common form of an inherited disorder of methionine metabolism that results in elevated homocysteine and homocystine. We believe pegtarviliase may reduce the adverse impact of CBS enzyme deficiency in the transsulfuration pathway by providing an alternate pathway for enzymatic degradation of high plasma total homocysteine levels. We are currently conducting a Phase 1/2 clinical trial for the treatment of patients with Classical Homocystinuria.

Our most advanced product candidate, pegzilarginase, is a recombinant human arginase 1 that is engineered to enzymatically degrade the amino acid arginine to lower arginine levels in patients with Arginase 1 Deficiency. We engineered pegzilarginase with modifications that enhance the stability and arginine-degrading activity of the enzyme in human plasma. For Arginase 1 Deficiency, which is a rare progressive disease, that presents in early childhood and results in severe complications and early mortality, we believe pegzilarginase may reduce the harmful metabolic effects caused by the accumulation of high levels of arginine and other arginine-derived metabolites. We are continuing to evaluate pegzilarginase in an open-label extension of our PEACE (Pegzilarginase Effect on Arginase 1 Deficiency Clinical Endpoints) Phase 3 trial and a Phase 2 open-label trial. Our intent is to discontinue these ongoing open-label studies and transition the patients in these trials to a single open-label study.

Our third program, AGLE-325 for Cystinuria, is in preclinical development and ongoing IND-enabling activities. 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 an amino acid transporter that leads to increased amounts of cystine in the urine. This results in high cystine concentrations in the urine and formation of kidney stones. As such, we engineered our Cystinuria program candidate to reduce plasma cystine and cysteine levels with accompanying reductions in urine cystine concentrations as an approach to inhibit both cystine crystal and kidney stone formation. While some IND-enabling activities continue, production of current good manufacturing practices, drug supply and other activities have been postponed pending availability of raw materials and additional capital resources.

We have incurred net losses in each year since inception. Our net losses were $65.0 million and $45.4 million for the nine months ended September 30, 2022 and 2021, 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 September 30, 2022, we had an accumulated deficit of $406.8 million. We anticipate that our expenses will increase as we continue our clinical development activities for our product candidates and prepare for the potential commercialization of our most advanced product candidate, pegzilarginase; concurrently develop our pipeline product candidates; expand and protect our intellectual property portfolio; hire additional personnel; and continue to operate as a public company. Accordingly, based on recurring losses from operations incurred since inception, the expectation of continued operating losses, and the need to raise additional capital to finance our future operations, we determined that there is substantial doubt about our ability to continue as a going concern within one year after the date that the financial statements included herein are issued.

Recent Developments

The following summarizes our most advanced product candidates, each of which is described in further detail below.

Pegtarviliase in Patients with Homocystinuria

We are currently conducting 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 patients with Classical Homocystinuria. As a secondary objective, the trial will also characterize the pharmacokinetics and pharmacodynamics relationship of pegtarviliase after single and multiple doses following intravenous and subcutaneous administration, as well as the magnitude of change in plasma total homocysteine, or tHcy.

We plan to enroll 16 to 20 patients diagnosed with Classical Homocystinuria, aged 12 years or older in the United Kingdom and Australia and aged 18 years or older in the United States with plasma homocysteine levels greater than 80 µM. Patients will be dosed once weekly for four weeks, with four patients planned in each of the four dosing cohorts and an option to include a fifth cohort as needed.

In October 2022, we announced that we are currently dosing patients in the third cohort of the Phase 1/2 clinical trial at a dose level of 1.35 mg/kg delivered subcutaneously. Further, in October 2022, we received a letter from the FDA regarding our recently submitted protocol amendment for the Phase 1/2 clinical trial of pegtarviliase for the treatment of Classical Homocystinuria. The protocol amendment, among other things, requested 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 at this time. We intend to address the feedback from the FDA and aim to satisfy the requirements for prospective benefit for future inclusion of pediatric patients under the investigational new drug, including in a potential pivotal trial. The partial clinical hold only applies to the investigational new drug with the FDA, and we believe that the letter should not impact the planned enrollment and dosing of patients aged 18 years and older in the United States or patients aged 12 years and older in the United Kingdom and Australia. In March 2022, we announced that data from the 0.15 mg/kg intravenous cohort showed that pegtarviliase was well tolerated with no safety concerns and reductions in total homocysteine were seen in all patients. We expect to report initial clinical data from the Phase 1/2 trial in the fourth quarter of 2022, including data from the third cohort.

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 a Rare Pediatric Disease designation for pegtarviliase for the treatment of Homocystinuria. This designation by the FDA enables the potential to receive a Rare Pediatric Disease priority review voucher upon approval of a qualifying BLA for pegtarviliase if approved before October 1, 2026.

Given recent developments relating to the COVID-19 pandemic, we have been taking steps to minimize potential impacts of COVID-19 related disruptions on our Phase 1/2 clinical trial. We currently have sufficient supply available for completion of our ongoing clinical trials. Patient screening and dosing have been impacted by COVID-19, and there is uncertainty as to the cadence of screenings as sites are impacted by COVID-19 related restrictions, including staff members contracting COVID-19 and limiting operations.

Pegzilarginase in Patients with Arginase 1 Deficiency

Pegzilarginase is 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. We announced the topline data from the double-blind placebo-controlled portion of our PEACE Phase 3 trial in December 2021 and are currently conducting a long-term extension study to evaluate the safety and efficacy of pegzilarginase. In April 2022 and August 2022, we announced additional data from our ongoing 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.
- In an analysis of individual patients that were Gross Motor Function Classification System (GMFCS) Level I-III with predefined clinical response criteria there were clinically important differences between the pegzilarginase treated patients (n=17) and the placebo arm (n=9).

    - Eleven pegzilarginase treated patients (65%) reached or exceeded prespecified response criteria for at least one mobility assessment compared to four patients (44%) in the placebo arm.
    - Eight pegzilarginase treated patients (47%) met or exceeded prespecified clinical response criteria for at least two of the mobility outcomes compared to no patients in the placebo arm.
- Six of the pegzilarginase treated patients reaching the clinical response threshold for at least two mobility outcomes also showed no worsening on any other endpoints.
- In a post hoc analysis correcting for a missed assessment that was improperly scored as 0 rather than “not assessed,” the least squares mean Gross Motor Function Measure Part D score improved from baseline by 2.25 units compared to the placebo arm (p=0.0896).
- Pegzilarginase treated patients also showed statistically significant biochemical improvements in measures of ornithine and guanidino compounds compared to the placebo arm, consistent with the pegzilarginase mechanism of action.

Regulatory: On February 28, 2022, we participated in a Type B Guidance – Breakthrough Therapy Meeting, or the “February Meeting” with the U.S. Food and drug Administration, or FDA, regarding our product candidate, pegzilarginase. In the minutes of the February Meeting, the FDA noted that while the data presented in the PEACE Phase 3 trial overall appeared promising and hypothesis-generating, it disagreed that the efficacy results provide substantial evidence of effectiveness for pegzilarginase. The FDA reiterated the need to generate evidence of effectiveness of the product candidate through an additional randomized placebo-controlled trial of a duration longer than 24 weeks given that efficacy data based on effort-dependent clinical outcome assessments and related endpoints have a high potential for bias and that the Biologics License Application, or BLA, submission was not reasonable at this time.

In April 2022, we announced that after careful consideration and further review of the efficacy and safety data from the ongoing PEACE Phase 3 trial, including the updated efficacy data from that trial and long-term safety data from the pegzilarginase program, we submitted a BLA to the FDA in order to provide all the study results for the FDA to review in detail.

On June 2, 2022, we announced that we received a Refusal to File, or 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 (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 continue to engage in dialogue with the FDA to identify a viable regulatory approach and path to BLA resubmission.

In August 2022, we announced that the European Medicines Agency, or EMA, had validated the Marketing Authorization Application, or MAA, for pegzilarginase for the treatment of Arginase 1 Deficiency that was submitted by Immedica, our commercialization partner in certain countries in Europe and the Middle East.

We have obtained Orphan Drug Designation from the FDA and the European Medicines Agency, or 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. This designation by the FDA confirms our eligibility to receive a Rare Pediatric Disease priority review voucher upon approval of a qualifying BLA for pegzilarginase if 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 $113.4 million in regulatory and commercial milestone payments, assuming an exchange rate of $0.98 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. 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 our BLA package performance obligations. We will continue to be responsible for certain clinical development activities and the manufacturing of pegzilarginase and will retain commercialization rights in the United States and the rest of the world. We reported in August

2022, that an MMA for pegzilarginase for the treatment of Arginase 1 Deficiency was submitted by Immedica to and validated by the EMA.

For the three and nine months ended September 30, 2022, we recognized revenue of $0.2 million and $2.2 million, respectively, 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 and nine months ended September 30, 2021, we recognized $1.4 million and $3.1 million, respectively relating to the PEACE Phase 3 trial and BLA package performance. For the three and nine months ended September 30, 2021, we recognized no revenue and $12.0 million, respectively, related to the transfer of the license.

AGLE-325 in Cystinuria

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 and consequently, 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. Given the compelling preclinical data and the limitations of current disease management approaches, we have advanced AGLE-325 into IND-enabling activities. While some IND-enabling activities continue, production of current good manufacturing practices, or cGMP, drug supply and other activities have been postponed pending availability of raw materials and additional capital resources.

Registered Direct Offering

In May 2022, we issued and sold 10,752,688 shares of common stock at an offering price of $1.60 per share and prefunded warrants to purchase 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 us from this offering were approximately $42.9 million, after deducting placement agent fees and offering costs of $2.1 million.

Corporate

In August 2022, we announced a corporate restructuring including a headcount reduction. James Kastenmayer, our General Counsel and Corporate Secretary, succeeded Dr. Anthony Quinn as Interim Chief Executive Officer. In addition, Michael Hanley was appointed Chief Business Officer. Mr. Hanley previously served as our Chief Commercial Officer.

COVID -19 Pandemic

The extent of the impact of COVID-19 and its variants on our operational and financial performance will continue to depend on certain developments, including the duration and spread of the outbreak, new variants, the vaccination and booster rate, impact on our clinical studies, employee or industry events, and effect on our suppliers and manufacturers, all of which are uncertain and cannot be predicted. The COVID-19 pandemic and its adverse effects have been prevalent in many of the locations where we, our CROs, suppliers or third-party business partners conduct business and as a result, we have experienced disruptions and may continue to experience more pronounced disruptions in our operations. With respect to our clinical trials, we have had patients miss scheduled dosings and experienced delays in enrollment. We may continue to experience such delays as well as delays in distribution of clinical trial materials, study monitoring and data analysis that could materially adversely impact our business, results of operations and overall financial performance in future periods. Specifically, we have experienced and expect to continue to experience impact from changes in how we and companies worldwide conduct business due to the COVID-19 pandemic, including but not limited to restrictions on travel and in-person meetings, disruptions in the supply chain including the raw materials needed for manufacturing, animals used in research, delays in site activations and enrollment of clinical trials, and prioritization of hospital resources toward pandemic effort. We may also experience delays in review by the FDA and comparable foreign regulatory agencies for our product candidates. As of the filing date of this Form 10-Q, the extent to which COVID-19 may impact our financial condition, results of operations or guidance is uncertain. The effect of the COVID-19 pandemic may not be fully reflected in our results of operations and overall financial performance until future periods. See Risk Factors for further discussion of the possible impact of the COVID-19 pandemic on our business.

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, 2021.

Results of Operations

Comparison of the Three Months Ended September 30, 2022 and 2021

The following table summarizes our results of operations for the three months ended September 30, 2022, and 2021, together with the changes in those items in dollars and as a percentage:

	Three Months Ended September 30,		Dollar Change	% Change
	2022	2021		
	(dollars in thousands)			
Revenue:				
Development fee	$ 174	$ 1,399	$ (1,225)	88%
Total revenue	174	1,399	(1,225)	88%
Operating expenses:				
Research and development	11,977	14,853	(2,876)	19%
General and administrative	6,952	6,839	113	2%
Total operating expenses	18,929	21,692	(2,763)	13%
Loss from operations	(18,755)	(20,293)	1,538	8%
Interest income	288	36	252	*
Other (expense) income, net	24	(24)	48	*
Loss before income tax expense	(18,443)	(20,281)	1,838	9%
Income tax benefit (expense)	209	(26)	235	*
Net loss	$ (18,234)	$ (20,307)	$ 2,073	10%

* Percentage not meaningful

Development Revenue. For the three months ended September 30, 2022, we recognized $0.2 million of development fee revenue in connection with the Immedica Agreement. The total revenue generated of $0.2 million was attributable to the PEACE Phase 3 trial and BLA package. For the three months ended September 30, 2021, 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 $2.9 million, or 19%, to $12.0 million for the three months ended September 30, 2022, from $14.9 million for the three months ended September 30, 2021. The change in research and development expenses was primarily due to:

- a $1.2 million decrease in expense associated with the PEACE Phase 3 trial of pegzilarginase for the treatment of patients with Arginase 1 Deficiency;
- a $1.0 million decrease related to cGMP production, equipment and readiness expenses in the prior year associated with pegtarviliase for the treatment of patients with Homocystinuria; and
- a $0.8 million decrease in corporate related research and development expenses, primarily due to a reduction in external professional services and change in headcount.

General and Administrative Expenses. General and administrative expenses increased by $0.1 million, or 2%, to $7.0 million for the three months ended September 30, 2022, from $6.8 million for the three months ended September 30, 2021. The increase in general and administrative expenses was due to a $0.2 million increase in compensation and other personnel expenses associated with severance pay and benefits, and a $0.1 million decrease related to our commercial expenses.

Results of Operations

Comparison of the Nine Months Ended September 30, 2022 and 2021

The following table summarizes our results of operations for the nine months ended September 30, 2022, and 2021, together with the changes in those items in dollars and as a percentage:

	Nine Months Ended September 30,		Dollar Change	% Change
	2022	2021		
	(dollars in thousands)			
Revenue:				
License revenue	$ —	$ 12,000	$ (12,000)	*
Development fee	2,161	3,095	(934)	30%
Total revenue	2,161	15,095	(12,934)	86%
Operating expenses:				
Research and development	44,328	40,287	4,041	10%
General and administrative	23,452	20,015	3,437	17%
Total operating expenses	67,780	60,302	7,478	12%
Loss from operations	(65,619)	(45,207)	(20,412)	45%
Interest income	427	77	350	*
Other expense, net	25	(107)	132	123%
Loss before income tax expense	(65,167)	(45,237)	(19,930)	44%
Income tax benefit (expense)	174	(118)	292	*
Net loss	$ (64,993)	$ (45,355)	$ (19,638)	43%

* Percentage not meaningful

License and Development Revenue. For the nine months ended September 30, 2022, we recognized $2.2 million of development fee revenue in connection with the Immedica Agreement. The total revenue generated of $2.2 million was attributable to the PEACE Phase 3 trial and BLA package. For the nine months ended September 30, 2021, we recognized $15.1 million of license and development revenue in connection with the Immedica Agreement. The total revenue generated of $15.1 million was attributable to $12.0 million allocated to the license and $3.1 million allocated to the PEACE Phase 3 trial and BLA package.

Research and Development Expenses. Research and development expenses increased by $4.0 million, or 10%, to $44.3 million for the nine months ended September 30, 2022, from $40.3 million for the nine months ended September 30, 2021. The change in research and development expenses was due to:

- a $2.8 million increase to support our BLA submission and launch activities for pegzilarginase, partially offset by a $0.6 million decrease related to the reduction of Phase 1/2 activities for pegzilarginase for the treatment of patients with Arginase 1 Deficiency;
- a $2.6 million increase in expense associated with IND-enabling activities of AGLE-325 for the treatment of patients with Cystinuria;
- a $1.3 million decrease in expenses associated with the completion of non-clinical toxicology studies in the prior year for pegtarviliase for the treatment of patients with Homocystinuria;
- a $0.4 million decrease due to a reduction in preclinical lab work; and
- higher personnel-related expenses, which increased by $1.5 million as a result of changes to employee headcount and additional compensation to support our clinical and research development capabilities.

General and Administrative Expenses. General and administrative expenses increased by $3.4 million, or 17%, to $23.5 million for the nine months ended September 30, 2022, from $20.0 million for the nine months ended September 30, 2021. The increase in general and administrative expenses was primarily due to a $2.1 million increase in commercial development expenses, and to a $1.3 million increase in compensation and other personnel expenses, including a $0.2 million decrease in non-cash stock compensation.

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 September 30, 2022, 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 stock 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 $113.4 million in regulatory and commercial milestone payments, assuming an exchange rate of $0.98 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.

During the year ended December 31, 2020, we raised $163.3 million of gross proceeds through an underwritten public offering and an at-the-market offering program. We sold 15,442,303 shares of common stock and pre-funded warrants to purchase up to 13,610,328 shares of common stock in an underwritten public offering, or the 2020 Public Offering, for gross proceeds of $138.0 million, resulting in net proceeds of $129.0 million after deducting underwriting discounts, commissions, and offering costs. Additionally, we sold an aggregate of 3,245,077 shares of common stock under an at-the-market offering program, or the 2020 ATM, for gross proceeds of $25.3 million, resulting in net proceeds of $24.6 million, after deducting underwriting discounts, commissions, and offering costs.

The shares of common stock and pre-funded warrants sold in the 2020 Public Offering were offered pursuant to a shelf registration statement on Form S-3, or the 2019 Registration Statement, declared effective in February 2019 by the SEC for the potential offering, issuance and sale by us of up to $200.0 million of our common stock, warrants to purchase common stock, and other security types and subscription rights. The shares of common stock sold under the 2020 ATM were offered under the 2019 Registration Statement and pursuant to an April 2020 sales agreement, or the Sales Agreement, with Jones Trading Institutional Services LLC, as sales agent, to issue and sell shares of our common stock for an aggregate offering price of $60.0 million. In February 2022, the 2019 Registration Statement and Sales Agreement expired and, as such, no further sales will be made pursuant to the Sales Agreement.

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, pursuant to the 2019 Registration Statement. 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.

Our primary use of cash is to fund the development of our product candidates pegzilarginase and pegtarviliase, prepare for the potential commercialization of our most advanced product candidate, pegzilarginase, and advance our pipeline. This includes both the research and development costs and the general and administrative expenses required to support those operations. Since we are a clinical-stage biotechnology company, we have incurred significant operating losses since our inception and we anticipate such losses, in absolute dollar terms, to increase as we continue clinical

development of our product candidates, prepare for the potential commercialization of pegzilarginase, and expand our development efforts in our pipeline of clinical and nonclinical candidates.

Future funding requirements and operational plan

Our operational plan for the near future is to continue regulatory work and an open-label trial for pegzilarginase in Arginase 1 Deficiency and continue clinical development for pegtarviliase for the treatment of Homocystinuria, prepare for the potential commercialization of pegzilarginase, and continue certain early development activities for AGLE-325 for Cystinuria As such, we plan to focus our research and development expenditures and general and administrative expenditures on nonclinical studies, clinical trials, manufacturing, and commercial development. We expect our principal expenditures during this time period to include expenses for the following:

- funding the continuing development of pegzilarginase and pegtarviliase;
- funding the establishment of commercial operations;
- funding the discovery and advancement of additional product candidates; 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 $406.8 million as of September 30, 2022. We anticipate that we will continue to generate losses into the foreseeable future as we develop our product candidates, seek regulatory approval of those candidates and begin to commercialize any approved products. Until such time as we can generate substantial product revenue, we expect to finance our cash needs through a combination of equity or debt financings, research grants, collaborations, license and development agreements, or other sources. We currently have no debt, credit facility or additional committed capital. To the extent that we raise additional equity, the ownership interest of our stockholders will be diluted.

Based on our available cash, cash equivalents, marketable securities, and restricted cash of $75.2 million as of September 30, 2022, we believe that we have sufficient resources to fund our operations into the fourth quarter of 2023. We estimate such funds will be sufficient for us to (i) fund our two ongoing extension studies for patients with Arginase 1 Deficiency through completion and transition the patients in these trials to a single open-label study, (ii) advance the clinical development of pegtarviliase through our Phase 1/2 clinical trial and prepare for a potential Phase 3 trial for the treatment of patients with Classical Homocystinuria, and (iii) to continue certain early development activities for AGLE-325. Accordingly, based on recurring losses from operations incurred since inception, the expectation of continued operating losses, and the need to raise additional capital to finance our future operations, we determined that there is substantial doubt about our ability to continue as a going concern within one year after the date that the financial statements included herein are issued. As a result, in order to continue to operate our business beyond that time, we will need to raise additional funds. However, there can be no assurance that we will be able to generate funds on terms acceptable to us, on a timely basis, or at all. In addition, we have based this estimate on assumptions that may prove to be wrong, and we could deplete our capital resources sooner than we currently anticipate.

Cash flows

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

	Nine Months Ended September 30,	
	2022	2021
Net cash, cash equivalents, and restricted cash (used in) provided by:		
Operating activities	$ (62,004)	$ (34,448)
Investing activities	43,008	(32,282)
Financing activities	42,686	1,313
Effect of exchange rate on cash, cash equivalents, and restricted cash	(152)	(18)
Net increase (decrease) in cash, cash equivalents, and restricted cash	$ 23,538	$ (65,435)

Cash used in operating activities

Cash used in operating activities for the nine months ended September 30, 2022, was $62.0 million and reflected a net loss of $65.0 million. Our net loss was offset in part by non-cash expenses of $5.7 million for stock-based compensation, $1.2 million for depreciation and amortization, and $0.3 million for operating lease expense. The net change in operating assets and liabilities of $4.3 million was primarily related to a $2.9 million increase in prepaid and other current assets, a $1.3 million decrease in accrued and other liabilities.

Cash used in operating activities for the nine months ended September 30, 2021 was $34.4 million and reflected a net loss of $45.4 million. Our net loss was offset in part by a non-cash expense of $5.9 million for stock-based compensation, $1.2 million for depreciation and amortization, and $0.3 million for operating lease expense. The net change in operating assets and liabilities of $3.3 million was primarily related to a $6.4 million increase in deferred revenue due to receiving a $21.5 million upfront payment under the Immedica Agreement offset by the recognition of revenue allocated to the license, PEACE Phase 3 trial and BLA filing. Additional offset included a $1.6 million increase in prepaid expenses and other assets due to advance payment for the Phase 1/2 trial of pegtarviliase and a $1.2 million decrease in accrued liabilities and accounts payable due to payments for pre-commercial manufacturing and compensation costs.

Cash provided by (used in) investing activities

Cash provided by investing activities for the nine months ended September 30, 2022 was $43.0 million and consisted of $78.0 million in maturities and sales of marketable securities, offset by $35.0 million in purchases of marketable securities.

Cash used in investing activities for the nine months ended September 30, 2021, was $32.3 million and consisted of $119.8 million in purchases of marketable securities and $0.6 million in purchases of property and equipment, offset by $88.1 million in maturities of marketable securities.

Cash provided by financing activities

Cash provided by financing activities for the nine months ended September 30, 2022, was $42.7 million, which consisted of $45.0 million from the registered direct offering of our common stock and pre-funded warrants in May 2022, offset by $2.1 million of placement agent fees and offering costs, and $0.2 million sale of common stock under our 2016 Employee Stock Purchase Plan, offset by $0.4 million in principal payments made on our finance lease obligations.

Cash provided by financing activities for the nine months ended September 30, 2021, was $1.3 million, which consisted of $1.7 million in stock option exercises and sale of common stock under our 2016 Employee Stock Purchase Plan, offset by $0.3 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 $6.3 million. See Note 7, “Leases,” included in our Annual Report on Form 10-K for the year ended December 31, 2021, 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 September 30, 2022, we held $75.2 million in cash, 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 nine months ended September 30, 2022, 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 September 30, 2022, 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 September 30, 2022, 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. You should carefully consider the risks and uncertainties described below, together with all of the other information in this quarterly report on Form 10-Q, including our consolidated financial statements and related notes and "Management's Discussion and Analysis of Financial Condition and Results of Operations," before investing in our common stock. 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.

Summary Risk Factors

Our business is subject to a number of risks and uncertainties, including those highlighted in the section titled "Risk Factors" immediately following this summary. Some of these risks are:

- *We and our independent auditors have expressed doubt about our ability to continue as a going concern.*
- *We will need substantial additional funding. If we are unable to raise capital when needed, we would be compelled to delay, reduce or eliminate our product development programs or commercialization efforts.*
- *We depend heavily on the success of our most advanced product candidates, pegzilarginase and pegtarviliase. Existing and future clinical trials of our product candidates, including pegzilarginase and pegtarviliase, may not be successful. If we are unable to commercialize our product candidates or experience significant delays in doing so, our business will be materially harmed.*
- *The results from our global pivotal PEACE Phase 3 trial may not support marketing approval, and the FDA or other regulatory authorities may require us to conduct additional clinical trials or evaluate current subjects for an additional follow-up period.*
- *The outbreak of the novel strain of coronavirus, SARS-CoV-2 and its emerging variants, which causes COVID-19, has, and may continue to, adversely impact our business, including the timing of our clinical trials and supply chain interruptions.*
- *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.*
- *Our engineered human enzyme product candidates represent a novel therapeutic approach, which could result in heightened regulatory scrutiny, delays in clinical development, or delays in our ability to achieve regulatory approval or commercialization of our product candidates.*
- *We have only initiated clinical trials for pegzilarginase and pegtarviliase for the treatment of certain conditions a. We have not dosed any of our other product candidates in humans. Our existing and future planned clinical trials may reveal significant adverse events, toxicities or other side effects not seen in our nonclinical studies or early-stage clinical trials and may result in a safety profile that could inhibit regulatory approval or market acceptance of any of our product candidates.*
- *Delays or difficulties in the enrollment of patients in our ongoing or planned clinical trials could delay or prevent our receipt of necessary regulatory approvals.*
- *We contract with third parties for the manufacture of our product candidates for nonclinical studies and our ongoing and future planned clinical testing and expect to continue to do so for commercialization. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates at an acceptable cost and quality, which could delay, prevent or impair our development or commercialization efforts.*

- *If there are delays in obtaining, or we are not able to obtain, required regulatory approvals in the United States or in foreign jurisdictions, we will not be able to commercialize our product candidates, and our ability to generate revenue will be materially impaired.*
- *If we are unable to obtain and maintain intellectual property protection for our technology and product candidates, or if the scope of the intellectual property protection obtained is not sufficiently broad, our competitors could develop and commercialize technology and product candidates similar or identical to ours, and our ability to successfully commercialize our technology and product candidates may be impaired.*

Risks Related to Our Financial Position and Need for Additional Capital

We and our independent auditors have expressed doubt about our ability to continue as a going concern.

The independent registered public accounting firm auditors' report accompanying our financial statements for the year ended December 31, 2021 contained an explanatory paragraph expressing substantial doubt about our ability to continue as a going concern. 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 intend 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 partnerships could adversely affect our ability to achieve our business objectives and continue as a going concern.

Our limited operating history may make it difficult for you to evaluate the success of our business to date and to assess our future viability.

We are a clinical-stage biotechnology company. We began operations as a limited liability company in December 2013 and converted to a Delaware corporation in March 2015. Our operations to date have been limited to organizing and staffing our company, business planning, raising capital, acquiring and developing our technology, identifying potential product candidates, undertaking nonclinical studies, and preparing for, commencing and conducting clinical trials of our most advanced product candidates, pegzilarginase and pegtarviliase.

Other than the PEACE Phase 3 trial of pegzilarginase, we have not demonstrated our ability to successfully complete a pivotal clinical trial. We have not yet demonstrated our ability to successfully obtain marketing approvals, manufacture a commercial scale product or arrange for a third party to do so on our behalf other than for pegzilarginase, or conduct sales and marketing activities necessary for successful product commercialization. Products, on average, take ten to 15 years to be developed from the time they are discovered to the time they are approved and available for treating patients. Although we have recruited a team that has experience with clinical trials, as a company we have limited experience in conducting clinical trials. In part because of this limited experience, we cannot be certain that planned or ongoing clinical trials will begin or be completed on time, if at all. Consequently, any predictions you make about our future success or viability based on our short operating history to date may not be as accurate as they could be if we had a longer operating history or an established track record in commercializing products or conducting clinical trials.

In addition, as a new business, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors. We will need to transition from a company with a research focus to a company also capable of supporting commercial activities. We may not be successful in such a transition.

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 pegzilarginase and pegtarviliase, 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 nine months ended September 30, 2022, we reported a net loss of $65.0 million. For the years ended December 31, 2021 and 2020, we reported a net loss of $65.8 million and $80.9 million, respectively. As of September 30, 2022, we had an accumulated deficit of $406.8 million. Based upon our current operating plans, we believe that we have sufficient resources to fund operations into the fourth quarter of 2023 with our existing cash, cash equivalents, and marketable securities. Accordingly, based on recurring losses

from operations incurred since inception, the expectation of continued operating losses, and the need to raise additional capital to finance our future operations, we determined that there is substantial doubt about our ability to continue as a going concern within twelve months of the issuance date of these financial statements. We plan to address this condition 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 certain countries in the Middle East. We have devoted substantially all of our efforts to research and development. Currently, we are conducting clinical development for pegzilarginase for the treatment of Arginase 1 Deficiency and for pegtarviliase for the treatment of Homocystinuria. We have not initiated clinical development of our other product candidates and none of our product candidates are ready for commercialization. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future, and the net losses we incur may fluctuate significantly from quarter to quarter. We anticipate that our expenses will increase substantially if and as we:

- continue our research, nonclinical and clinical development of our product candidates;
- seek to identify additional product candidates;
- conduct additional nonclinical studies and initiate clinical trials for our product candidates;
- seek marketing approvals for any of our product candidates that successfully complete clinical trials, including pivotal trials;
- establish a sales, marketing and distribution infrastructure to commercialize any product candidates for which we may obtain marketing approval;
- maintain, expand and protect our intellectual property portfolio;
- hire additional executive, clinical, quality control and scientific personnel;
- add operational, financial and management information systems and personnel, including personnel to support our product development; and
- acquire or in-license other product candidates and technologies.

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 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 reported in April 2022 that we submitted a BLA to the FDA for pegzilarginase for the treatment of Arginase 1 Deficiency and on June 2, 2022, announced that we received a Refusal to File letter, or RTF Letter, from the FDA regarding our BLA submission. In the RTF Letter, the FDA requested additional data to support effectiveness and additional information relating to Chemistry Manufacturing and Controls. 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, we would be compelled to delay, reduce or eliminate our product development programs or commercialization efforts.

We expect our expenses to increase in parallel with our ongoing activities, particularly as we continue our research and nonclinical development to identify new clinical candidates and initiate and continue clinical trials of, and seek marketing approval for, our product candidates. In addition, if we obtain marketing approval for any of our product candidates, we

expect to incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution. 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 a U.S. federal government shutdown, or on acceptable terms, we would be forced to delay, reduce or eliminate our discovery and nonclinical development programs, our ongoing clinical development, or any future clinical development or commercialization efforts.

Our future capital requirements will depend on many factors, including:

- the costs associated with the scope, progress and results of compound discovery, nonclinical development, laboratory testing and clinical trials for our product candidates;
- the extent to which we enter into partnerships or other arrangements with third parties in order to further develop our product candidates;
- the costs and fees associated with the discovery, acquisition or in-license of product candidates or technologies;
- our ability to establish collaborations on favorable terms, if at all;
- the costs of commercialization activities, including product sales, marketing, manufacturing and distribution, for any of our product candidates for which we receive marketing approval;
- revenue, if any, received from commercial sales of our product candidates, should any of our product candidates receive marketing approval; and
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims.

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 (e.g., "baby shelf restriction") or other reasons. If we are unable to raise sufficient amounts of capital it could similarly affect our progress and we could be forced to delay, reduce, or eliminate our discovery and nonclinical development programs, our ongoing clinical development, or any future clinical development or commercialization efforts.

Our product candidates, if approved, may not achieve commercial success. Our commercial revenues, if any, will be derived from sales of products, none of which have been approved to date. Accordingly, we will continue to rely on additional financing to achieve our business objectives, which may not be available to us on acceptable terms, or at all.

Raising additional capital may cause dilution to our stockholders, restrict our operations or require us to relinquish rights to our technologies or product candidates.

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity or equity-linked offerings, debt financings, grants from research organizations, collaborations, and license and development agreements. We do not have any committed external source of funds. To the extent that we raise additional capital through the sale of equity or convertible debt securities, or if existing holders of warrants exercise their rights to purchase common stock, your ownership interest will be diluted, and the terms of these securities may rank senior to our common stock and include liquidation or other preferences, covenants or other terms that adversely affect your rights as a common stockholder. Further, any future sales of our common stock by us or resale of our common stock by our existing stockholders could cause the market price of our common stock to decline. A decline in the value of our company would also cause you to lose part or even all of your investment. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends.

If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or grant licenses on terms that may not be favorable to us and/or that may reduce the value of our common stock.

Risks Related to Our Product Development and Regulatory Approval

We may not be successful in advancing the clinical development of our product candidates, including pegzilarginase and pegtarviliase.

In order to execute on our strategy of advancing the clinical development of our product candidates, we completed the double-blind placebo-controlled portion of our global pivotal PEACE Phase 3 clinical trial. We are conducting two long-term extension studies in the PEACE Phase 3 clinical trial and Phase 1/2 open-label extension study for the treatment of Arginase 1 Deficiency, and a Phase 1/2 clinical trial of pegtarviliase for the treatment of patients with Classical Homocystinuria. If our product candidates fail to work as we expect, or if we need to conduct additional studies to better understand the relationship between our product candidates and clinical activity (i.e. efficacy and safety), our ability to assess the therapeutic effect, seek regulatory approval or otherwise begin or further clinical development, could be compromised. We announced on August 18, 2022 that a MAA for pegzilarginase for the treatment of Arginase 1 Deficiency (ARG1-D) has been submitted to and successfully validated by the EMA. The MAA was submitted by Immedica Pharma AB, our commercialization partner in Europe and the Middle East. Although we submitted our BLA to the FDA to support approval for pegzilarginase based on the results of PEACE Phase 3 trial, on June 2, 2022, we announced that we received a RTF Letter from the FDA regarding our BLA submission. In the RTF Letter, the FDA requested additional data to support effectiveness and additional information relating to Chemistry Manufacturing and Controls. The FDA has noted that, while the data presented in the PEACE Phase 3 trial overall appeared promising and hypothesis-generating, it disagreed that the efficacy results provide substantial evidence of effectiveness for pegzilarginase. The FDA also previously reiterated the need to generate evidence of effectiveness of the product candidate through an additional randomized placebo-controlled trial of a duration longer than 24 weeks given that efficacy data based on effort-dependent clinical outcome assessments and related endpoints have a high potential for bias. If we re-submit a BLA, the FDA may again decide not to file our BLA or approve the BLA in a timely manner, or at all. If the FDA does not approve our BLA, we may need to conduct additional studies and our expected timing of commercialization of pegzilarginase could be delayed, or we may never commercialize pegzilarginase.

We have in the past had to cease clinical development of a product candidate for another indication. We discontinued clinical development of pegzilarginase for the treatment of the hematological malignancies acute myeloid leukemia, or AML, and myelodysplastic syndrome, or MDS, in December 2017 due to lack of evidence of clinical benefit. Additionally, we completed our Phase 1 clinical trial of pegzilarginase for the treatment of advanced solid tumors to study small cell lung cancer, uveal melanoma, and cutaneous melanoma and our combination trial of pegzilarginase with pembrolizumab for the treatment of patients with SCLC. We are currently exploring partnership opportunities for further development in oncology. Such a discontinuation as in our prior oncology program may result in longer development times, larger trials and a greater likelihood of terminating the trial or not obtaining regulatory approval.

We depend heavily on the success of our most advanced product candidates, pegzilarginase and pegtarviliase. Existing and future clinical trials of our product candidates, including pegzilarginase and pegtarviliase, may not be successful. If we are unable to commercialize our product candidates or experience significant delays in doing so, our business will be materially harmed.

We have invested a significant portion of our efforts and financial resources in the nonclinical and clinical development and testing of our most advanced product candidate, pegzilarginase, for the treatment of patients with Arginase 1 Deficiency and in certain oncology trials. Our ability to generate product revenues, if ever, will depend heavily on the successful development and commercialization of pegzilarginase and pegtarviliase. The success of pegzilarginase, pegtarviliase, and our other product candidates will depend 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.

The results from our global pivotal PEACE Phase 3 trial may not support marketing approval, and the FDA or other regulatory authorities may require us to conduct additional clinical trials to evaluate subjects for an additional follow-up period.

We announced updated data from our ongoing PEACE Phase 3 trial in December 2021 and additional data in April 2022, and submitted a BLA to the FDA seeking full approval of pegzilarginase. On June 2, 2022, we reported that we received a RTF Letter from the FDA regarding the BLA. In the RTF Letter, the FDA requested additional data to support effectiveness and additional information relating to Chemistry Manufacturing and Controls. Even though the PEACE Phase 3 trial achieved statistical significance on its primary endpoint and a positive trend in a component of the key secondary endpoint was observed, nominal statistical significance was not reached on any of the prespecified key secondary or secondary endpoints evaluating motor assessments. Even if we re-submit a BLA and the FDA files our BLA, the FDA may not conclude that the design of or results seen in the trial sufficiently demonstrate substantial evidence of effectiveness, including the demonstration of a clinically meaningful effect. The FDA also weighs the benefits of a product against its risks and the FDA may view the efficacy results in the context of safety as not being supportive of regulatory approval. We cannot predict whether any BLA we may submit in the future for pegzilarginase will be filed or approved in a timely manner or at all.

The outbreak of the novel strain of coronavirus, SARS-CoV-2 and its variants, which causes COVID-19, has, and may continue to, adversely impact our business, including our clinical trials and nonclinical studies, supply chain interruptions, and delays for raw materials.

Public health crises such as pandemics or similar outbreaks could adversely impact our business. In response to the COVID-19 pandemic and the ongoing vaccination campaign, we have reopened our executive offices and research laboratory in adherence with our COVID-19 protective protocols. While some of our administrative employees continue their work outside of our offices, a significant portion of our employees, including laboratory personnel, have returned to the office either full- or part-time.

Timely enrollment in our clinical trials is dependent upon global clinical trial sites which may be adversely affected by global health matters, such as pandemics. We are currently conducting clinical trials for our product candidates in many countries, including the United States, Canada, Australia, United Kingdom and throughout the European Union. The regions in which we operate are currently being or may in the future be affected by COVID-19.

As a result of the COVID-19 outbreak, or similar pandemics, we have experienced and may continue to experience disruptions that could severely impact our business, clinical trials and nonclinical studies, including:

- delays or difficulties in enrolling patients in our clinical trials;
- delays or difficulties in clinical site initiation, including difficulties in recruiting clinical site investigators and clinical site staff;
- delays or disruptions in nonclinical experiments and supplies for such experiments, including animals required for such experiments;
- delays or disruptions in investigational new drug application-enabling good laboratory practice standard toxicology studies due to unforeseen circumstances in our supply chain;
- increased rates of patients missing dosing appointments or withdrawing from our clinical trials following enrollment as a result of contracting COVID-19, being forced to quarantine, and other travel restrictions, or not accepting home health visits;

- diversion of healthcare resources away from the conduct of clinical trials, including the diversion of hospitals serving as our clinical trial sites and hospital staff supporting the conduct of our clinical trials, or restricted access to clinical trial sites for on-site monitoring activities;
- interruption of key clinical trial activities, such as clinical assessments at pre-specified timepoints during the trial and clinical trial site data monitoring, due to limitations on travel imposed or recommended by federal, state, or foreign governments, employers and others or interruption of clinical trial subject visits and study procedures (particularly any procedures that may be deemed non-essential), which may impact the integrity of subject data and clinical study endpoints;
- interruption or delays in the operations of the FDA and comparable foreign regulatory agencies, which may impact feedback and approval timelines;
- limitations on employee resources that would otherwise be focused on the conduct of our nonclinical studies and clinical trials, including because of sickness of employees or their families, the desire of employees to avoid contact with large groups of people, an increased reliance on working from home or mass transit disruptions;
- interruption of, or delays in receiving, supplies of our product candidates from our CMOs due to staffing shortages, production slowdowns or stoppages, disruptions in delivery systems and commandeering of manufacturing facilities for COVID-19 vaccines and treatments;
- reduced ability to engage with the scientific, medical and investor communities due to the cancellation of conferences scheduled throughout the year; and
- delays and interruptions to the supply chain, including the raw materials and other supplies needed for analysis and manufacturing of our product candidates.

For example, the timing of our double-blind placebo-controlled portion of our PEACE Phase 3 trial was impacted by COVID-19 as a result of all of our clinical trial sites temporarily suspending screening. All patients that had initially paused dosing due to COVID-19 had restarted treatment by September 2020. We completed enrollment and randomization of patients in the PEACE Phase 3 trial in April 2021 and announced topline data from the trial in December 2021 and pegzilarginase is continuing to be evaluated in two long-term extension studies in the PEACE Phase 3 trial and a Phase 1/2 open-label extension study for the treatment of patients with Arginase 1 Deficiency. In addition, we are conducting a Phase 1/2 open-label clinical trial of pegtarviliase for the treatment of patients with Classical Homocystinuria. These studies require in-person visits to clinical trial sites. Many of these sites are located in areas that have experienced significant impacts and may continue to experience more pronounced impacts to their healthcare systems due to COVID-19 and consequently many previously suspended patient recruitment and may do so again in the future. While we initiated dosing in our Phase 1/2 clinical trial investigating pegtarviliase for the treatment of Classical Homocystinuria in June 2021, the timing of continued enrollment may be delayed in the future due to the impact of COVID-19 and local restrictions. Additionally, missed doses by patients in the study may adversely affect the usefulness of the data collected in the trial.

These and other factors arising from the COVID-19 pandemic could worsen in countries that are already afflicted with COVID-19, could continue to spread to additional countries, or could return to countries where the pandemic has been partially contained, each of which could further adversely impact our ability to conduct clinical trials and our business generally, and could have a material adverse impact on our operations and financial condition and results.

In addition, the trading prices for our common stock and other biopharmaceutical companies, as well as the broader equity and debt markets, have been highly volatile as a result of the COVID-19 pandemic and the resulting impact on economic activity. The COVID-19 pandemic has also contributed to other macroeconomic conditions, including rising interest rates and inflation. As a result, we may face difficulties raising capital when needed, and any such sales may be on unfavorable terms to us. Further, to the extent we raise additional capital through the sale of equity or convertible debt securities, the ownership interest of existing stockholders will be diluted.

The COVID-19 outbreak, including the emergence of its variants and their effects, continues to rapidly evolve. The extent to which the outbreak may impact our business, clinical trials and nonclinical studies will depend on future developments, which are highly uncertain and cannot be predicted with confidence, such as the ultimate geographic spread of COVID-19, the duration of the outbreak, the speed and breadth of mass vaccinations and boosters for COVID-19 and the efficacy of such vaccines and treatments, travel restrictions and actions to contain the outbreak or treat its impact, such as social distancing and quarantines or lock-downs in the United States and other countries, business closures or business disruptions and the effectiveness of actions taken in the United States and other countries to contain and treat the disease.

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.

We have initiated clinical trials with our lead product candidate, pegzilarginase, and 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 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 intended to be enrolled in our ongoing or future clinical trials, 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.

We completed enrollment in our single, global pivotal PEACE Phase 3 clinical trial to evaluate the safety and efficacy of pegzilarginase in patients with Arginase 1 Deficiency. Due to COVID-19, all of our clinical trial sites temporarily suspended screening, limiting patient access, and resulting in some missed dosing appointments for patients. All patients that had initially paused dosing due to COVID-19 had restarted treatment by September 2020. In addition, while we initiated dosing in our Phase 1/2 clinical trial investigating pegtarviliase for the treatment of Classical Homocystinuria in June 2021, the timing of continued enrollment may be delayed in the future due to the impact of COVID-19 and local restrictions. Additionally, missed doses by patients in the study may adversely affect the usefulness of the data collected in the trial.

Furthermore, while we have conducted prior clinical trials of pegzilarginase in certain oncology indications, we are currently exploring partnership opportunities for further development in oncology. 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 ongoing and planned 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 they 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 ongoing and planned 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, etc.;

- 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, 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 and one patient withdrew from the Phase 1/2 clinical trial of pegtarviliase for Classical Homocystinuria;
- 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 ongoing or planned clinical trials, including for pegzilarginase or pegtarviliase, where a clinical hold in a trial in one indication could result in a clinical hold for clinical trials in other indications;
- 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 Arginase 1 Deficiency and Homocystinuria;
- 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;
- 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 and/or testing requirements; or
- have the product removed from the market after obtaining marketing approval.

We do not know whether any of our planned or current nonclinical studies, or ongoing or planned clinical trials, will need to be restructured or will be completed on schedule, or at all. 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. 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 the 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.

We may not be able to submit INDs, or foreign equivalents outside of the United States, to commence clinical trials for product candidates on the timeframes we expect, and even if we are able to, the Health Authorities may not permit us to proceed with planned clinical trials.

We are currently conducting nonclinical development of our product candidates other than our clinical trials for pegzilarginase for the treatment of patients with Arginase 1 Deficiency and pegtarviliase for the treatment of patients with Homocystinuria. Progression of any candidate into clinical trials is inherently risky and dependent on the results obtained in nonclinical programs, and other potential results such as the results of other clinical programs and results of third-party programs. If results are not available when expected or problems are identified during therapy development, we may experience significant delays in clinical development. This may also impact our ability to achieve certain financial milestones and the expected timeframes to market any of our product candidates. Additionally, commencing any future clinical trials is subject to finalizing the trial design and submitting an IND, CTA or comparable submission in other jurisdictions. We plan to advance AGLE-325 for the treatment of patients with Cystinuria through IND-enabling studies and potential subsequent initiation of clinical development. Even after we submit an IND, CTA or comparable submission in other jurisdictions, the Health Authorities could disagree that we have satisfied their requirements to commence our clinical trials, disagree with our study design, or may change their guidance criteria, which may require us to complete additional nonclinical studies or amend our protocols or impose stricter conditions on the commencement of clinical trials. Failure to submit or have effective INDs, CTAs or other comparable foreign equivalents and commence clinical programs will ultimately limit our opportunity to generate revenue.

Our engineered human enzyme product candidates represent a novel therapeutic approach, which could result in heightened regulatory scrutiny, delays in clinical development, or delays in our ability to achieve regulatory approval or commercialization of our product candidates.

Engineered human enzyme products are a new category of therapeutics. Because this is a relatively new and expanding area of novel therapeutic interventions, there can be no assurance as to the length of the trial period, the manufacturing and quality control standards required to be met by regulators, the number of patients the Health Authorities will require to be enrolled in the trials in order to establish the safety, efficacy, purity and potency of engineered human enzyme products, or that the data generated in these trials will be acceptable to the FDA or another applicable regulatory authority to support marketing approval.

We have only initiated clinical trials for pegzilarginase and pegtarviliase for the treatment of certain conditions. We have not dosed any of our other product candidates in humans. Our existing and future planned clinical trials may reveal significant adverse events, toxicities or other side effects not seen in our nonclinical studies or early stage

clinical trials and may result in a safety profile that could inhibit regulatory approval or market acceptance of any of our product candidates.

In order to obtain marketing approval for any of our product candidates, we must demonstrate the safety and efficacy of the product candidate for the relevant clinical indication or indications through nonclinical studies and clinical trials as well as additional supporting data. If our product candidates are associated with undesirable side effects in nonclinical studies or clinical trials, in monotherapy or combination therapy, or have characteristics that are unexpected, we may need to interrupt, delay or abandon their development or limit development to more narrow uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective.

We completed the double-blind placebo-controlled portion of our global pivotal PEACE Phase 3 trial and pegzilarginase is continuing to be evaluated in two long-term extension studies in the PEACE Phase 3 trial and a Phase 1/2 open-label extension study for the treatment of patients with Arginase 1 Deficiency. We are also conducting a Phase 1/2 trial of pegtarviliase for the treatment of patients with Classical Homocystinuria. Given the nature of the patient populations enrolled in these trials, we have observed and expect to continue to observe serious adverse events that could be related or unrelated to pegzilarginase and could impact the safety or efficacy of pegzilarginase and we may observe serious adverse events that could be related or unrelated to pegtarviliase and could impact the safety or efficacy of pegtarviliase. We have also dosed, and may continue to dose, patients with pegzilarginase following compassionate use requests. While such patients are not monitored as part of our ongoing clinical trials, the occurrence of significant adverse events in such patients may negatively impact the prospects of our programs.

In our prior clinical trials of pegzilarginase for the treatment of patients with advanced solid tumors and for the treatment of the patients with hematological malignancies AML and MDS, we have observed serious adverse events in some patients, including death. We have reported results from these trials in which we observed serious adverse events that were considered possibly or probably related to the administration of pegzilarginase including asthenia, fatigue, failure to thrive, hypertension, diarrhea, nausea, vomiting, dehydration, dizziness, intracranial hemorrhage, and encephalopathy. In our completed combination trial of pegzilarginase and pembrolizumab in patients with previously-treated small cell lung cancer, safety observations were consistent with prior studies of pegzilarginase in patients with cancer.

In a completed Phase 1/2 clinical trial and an ongoing Phase 2 open-label extension study of pegzilarginase for the treatment of patients with Arginase 1 Deficiency, as well as the PEACE Phase 3 clinical trial, we have observed serious adverse events in some patients, including hypersensitivity and hyperammonemia, which were infrequent, expected and manageable. Hyperammonemia is an important metabolic effect experienced by some patients with Arginase 1 Deficiency. None of the patients in these trials discontinued due to adverse events, while three patients discontinued for non-medical reasons.

Subjects in our ongoing and planned clinical trials with pegzilarginase and pegtarviliase may suffer minor, significant, serious, or even life-threatening adverse events, including those that are drug-related. Subjects in our ongoing and planned clinical trials may also suffer side effects not yet observed in any of our prior and ongoing clinical or nonclinical studies, including, but not limited to, toxicities to the nervous system, liver, heart, lung, kidney, blood, pulmonary or immune system. We have not dosed any of our other product candidates in humans.

Testing in animals, such as our primate studies for pegzilarginase, pegtarviliase and AGLE-325, may not uncover all side effects in humans or any observed side effects in animals may be more severe in humans. For example, it is possible that patients' immune systems may recognize our engineered human enzymes as foreign and trigger an immune response. This risk is heightened in patients with many genetic enzyme deficiencies who lack the target enzyme, including patients with Arginase 1 Deficiency that we are treating in our global pivotal PEACE Phase 3 trial, our Phase 2 trial open-label extension study, and any future clinical trials we conduct for this rare genetic disease. In addition, our product candidates such as pegzilarginase, pegtarviliase and AGLE-325 break down target amino acids, thereby releasing metabolites into the bloodstream. Some patients may be sensitive to these metabolites, increasing the risk of an adverse reaction due to treatment, which risk may not be able to be mitigated through dosing. Finally, although our engineered human enzyme product candidates such as pegzilarginase and pegtarviliase are engineered from the human genome, pegzilarginase and pegtarviliase are produced in *E. coli*. This manufacturing process could lead to the products being more likely to trigger an immune response than we expect.

To the extent significant adverse events or other side effects are observed in any of our clinical trials, we may have difficulty recruiting patients to the clinical trial, patients may drop out of our trial, or we may be required to abandon the trial or our development efforts of that product candidate altogether. Some potential therapeutics developed in the biotechnology

industry that initially showed therapeutic promise in early-stage studies have later been found to cause side effects that prevented their further development. Even if the side effects do not preclude the drug from obtaining or maintaining marketing approval, undesirable side effects may inhibit market acceptance of the approved product due to its tolerability versus other therapies. Any of these developments could materially harm our business, financial condition and prospects.

Further, toxicities associated with our product candidates may also develop after regulatory approval and lead to the withdrawal of the product from the market. We cannot predict whether our product candidates will cause organ or other injury in humans that would preclude or lead to the revocation of regulatory approval based on nonclinical studies or early stage clinical testing.

Delays or difficulties in the enrollment of patients in our ongoing or planned clinical trials could delay or prevent our receipt of necessary regulatory approvals.

We may not be able to initiate or continue our ongoing or planned clinical trials if we are unable to locate and enroll a sufficient number of eligible patients to participate in these trials as required by the Health Authorities. For example, although we have completed the double-blind placebo-controlled portion of our PEACE Phase 3 trial and are currently enrolling in our Phase 1/2 clinical trial investigating pegtarviliase for the treatment of Classical Homocystinuria, the timing of each trial has been impacted by COVID-19. All of our clinical trial sites for the PEACE Phase 3 trial temporarily suspended screening, limiting patient access, and resulting in some missed dosing appointments for patients. All patients that had initially paused dosing due to COVID-19 had restarted treatment by September 2020. Additionally, while we initiated dosing in our Phase 1/2 clinical trial investigating pegtarviliase for the treatment of Classical Homocystinuria in June 2021, the timing of continued enrollment may be delayed in the future due to the impact of COVID-19 and local restrictions. Further, we recently submitted a protocol amendment for our Phase 1/2 clinical trial of pegtarviliase, which, among other things, requested 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 IND at this time. The partial clinical hold only applies to the IND with the FDA, and the Company believes that the letter should not impact the planned enrollment and dosing of patients aged 18 years and older in the United States or patients aged 12 years and older in the UK and Australia. Furthermore, many of our product candidates, including pegzilarginase and pegtarviliase, initially target indications that may be characterized as orphan markets, which can prolong the clinical trial timeline if sufficient patients cannot be enrolled in a timely manner. Arginase 1 Deficiency is a rare disorder, and there are no published reports of disease prevalence.

We commissioned a genetic prevalence analysis and based on that analysis estimate the Arginase 1 Deficiency population is greater than 2,500 patients in the global addressable markets and greater than 1,150 patients in the territories with regulatory and launch plans underway. The genetic prevalence-based methodology is intended to account for misdiagnosis of the disease and to address limitations in newborn screening methodology, including naturally low arginine levels in newborns and lack of geographic availability or standardization of testing. Presently, only 34 U.S. states perform newborn screening for Arginase 1 Deficiency, and newborn screening is not currently widely performed in European countries. We estimate the patient population for Homocystinuria in global addressable markets may exceed 30,000 patients, over 80% of whom are believed to be either partially responsive or non-responsive to Vitamin B6. This translates to a total of approximately 8,500 partial responders and non-responders in the key commercial markets of the United States, France, Germany, Italy, Spain, and the United Kingdom), but we may not be able to continue to enroll the trial as expected or locate and enroll a sufficient number of eligible patients as required by the Health Authorities, and the necessary regulatory approvals could be delayed or prevented

Delays in patient enrollment could result in increased costs, delays in advancing our product development, delays in testing the effectiveness of our technology or termination of the clinical trials altogether.

Patient enrollment is affected by factors including:

- the impact of COVID-19 and related local restrictions;
- the severity of the disease under investigation;
- the design of the clinical trial protocol;
- the novelty of the product candidate and acceptance by physicians;
- the patient eligibility criteria for the study in question;
- the size of the total patient population;

- the design of the clinical trials;
- the perceived risks and benefits of the product candidate under study;
- the availability and efficacy of competing therapies and clinical trials;
- our payments for conducting clinical trials;
- the patient referral practices of physicians;
- the ability to monitor patients adequately during and after treatment with the product candidate; and
- the proximity and availability of clinical trial sites for prospective patients.

In addition, some patients with Arginase 1 Deficiency suffer from heightened levels of ammonia, or hyperammonemia. Horizon Therapeutics plc actively markets both RAVICTI® (glycerol phenylbutyrate) and BUPHENYL® (sodium phenylbutyrate) to treat patients with urea cycle disorders suffering from hyperammonemia. Some patients who may be eligible for our ongoing or planned clinical trials may instead pursue treatment for this aspect of their condition by taking RAVICTI® (glycerol phenylbutyrate). Our inability to enroll a sufficient number of patients for any of our clinical trials could result in significant delays and could require us to abandon one or more clinical trials altogether. Enrollment delays in our clinical trials may result in increased development costs for our product candidates and in delays to commercially launching our product candidates, if approved, which would cause the value of our company to decline and limit our ability to obtain additional financing.

The safety or efficacy profile of pegzilarginase, or any current or future product candidates, may differ in combination therapy with other existing or future drugs, and therefore may preclude its further development or approval, which would materially harm our business.

From time to time, our commercialization strategy may include the combination of our product candidates with third-parties' products or product candidates. For example, we completed a combination trial with Merck to evaluate the combination of pegzilarginase with Merck's anti-PD-1 therapy, KEYTRUDA® (pembrolizumab), for the treatment of patients with small cell lung cancer. Such combination studies involve additional risks due to their reliance on circumstances outside our control, such as those relating to the availability and marketability of the third-party product involved in the study. Additionally, we may be unable to secure and maintain a sufficient supply of such third-party products when needed on commercially reasonably terms. Any such shortages could cause us to delay or terminate our combination trials.

It is also difficult to predict the way in which pegzilarginase, or any current or future product candidate, will interact with third-party products used in combination clinical trials. As a result, such combination trials may demonstrate reduced efficacy, increase or exacerbate side effects that have been seen with pegzilarginase, or any current or future product candidate, alone, or result in new side effects that have not previously been identified with pegzilarginase, or any current or future product candidate, alone. In addition, data obtained from any combination trials may be subject to a variety of interpretations. For instance, positive data may not guarantee the ability to move forward due to changes in the competitive or regulatory environment for the treatment of targeted indications, and failure to achieve our primary endpoints may not necessarily preclude a viable commercial path. Any undesirable side effects, lack of efficacy seen in combination trials, changing regulatory and commercial requirements for approval, differing interpretation of clinical data or other unforeseen circumstances may affect our ability to continue with and obtain regulatory approval for the combination therapy, as well as our ability to continue with and obtain regulatory approval for pegzilarginase monotherapy.

Further, evaluating pegzilarginase, or any current or future product candidate, in combination with other products in clinical development may require us to establish collaborations, licensing arrangements or alliances with third parties. There is no assurance that we will be able to enter into such arrangements on favorable terms, or at all.

Even though we have obtained orphan drug designation for pegzilarginase in the United States and Europe for the treatment of Arginase 1 Deficiency (hyperargininemia), and for pegtarviliase in the United States and Europe for the treatment of patients with Homocystinuria, we may not obtain or maintain orphan drug exclusivity for pegzilarginase or pegtarviliase and we may not obtain orphan drug designation or exclusivity for any of our other product candidates or indications.

Regulatory authorities in some jurisdictions, including the United States and Europe, may designate drugs or biologics for relatively small patient populations as orphan drugs. Under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is a drug or biologic intended to treat a rare disease or condition, which is generally defined as a patient

population of fewer than 200,000 individuals in the United States. Similarly, the European Commission may designate a product as an orphan drug under certain circumstances.

Generally, if a product with an orphan drug designation subsequently receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of marketing exclusivity, which precludes the FDA or the EMA from approving another marketing application for the same drug for the same disease for that time period. The applicable period is seven years in the United States and ten years in the European Union. The European exclusivity period can be reduced to six years if a drug no longer meets the criteria for orphan drug designation or if the drug is sufficiently profitable so that market exclusivity is no longer justified. Orphan drug exclusivity may be lost if the FDA or EMA determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the drug to meet the needs of patients with the rare disease or condition.

We have obtained orphan drug designation in the United States and Europe for pegzilarginase for the treatment of patients with Arginase 1 Deficiency. We have also received orphan drug designation in the United States and Europe for pegtarviliase for the treatment of patients with Homocystinuria. This orphan drug exclusivity prevents the FDA or EMA from approving another application, including a Biologics License Application, or BLA, in the United States or a MAA in the European Union, to market a drug containing the same principal molecular structural features for the same orphan indication, except in very limited circumstances, including when the FDA or the EMA concludes that the later drug is safer, more effective or makes a major contribution to patient care. In addition, a designated orphan drug may not receive orphan drug exclusivity if it is approved for a use that is broader than the indication for which it received orphan designation.

Even though we have received orphan drug designation for pegzilarginase for the treatment of Arginase 1 Deficiency in the United States and Europe, and for pegtarviliase for the treatment of patients with Homocystinuria in the United States and Europe, we may not be the first to obtain marketing approval for the orphan-designated indication in these jurisdictions due to the uncertainties associated with developing pharmaceutical product candidates. We may also seek to obtain orphan drug designations in other international jurisdictions. However, there is no guarantee that we would be able to do so on a timely basis, or at all. Further, even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different drugs with different active moieties can be approved for the same condition or a drug with the same principal molecular structural features can be approved for a different indication. Orphan drug designation by FDA or EMA neither shortens the development time or regulatory review time of a drug nor gives the drug any advantage in the regulatory review or approval process. In addition, even if we intend to seek orphan drug designation for other product candidates or indications, we may never receive such designations or obtain orphan drug exclusivity.

A Rare Pediatric Disease designation by the FDA does not guarantee that the NDA or BLA for the product will qualify for a priority review voucher upon approval, and it does not necessarily lead to a faster development or regulatory review process, or increase the likelihood that any of our product candidates will receive marketing approval.

Under the Rare Pediatric Disease Priority Review Voucher program, upon the approval of a qualifying BLA or NDA for the treatment of a rare pediatric disease, the sponsor of such an application would be awarded a transferable rare pediatric disease priority review voucher that can be used to obtain priority review for a subsequent BLA or NDA. In September 2018, the FDA notified us that we obtained Rare Pediatric Disease designation for pegzilarginase for the treatment of patients with Arginase 1 Deficiency, and in November 2020, the FDA notified us that we obtained Rare Pediatric Disease designation for pegtarviliase for the treatment of Homocystinuria. On December 27, 2020, the Creating Hope Reauthorization Act extended the Rare Pediatric Disease Priority Review Voucher Program, and after September 30, 2024, the FDA may only award a voucher for an approved rare pediatric disease product application if the sponsor has rare pediatric disease designation for the drug, and that designation was granted by September 30, 2024. After September 30, 2026, the FDA may not award any rare pediatric disease priority review vouchers. However, there is no guarantee that any of our product candidates will be approved by that date, or at all, and, therefore, we may not be in a position to obtain a priority review voucher prior to expiration of the program, unless Congress further reauthorizes the program. Additionally, designation of a drug for a rare pediatric disease does not guarantee that a BLA will meet the other eligibility criteria for a rare pediatric disease priority review voucher at the time the application is approved. Finally, a Rare Pediatric Disease designation does not necessarily lead to faster development or regulatory review of the product, or increase the likelihood that it will receive marketing approval.

Failure to obtain marketing approval in international jurisdictions would prevent our product candidates from being marketed abroad.

In order to market and sell our products in the European Union and many other jurisdictions, we or our third-party collaborators must obtain separate marketing approvals and comply with numerous and varying regulatory requirements.

The approval procedure varies among countries and can involve additional testing and different criteria for approval. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The regulatory approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, it is required that the product be approved for reimbursement before the product can be approved for sale in that country. We, or our third-party collaborators, may not obtain approvals from regulatory authorities outside the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. However, failure to obtain approval in some countries or jurisdictions may compromise our ability to obtain approval elsewhere. We may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our products in any market.

We or third parties may not be successful in developing diagnostic assays, or enhanced biomarker approaches, if required for our product candidates.

In developing a product candidate for some indications, we may decide to use a biomarker-based test to identify patients for enrollment and, or, monitor patients in clinical trials or in the commercial environment, which could require development of new and/or modification of existing biochemical monitoring approaches. In such case, the FDA may require the development and regulatory approval of a companion diagnostic assay as a condition to approval of the product candidate. Alternatively, there may be clinical benefits for some enzyme-based therapies in enhancing currently available biochemical monitoring approaches. While we are not aware of any precedents requiring such approaches for regulatory approval, FDA or other regulatory authorities could request that new biochemical monitoring approaches are available to support some product candidates. Clinical trials that utilize a biomarker-based test to select patients are likely to take longer and require additional funding. We do not have experience or capabilities in developing or commercializing these companion diagnostics and plan to rely in large part on third parties to perform these functions. Some diagnostic assays are subject to regulation by the FDA as medical devices and require separate regulatory approval prior to the use of such diagnostic assays with a therapeutic product candidate. If we, or any third parties that we engage to assist us, are unable to successfully develop companion diagnostic assays for use with our product candidates, or experience delays in development, we may be unable to identify patients with the specific profile targeted by our product candidates for enrollment in our clinical trials. Accordingly, further investment may be required to further develop or obtain the required regulatory approval for the relevant diagnostic assay, which would delay or substantially impact our ability to conduct further clinical trials or obtain regulatory approval. In addition, if a companion diagnostic is necessary for any of our product candidates, a delay in the development of the assay, or the delay or failure to obtain regulatory approval of the companion diagnostic would delay or prevent the approval of the therapeutic product candidate. Alternatively, we may also make the decision that our therapy does not require a companion diagnostic, however the Health Authorities may disagree and require the development and regulatory approval of a companion diagnostic assay as a condition of approval of the product candidate, creating additional costs and a delay in bringing our product candidate to market.

We expect to expand our development and regulatory capabilities and potentially implement commercialization capabilities, and, as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.

We expect to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of product candidate development, regulatory affairs and, if any of our product candidates receives marketing approval, sales, marketing, access, reimbursement, and distribution.

We currently do not have a fully integrated commercial team to distribute and market our product candidates following regulatory approval, if approved. In order to commercialize any product candidates, we must build on a territory-by-territory basis marketing, sales, distribution, managerial and other non-technical capabilities or make arrangements with third parties to perform these services, and we may not be successful in doing so. If our product candidates receive regulatory approval, we intend to establish a fully integrated commercial organization with technical expertise and supporting distribution capabilities to commercialize our product candidates, which will be expensive and time consuming and will require significant attention of our executive officers to manage. We will also have to compete with other pharmaceutical and biotechnology companies to recruit, hire, train and retain commercial personnel. Any failure or delay in the development of our internal sales, marketing, access, reimbursement, and distribution capabilities would adversely impact the commercialization of any of our product candidates that we obtain approval to market.

With respect to the commercialization of all or certain of our product candidates, we may choose to collaborate, either globally or on a territory-by-territory basis, with third parties that have direct sales forces and established distribution systems, either to augment our own sales force and distribution systems or in lieu of our own sales force and distribution systems. In particular, we have and expect to continue to partner with third parties to commercialize pegzilarginase outside the United States. For example, in March 2021, we entered into a licensing agreement with Immedica, in which Immedica

acquired the product rights for commercialization of pegzilarginase in the European Economic Area and certain Middle East jurisdictions. We may have little or no control over the marketing and sales efforts of such third parties and our revenue from product sales may be lower than if we had commercialized our product candidates ourselves. We also face competition in our search for third parties to assist us with the sales and marketing efforts of our product candidates. If we are unable to enter into such arrangements when needed on acceptable terms, or at all, we may not be able to successfully commercialize any of our product candidates that receive regulatory approval or any such commercialization may experience delays or limitations. If we are not successful in commercializing our product candidates, either on our own or through collaborations with one or more third parties, our future product revenue will suffer and we may incur significant additional losses.

To manage our anticipated future growth, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Due to our limited financial resources and the limited experience of our management team in managing a public company with such anticipated growth, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. The expansion of our operations may lead to significant costs and may divert our management and business development resources. Any inability to manage growth could delay the execution of our business plans or disrupt our operations.

We may not be successful in our efforts to identify additional product candidates. Due to our limited resources and access to capital, we must prioritize development of certain product candidates, which may prove to be wrong and may adversely affect our business.

Although we intend to explore other therapeutic opportunities, in addition to the product candidates that we are currently developing, we may fail to identify viable new product candidates for clinical development for a number of reasons. If we fail to identify additional potential product candidates, our business could be materially harmed.

Research programs to pursue the development of our existing and planned product candidates for additional indications and to identify new product candidates and disease targets require substantial technical, financial and human resources whether or not they are ultimately successful. Our research programs may initially show promise in identifying potential indications and/or product candidates, yet fail to yield results for clinical development for a number of reasons, including:

- the research methodology used may not be successful in identifying potential indications and/or product candidates;
- potential product candidates may, after further study, be shown to have harmful adverse effects or other characteristics that indicate they are unlikely to be effective drugs;
- it may take greater human and financial resources than we will possess to identify additional therapeutic opportunities for our product candidates or to develop suitable potential product candidates through internal research programs, thereby limiting our ability to develop, diversify and expand our product portfolio; or
- alternative research or therapeutic methodologies may be more efficient than the research approaches we have provided.

Because we have limited financial and human resources, we intend to initially focus on research programs and product candidates for a limited set of indications. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater commercial potential or a greater likelihood of success. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities.

Accordingly, there can be no assurance that we will ever be able to identify additional therapeutic opportunities for our product candidates or to develop suitable potential product candidates through internal research programs, which could materially adversely affect our future growth and prospects. We may focus our efforts and resources on potential product candidates or other potential programs that ultimately prove to be unsuccessful.

Risks Related to Commercialization

If the market opportunities for our product candidates are smaller than we believe they are, our future product revenues may be adversely affected, and our business may suffer.

Our understanding of both the number of people who suffer from conditions such as Arginase 1 Deficiency or Homocystinuria, as well as the potential subset of those who have the potential to benefit from treatment with our product

candidates, are based on estimates. We expect our product candidates targeting rare diseases to target a smaller subset of patient populations that suffer from the respective diseases we seek to treat. These estimates may prove to be incorrect and new studies may reduce the estimated incidence or prevalence of these diseases. The number of patients in the United States, Europe or elsewhere may turn out to be lower than expected, may not be otherwise amenable to treatment with our product candidates or patients may become increasingly difficult to identify and access, all of which would adversely affect our business, financial condition, results of operations and prospects.

Further, there are several factors that could contribute to making the actual number of patients who receive our potential product candidates less than the potentially addressable market. These include the lack of widespread availability of, and limited reimbursement for, new therapies in many underdeveloped markets. Additionally, our assumptions regarding the addressable market may be incorrect and the addressable market may change over time, including from the announcement date of a product candidate to the approval by Health Authorities and commercialization. Even if we obtain significant market share for our product candidates, because certain of the potential target populations are small, we may never achieve profitability without obtaining regulatory approval for additional indications.

Even if any of our product candidates receives marketing approval, it may fail to achieve the degree of market acceptance by physicians, patients, third-party payors and others in the medical community necessary for commercial success.

Even if any of our product candidates receives marketing approval, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community necessary for commercial success. Current treatments for Arginase 1 Deficiency and Homocystinuria include dietary protein restrictions and for Arginase 1 Deficiency, in some instances, ammonia-scavenging drugs such as RAVICTI® (glycerol phenylbutyrate), and CYSTADANE® (betaine anhydrous for oral solution) for Homocystinuria. If our product candidates do not achieve an adequate level of acceptance, we may never generate significant product revenues and we may not become profitable. The degree of market acceptance of our product candidates, if approved for commercial sale, will depend on a number of factors, including:

- their efficacy, safety and other potential advantages compared to alternative treatments;
- our ability to offer them for sale at competitive prices;
- their convenience and ease of administration compared to alternative treatments;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the ability of healthcare professionals to accurately identify and diagnose patients with the relevant/indicated condition;
- the strength of marketing and distribution support;
- the availability of third-party payor coverage and adequate reimbursement for our product candidates;
- the prevalence and severity of their side effects;
- any restrictions on the use of our product candidates together with other medications;
- interactions of our product candidates with other products patients are taking; and
- inability of patients with certain medical histories to take our product candidates.

We face significant competition from other biotechnology and pharmaceutical companies and our operating results will suffer if we fail to compete effectively.

The biotechnology and pharmaceutical industries are intensely competitive. We have competitors both in the United States and internationally, including major multinational pharmaceutical companies, biotechnology companies, universities and other research institutions. Many of our competitors have substantially greater financial, technical and other resources, such as larger research and development staff and experienced marketing and manufacturing organizations and well-established sales forces. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our competitors may succeed in developing, acquiring or licensing, on an exclusive basis, product candidates that are more effective or less costly than any product candidate that we are currently developing or that we may develop.

There are multiple approved treatments and investigational therapies for the management of hyperammonemia commonly experienced by patients with urea cycle disorders. While these products – known as ammonia scavengers – do not target the core metabolic defect of Arginase 1 Deficiency, they can help patients manage their elevated ammonia levels. Horizon Therapeutics plc actively markets two branded ammonia scavenger therapies (RAVICTI® (glycerol phenylbutyrate) and BUPHENYL® (sodium phenylbutyrate)), and at least one generic formulation of sodium phenylbutyrate is commercially available. From a clinical development perspective, Acer Therapeutics Inc. is developing a taste-masked, immediate-release formulation of sodium phenylbutyrate (ACER-001) for the treatment of hyperammonemia and has been assigned a PDUFA target action date of January 15, 2023 following a Complete Response Letter and subsequent NDA resubmission. We are aware of one other company with an investigational therapy for Arginase 1 Deficiency in preclinical stages, Erytech Pharma SA, who in February 2022 announced the allowance of a U.S. patent application covering arginine deiminase encapsulated into red blood cells for the treatment of Arginase 1 Deficiency.

We anticipate a competitive landscape in Homocystinuria. There is currently one FDA-approved therapy for the treatment of Homocystinuria and multiple medical foods. CYSTADANE® (betaine anhydrous for oral solution) was approved by the FDA in 1996 and is currently marketed in North America by Recordati Rare Diseases Inc. We are also aware of two investigational therapies in clinical development for the treatment of Homocystinuria. Travere Therapeutics Inc. is focused on the development of pegtibatinase, an enzyme replacement therapy in patients with Homocystinuria due to cystathionine β-synthase deficiency. Travere released topline data in December 2021 from its Phase 1/2 study of pegtibatinase which showed a 55% reduction in homocysteine at the highest dose cohort (1.5mg/kg, 2x/week). SNYB1353 from Synlogic, Inc. is in Phase 1 clinical development for the potential treatment of Homocystinuria. This investigational agent is an oral synthetic biotic platform that consumes methionine, an essential amino acid and precursor of homcysteine, in the gastrointestinal tract. We are also aware of two investigational therapies in preclinical development. The first is CDX-6512, an oral methionine-gamma-lyase enzyme therapy from Codexis. Erytech Pharma SA also has a product candidate for Homocystinuria in preclinical development. It is possible that competitors may produce, develop, and commercialize therapeutics, or utilize other approaches to treat Homocystinuria.

Our ability to compete successfully will depend largely on our ability to leverage our experience in product candidate discovery and development to:

- discover and develop product candidates that are sufficiently differentiated from other products in the market;
- attract qualified management, scientific, product development and commercial personnel;
- obtain and maintain patent and/or other proprietary protection for our product candidates and technologies;
- obtain required regulatory approvals;
- successfully launch and commercialize our approved products; and
- successfully collaborate with research institutions or pharmaceutical companies in the discovery, development and commercialization of new product candidates.

The availability and price of our competitors' products could limit the demand, and the price we are able to charge, for any of our product candidates, if approved. We will not achieve our business plan if acceptance is inhibited by price competition or the reluctance of patients, physicians, or payers to accept our product candidates.

Established biotechnology companies may invest heavily to accelerate discovery and development of products that could make our product candidates less competitive. In addition, any new product that competes with an approved product must demonstrate compelling advantages in efficacy, convenience, tolerability and/or safety to establish a meaningfully differentiated value proposition for patients, physicians, and payers. Accordingly, our competitors may succeed in obtaining patent protection, receiving FDA or non-U.S. regulatory approval or discovering, developing and commercializing product candidates before we do, which would have a material adverse impact on our business. Many of our competitors have greater resources than we do and have established sales, marketing, and market access capabilities, whether internally or through third parties. We will not be able to successfully commercialize our product candidates without establishing sales and marketing capabilities internally or through strategic partners.

The insurance coverage and reimbursement status of newly-approved products is uncertain. Failure to obtain or maintain adequate coverage and reimbursement for new or current product candidates could limit our ability to market those product candidates and decrease our ability to generate revenue.

The availability and extent of reimbursement by governmental and private payors is essential for most patients to be able to afford expensive treatments. Sales of any of our product candidates that receive marketing approval will depend

substantially, both in the United States and internationally, on the extent to which the costs of our product candidates will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or reimbursed by government health administration authorities, private health coverage insurers and other third-party payors. If reimbursement is not available, or is available only to limited levels, we may not be able to successfully commercialize our product candidates. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us to establish or maintain pricing sufficient to realize a sufficient return on our investment.

There is significant uncertainty related to the insurance coverage and reimbursement of newly approved products. In the United States, the principal decisions about reimbursement for new products are typically made by the Centers for Medicare & Medicaid Services, or CMS, an agency within the U.S. Department of Health and Human Services since CMS decides whether and to what extent a new product will be covered and reimbursed under Medicare. Private payors tend to follow CMS to a substantial degree. It is difficult to predict what CMS will decide with respect to reimbursement for novel products such as ours since there is no body of established practices and precedents for these new products. Reimbursement agencies in Europe may be more conservative than CMS. For example, a number of cancer drugs have been approved for reimbursement in the United States and have not been approved for reimbursement in certain European countries.

Outside the United States, international operations are generally subject to extensive governmental price controls and other market regulations, and we believe the increasing emphasis on cost-containment initiatives in Europe, Canada and other countries has and will continue to put pressure on the pricing and usage of therapeutics such as our product candidates. In many countries, particularly the United Kingdom and the countries of the European Union, the prices of medical products are subject to varying price control mechanisms as part of national health systems. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate to other available therapies. In general, the prices of products under such systems are substantially lower than in the United States. Other countries allow companies to fix their own prices for products but monitor and control company profits. Additional foreign price controls or other changes in pricing regulation could restrict the amount that we are able to charge for our product candidates. Accordingly, in markets outside the United States, the reimbursement for our products may be reduced compared with the United States and may be insufficient to generate commercially reasonable revenues and profits.

Moreover, increasing efforts by governmental and third-party payors, in the United States and internationally, to cap or reduce healthcare costs may cause such organizations to limit both coverage and level of reimbursement for new products approved and, as a result, they may not cover or provide adequate payment for our product candidates. The U.S. government has similarly expressed concerns over the pricing of pharmaceutical products and there can be no assurance as to how this scrutiny will impact future pricing of pharmaceutical products generally. We expect to experience pricing pressures in connection with the sale of any of our product candidates due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative changes. The downward pressure on healthcare costs in general, particularly prescription drugs and surgical procedures and other treatments, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products into the healthcare market.

In addition to CMS and private payors, professional organizations can influence decisions about reimbursement for new products by determining standards for care. In addition, many private payors contract with commercial vendors who sell software that provide guidelines that attempt to limit utilization of, and therefore reimbursement for, certain products deemed to provide limited benefit to existing alternatives. Such organizations may set guidelines that limit reimbursement or utilization of our product candidates.

Furthermore, some of our target indications, including for Arginase 1 Deficiency for pegzilarginase and for Homocystinuria for pegtarviliase, are orphan indications where patient populations are small. In order for therapeutics that are designed to treat smaller patient populations to be commercially viable, the reimbursement for such therapeutics must be higher, on a relative basis, to account for the lack of volume. Accordingly, we will need to implement a coverage and reimbursement strategy for any approved product candidate that accounts for the smaller potential market size. If we are unable to establish or sustain coverage and adequate reimbursement for any future product candidates from third-party payors, the adoption of those products and sales revenue will be adversely affected, which, in turn, could adversely affect the ability to market or sell those product candidates, if approved, and ultimately our financial results.

Our product candidates for which we intend to seek approval as biologic products may face competition sooner than anticipated.

With the enactment of the Biologics Price Competition and Innovation Act of 2009, or BPCIA, an abbreviated pathway for the approval of biosimilar biological products (both highly similar and interchangeable biological products) was created.

The abbreviated regulatory pathway establishes legal authority for the FDA to review and approve biosimilar biologics, including the possible designation of a biosimilar as interchangeable based on its similarity to an existing reference product. Under the BPCIA, an application for a biosimilar product cannot be approved by the FDA until 12 years after the first licensure of date of the reference product licensed under a BLA. On March 6, 2015, the FDA approved the first biosimilar product under the BPCIA and on July 28, 2021, approved the first interchangeable biosimilar. However, the law is complex and is still being interpreted and implemented by the FDA. As a result, its ultimate impact, implementation, and meaning are subject to uncertainty. While it is uncertain when the processes intended to implement BPCIA may be fully adopted by the FDA, any such processes could have a material adverse effect on the future commercial prospects for our biological products.

A biological product submitted for licensure under a BLA is eligible for a period of exclusivity that commences on the date of its licensure, unless its date of licensure is not considered a date of first licensure because it falls within an exclusion under the BPCIA. There is a risk that this exclusivity could be shortened due to congressional action or otherwise, potentially creating the opportunity for biosimilar competition sooner than anticipated. Additionally, this period of regulatory exclusivity does not apply to companies pursuing regulatory approval via their own traditional BLA, rather than via the abbreviated pathway. Most states have enacted substitution laws that permit substitution of only interchangeable biosimilars. The extent to which a biosimilar, once approved, will be substituted for any one of our reference products that may be approved in a way that is similar to traditional generic substitution for non-biological products is not yet clear, and will depend on a number of marketplace and regulatory factors that are still developing.

If we fail to develop additional product candidates, our commercial opportunity will be limited.

Developing and obtaining regulatory approval for and commercializing any additional product candidates we identify will require substantial additional funding and is prone to the risks of failure inherent in medical product development. We cannot provide you any assurance that we will be able to successfully advance additional product candidates, if any, through the development process.

Even if we receive FDA approval to market additional product candidates for the treatment of the diseases we target, we cannot assure you that any such product candidates will be successfully commercialized, widely accepted in the marketplace or more effective than other commercially available alternatives. If we are unable to successfully develop and commercialize additional product candidates, our commercial opportunity will be limited. Moreover, a failure in obtaining regulatory approval of additional product candidates may have a negative effect on the approval process of other product candidates of ours or result in losing approval of any approved product candidate.

If in the future we are unable to establish U.S. or global sales and marketing capabilities or enter into agreements with third parties to sell and market our product candidates, we may not be successful in commercializing our product candidates if they are approved, thus limiting our ability to generate any product revenue.

We do not yet have a fully integrated commercial organization with all of the functions required to market, sell and distribute our product candidates that may receive regulatory approval. In order to commercialize any product candidates after approval, we must build on a territory-by-territory basis marketing, sales, distribution, managerial and other non-technical capabilities or make arrangements with third parties to perform these services, and we may not be successful in doing so. If our product candidates receive regulatory approval, we may decide to establish an internal sales or marketing team with technical expertise and supporting distribution capabilities to commercialize our product candidates, which will be expensive and time-consuming and will require significant attention of our executive officers to manage. Any failure or delay in the development of our internal sales, marketing and distribution capabilities would adversely impact the commercialization of any of our product candidates that we obtain approval to market.

With respect to the commercialization of all or certain of our product candidates, we may choose to collaborate, either globally or on a territory-by-territory basis, with third parties that have direct sales forces and established distribution systems, either to augment our own sales force and distribution systems or in lieu of our own sales force and distribution systems. In particular, we have and expect to continue to partner with third parties to commercialize pegzilarginase outside the United States. In March 2021, we entered into a license and supply agreement with Immedica, in which Immedica acquired the product rights for commercialization of pegzilarginase for certain territories outside the U.S. If we are unable to enter into or maintain such arrangements when needed on acceptable terms, or at all, we may not be able to successfully commercialize any of our product candidates that receive regulatory approval or any such commercialization may experience delays or limitations. If we are not successful in commercializing our product candidates, either on our own or through collaborations with one or more third parties, our future product revenue will suffer and we may incur significant additional losses.

If we obtain approval to commercialize our product candidates outside of the United States, in particular in the EU, a variety of risks associated with international operations could materially adversely affect our business.

We expect that we will be subject to additional risks in commercializing our product candidates outside the United States, including:

- different regulatory requirements for approval of drugs and biologics in foreign countries;
- different processes and requirements to obtain adequate reimbursement for our approved therapies;
- reduced protection for intellectual property rights;
- unexpected changes in tariffs, trade barriers and regulatory requirements;
- economic weakness, including inflation, or political instability in particular foreign economies and markets;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations incident to doing business in another country;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geopolitical actions, including war and terrorism or natural disasters including earthquakes, typhoons, floods and fires.

Risks Related to Our Reliance on Third Parties

We currently rely and will rely on third parties to conduct our ongoing and future planned clinical trials, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials.

We currently rely and will continue to rely on third parties to provide manufacturing and clinical development capabilities. For example, we currently rely on third party contract manufacturing organizations to manufacture and supply nonclinical and clinical trial quantities of our lead product candidate, pegzilarginase, pegtarviliase, and for additional pipeline product candidates. We also expect to continue to rely on such third parties to manufacture and supply commercial quantities of pegzilarginase, as well as pegtarviliase for our Phase 1/2 clinical trial.

We have agreements with and rely on third-party CROs to conduct our ongoing and future planned clinical trials of pegzilarginase and pegtarviliase. We do not plan to independently conduct clinical trials of our other product candidates. These agreements might terminate for a variety of reasons, including a failure to perform by the third parties. If we need to enter into alternative arrangements, that would delay our product development activities.

Our reliance on these third parties for research and development activities will reduce our control over these activities but will not relieve us of our responsibilities. For example, we will remain responsible for ensuring that each of our ongoing and future planned clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA requires us to comply with regulatory standards, commonly referred to as good clinical practices for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. Other countries' regulatory agencies also have requirements for clinical trials with which we must comply. We also will be required to register ongoing clinical trials and post the results of completed clinical trials on a government-sponsored database, *ClinicalTrials.gov*, within specified timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

Furthermore, these third parties may also have relationships with other entities, some of which may be our competitors. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our ongoing and future planned clinical trials in accordance with regulatory requirements or our stated protocols, we will not be able to complete our clinical trials, obtain, or may be delayed in obtaining, marketing approvals for our product candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our product candidates. Further, to meet the demand for COVID-19 vaccine production, manufacturers are required to prioritize rated orders issued by the Federal Emergency Management Agency pursuant to the U.S. Defense Production Act of 1950, or the DPA. The potential for manufacturing facilities and materials to be commandeered under the DPA, or equivalent foreign legislation, could make it more difficult to obtain materials or manufacturing slots for the products needed for our clinical trials or commercialization of our product candidates, which could lead to delays in these trials and successful commercialization.

We also expect to rely on other third parties to store and distribute drug supplies for our clinical trials. Any performance failure, including due to COVID-19, on the part of our distributors could delay clinical development or marketing approval of our product candidates or commercialization of our product candidates, producing additional losses and depriving us of potential product revenue.

We contract with third parties for the manufacture of our product candidates for nonclinical studies and our ongoing and future planned clinical testing and expect to continue to do so for commercialization. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates at an acceptable cost and quality, which could delay, prevent or impair our development or commercialization efforts.

We do not own or operate facilities for the manufacture of our product candidates. We currently have no plans to build our own clinical or commercial scale manufacturing capabilities. We rely, and expect to continue to rely, on third parties, for the manufacture of our product candidates for nonclinical studies and for our existing and future planned clinical trials. We also expect to rely on third parties for commercial manufacture if any of our product candidates receive marketing approval. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or such quantities at an acceptable cost or quality, which could delay, prevent or impair our development or commercialization efforts.

Any performance failure, including due to COVID-19, on the part of our existing or future manufacturers could delay clinical development or marketing approval. We do not currently have arrangements in place for redundant supply or a source for bulk drug substance. Currently, third party manufacturers are supplying, and are expected to continue to supply, the drug substance requirements for our ongoing and planned clinical trials with pegzilarginase and pegtarviliase. If such third party manufacturers cannot supply us with sufficient amounts, pursuant to product requirements as agreed, we may be required to identify alternative manufacturers, which would lead us to incur added costs and delays in identifying and qualifying any replacement.

The formulation used in early studies may not be a final formulation for commercialization. If we are unable to demonstrate that our commercial scale product is comparable to the product used in clinical trials, we may not receive regulatory approval for that product without additional clinical trials. We have contracted with third party manufacturers for certain studies related to potential commercial scale manufacturing of pegzilarginase, but there is no guarantee that such studies, the transfer of technology to or any potential manufacturing at such facility, will be completed successfully, on time, or at all. We also cannot guarantee that we will be able to make any required modifications within currently anticipated timeframes or that such modifications, if and when made, will obtain regulatory approval or that the new processes or modified processes will be successfully implemented by or transferred to any third-party contract suppliers within currently anticipated timeframes. These may require additional studies and may delay our clinical trials and/or commercialization.

We expect to rely on third-party manufacturers, or third-party strategic partners for the manufacture of commercial supply of any product candidates for which our strategic partners or we obtain marketing approval. We may be unable to establish any additional agreements with third-party manufacturers, or to do so on acceptable terms. Even if we are able to establish agreements with third-party manufacturers on acceptable terms, such third-party manufacturers may have limited experience manufacturing pharmaceutical drugs for commercialization, and reliance on third-party manufacturers for the commercial supply of our products may expose us to various risks, including:

- the possible noncompliance by the third party with regulatory requirements and quality assurance;
- the possible breach of the manufacturing agreement by the third party;
- the operations of such third parties could be disrupted by conditions unrelated to our business or operations, including the bankruptcy of such party, the issuance of an FDA Form 483 notice or warning letter, or other enforcement action by the FDA or other regulatory authority;
- delays due to production shortages resulting from any events affecting supply or manufacturing capabilities domestically and abroad;
- the possible misappropriation of our proprietary information, including our trade secrets and know-how; and
- the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us.

Third-party manufacturers may not be able to comply with current good manufacturing practices, or cGMP, or similar regulatory requirements outside the United States. Although we do not have day-to-day control over third-party

manufacturers' compliance with these regulations and standards, we are responsible for ensuring compliance with such regulations and standards. Our failure, or the failure of our third-party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us, including clinical holds, fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates, operating restrictions and criminal prosecutions, any of which would significantly and adversely affect supplies of our product candidates and our business. If a third-party manufacturer's facilities do not pass a pre-approval inspection or do not have a cGMP compliance status acceptable to the FDA or a comparable foreign regulatory agency, our product candidate will not be approved.

In addition, the process of manufacturing and administering our product candidates is complex and highly regulated. As a result of the complexities, our manufacturing and supply costs are likely to be higher than those at more traditional manufacturing processes and the manufacturing process is less reliable and more difficult to reproduce.

We also expect to rely on other third parties to store and distribute drug supplies for our clinical trials. Any performance failure on the part of our distributors could delay clinical development or marketing approval of our product candidates or commercialization of our product candidates, producing additional losses and depriving us of potential product revenue.

Our product candidates and any products that we may develop may compete with other product candidates and products for access to manufacturing facilities. There are a limited number of manufacturers that operate under cGMP regulations and that might be capable of manufacturing for us.

Our current and anticipated future dependence upon others for the manufacture of our product candidates may adversely affect our future profit margins and our ability to commercialize any product candidates that receive marketing approval on a timely and competitive basis.

Failure of any future third-party collaborators to successfully commercialize diagnostics or monitoring assays developed for use with our therapeutic product candidates could harm our ability to commercialize these product candidates.

We do not plan to internally develop diagnostics or monitoring assays, or Assays. As a result, we are dependent on the efforts of our third-party strategic partners to successfully commercialize any needed Assays. Our strategic partners:

- may not perform their obligations as expected;
- may encounter production difficulties that could constrain the supply of the Assays;
- may have difficulties gaining acceptance of the use of the Assays in the clinical community;
- may not pursue commercialization of any Assays;
- may elect not to continue or renew commercialization programs based on changes in the strategic partners' strategic focus or available funding, or external factors, such as an acquisition, that divert resources or create competing priorities;
- may not commit sufficient resources to the marketing and distribution of such Assay product candidates; and
- may terminate their relationship with us.

If Assays needed for use with our therapeutic product candidates fail to gain market acceptance, our ability to derive revenues from sales of these therapeutic product candidates could be harmed. If our strategic partners fail to develop and commercialize these Assays, it could adversely affect and delay the development or commercialization of our therapeutic product candidates.

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 expect to 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 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.

We may be subject to claims by third parties asserting that our employees or we have misappropriated their intellectual property, or claiming ownership of what we regard as our own intellectual property.

Many of our employees were previously employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that these employees or we have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such employee's former employer. Litigation may be necessary to defend against these claims.

In addition, while it is our policy to require our employees and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own. Our and their assignment agreements may not be self-executing or may be breached, and we may be forced to bring claims against third parties, or defend claims they may bring against us, to determine the ownership of what we regard as our intellectual property.

If we fail in prosecuting or defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to management.

Risks Related to Government Regulation

If there are delays in obtaining, or we are not able to obtain, required regulatory approvals in the United States or in foreign jurisdictions, we will not be able to commercialize our product candidates, and our ability to generate revenue will be materially impaired.

Our product candidates must be approved by the FDA pursuant to a BLA in the United States, and by the EMA pursuant to an MAA, and by other comparable regulatory authorities outside the United States prior to commercialization. The process of obtaining marketing approvals, both in the United States and internationally, is expensive and takes many years, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval in Europe or another non-U.S. jurisdiction may differ substantially from that required to obtain FDA approval. The regulatory approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, it is required that the product be approved for reimbursement before the product can be approved for sale in that country. We or our third-party strategic partners may not obtain approvals from regulatory authorities outside the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. Furthermore, the implementation of Brexit may disrupt the operation of any pre-and post-authorization clinical trial infrastructure and regulatory frameworks in Europe, as discussed further below. We may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our product candidates in any market.

Failure to obtain marketing approval for a product candidate will prevent us from commercializing the product candidate. We have not received approval to market any of our product candidates from regulatory authorities in any jurisdiction. We have limited experience in filing and supporting the applications necessary to gain marketing approvals and

expect to rely on third-party CROs to assist us in this process. Securing marketing approval requires the submission of extensive nonclinical and clinical data and supporting information to regulatory authorities for each therapeutic indication to establish the product candidate's safety and efficacy. Securing marketing approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the regulatory authorities. Our product candidates may not be effective, may be only moderately effective or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining marketing approval or prevent or limit commercial use. Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional nonclinical, clinical or other studies. In addition, varying interpretations of the data obtained from nonclinical and clinical testing could delay, limit or prevent marketing approval of a product candidate. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted product application, may also cause delays in or prevent the approval of an application.

Approval of our product candidates may be delayed or refused for many reasons, including the following:

- the Health Authorities may disagree with the design or implementation of our clinical trials;
- we may be unable to demonstrate to the satisfaction of the Health Authorities that our product candidates are safe and effective for any of their proposed indications;
- the results of clinical trials may not meet the level of statistical significance required by the Health Authorities for approval;
- we may be unable to demonstrate that our product candidates' clinical and other benefits outweigh their safety risks;
- the Health Authorities may disagree with our interpretation of data from nonclinical programs or clinical trials;
- the data collected from clinical trials of our product candidates may not be sufficient to the satisfaction of the Health Authorities to support the submission of a BLA, MAA or other comparable submission in other jurisdictions or to obtain regulatory approval in the United States or elsewhere;
- the potential disruptions and uncertainty caused by Brexit implementation, as discussed below;
- the facilities of the third-party manufacturers with which we partner may not be adequate to support approval of our product candidates; and
- the approval policies or regulations of the Health Authorities may significantly change in a manner rendering our clinical data insufficient for approval.

New products for the treatment of cancer frequently are initially indicated only for patient populations that have not responded to an existing therapy or have relapsed. If any of our product candidates receives marketing approval for cancer or another indication, the approved labeling may limit the use of our product candidates in this or a similar way, which could limit sales of the product. Also, any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

Additionally, the implementation of the United Kingdom's exit from the European Union, or "Brexit," may cause disruptions and uncertainty in the current regulatory framework in Europe. Brexit has resulted in the EMA moving from the United Kingdom to the Netherlands. In the United Kingdom, this transition may cause disruption in the administrative and medical scientific links between the EMA and MHRA. Following the United Kingdom's departure from the European Union, it no longer automatically complies with the standards of clinical efficacy, safety and chemistry control, and manufacture as applied by the European Medicines Directive. Applications submitted for marketing authorization under the centralized EMA procedure will no longer be automatically validated for authorization in the United Kingdom, and the benefit-risk assessments conducted by the United Kingdom may not be consistent with the EMA conclusions. The cumulative effects of the disruption to the regulatory framework may add considerably to the development lead time to marketing authorization and commercialization of products in the European Union and/or the United Kingdom. In view of the current lack of detail and resolution with regard to the Brexit transition, we are unable to confidently predict the effects of such disruption to the regulatory framework in Europe, and as to how this may delay or impair any potential regulatory approvals, commercialization of any of our product candidates, and our ability to generate potential revenues. If we experience delays in obtaining approval or if we fail to obtain approval of our product candidates, the commercial prospects for our product candidates may be harmed and our ability to generate revenues will be materially impaired.

Any Fast Track Designation by the FDA, even if granted for any of our product candidates, may not lead to a faster development or regulatory review or approval process, and does not increase the likelihood that our product candidates will receive marketing approval.

We have received Fast Track Designation from the FDA for our lead product candidate pegzilarginase for the treatment of hyperargininemia secondary to Arginase 1 Deficiency and may seek such designation for some or all of our product candidates. If a drug or biologic is intended for the treatment of a serious or life-threatening condition and the drug or biologic demonstrates the potential to address unmet medical needs for this condition, the drug or biologic sponsor may apply for FDA Fast Track Designation. The FDA has broad discretion whether or not to grant this designation. Even if we believe a particular product candidate is eligible for this designation, we cannot assure you that the FDA would decide to grant it. Even though we have received Fast Track Designation for pegzilarginase for the treatment of hyperargininemia secondary to Arginase 1 Deficiency, and even if we receive Fast Track Designation for other product candidates or indications in the future, we may not experience a faster development process, review or approval compared to conventional FDA procedures. The FDA may withdraw Fast Track Designation if it believes that the designation is no longer supported by data from our clinical development program. Many drugs or biologics that have received Fast Track Designation have failed to obtain approval.

FDA may also consider approval of our products through the use of the accelerated approval program, but such mechanism may not lead to a faster development or regulatory review or approval process. Even if we receive approval from the FDA under the accelerated approval program, if our confirmatory postmarketing trial does not verify clinical benefit, or if we do not comply with rigorous postmarketing requirements, the FDA may seek to withdraw the approval.

Under the FDA's accelerated approval program, the FDA may approve a drug or biologic for a serious or life-threatening illness that provides meaningful therapeutic benefit to patients over existing treatments based upon a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that is thought to predict clinical benefit but is not itself a measure of clinical benefit, or a biomarker that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. The FDA bases its decision on whether to accept the proposed surrogate or intermediate clinical endpoint on the scientific support for that endpoint. Studies that demonstrate a drug's effect on a surrogate or intermediate clinical endpoint must be adequate and well controlled as required by the FDC Act.

If the FDA were to consider accelerated approval in the review of an application for any product candidates, the FDA may determine there is inadequate justification to support that our surrogate endpoint is reasonably likely to predict clinical benefit in patients.

For drugs or biologics granted accelerated approval, post-marketing well-controlled, adequately powered confirmatory trials of sufficient duration are typically required to describe the anticipated effect on irreversible morbidity or mortality or other clinical benefit. These confirmatory trials must be completed with due diligence, and the FDA could require that the trial be designed, initiated, and/or fully enrolled at the time of BLA submission. Moreover, the FDA may withdraw approval of our product candidate or indication approved under the accelerated approval pathway if, for example:

- the trial or trials required to verify the predicted clinical benefit of our product candidate fail to verify such benefit or do not demonstrate sufficient clinical benefit to justify the risks associated with the drug;
- other evidence demonstrates that our product candidate is not shown to be safe or effective under the conditions of use;
- we fail to conduct any required post-approval trial of our product candidate with due diligence; or
- we disseminate false or misleading promotional materials relating to the relevant product candidate.

A Breakthrough Therapy Designation by the FDA, even if granted for any of our product candidates, may not lead to a faster development or regulatory review or approval process, and does not increase the likelihood that our product candidates will receive marketing approval.

We have received Breakthrough Therapy Designation from the FDA for our lead product candidate pegzilarginase for the treatment of Arginase 1 Deficiency and may seek such designation for some or all of our product candidates. A Breakthrough Therapy is defined as a drug or biologic that is intended, alone or in combination with one or more other

drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug or biologic may demonstrate substantial improvement over existing therapies with respect to one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For drugs or biologics that have been designated as Breakthrough Therapies, interaction and communication between the FDA and the sponsor can help to identify the most efficient path for development.

Designation as a Breakthrough Therapy is within the discretion of the FDA. Accordingly, even if we believe, after completing early clinical trials, that one of our product candidates meets the criteria for designation as a Breakthrough Therapy, the FDA may disagree and instead determine not to make such designation. Even though we have received Breakthrough Therapy Designation for pegzilarginase for the treatment of Arginase 1 Deficiency, or even if we receive Breakthrough Therapy Designation for other product candidates or indications in the future, we may not experience a faster development process, review or approval compared to drugs or biologics considered for approval under conventional FDA procedures and such a designation does not assure ultimate approval by the FDA. In addition, even though we have received Breakthrough Therapy Designation for pegzilarginase for the treatment of Arginase 1 Deficiency, or if one or more of our other product candidates qualify as Breakthrough Therapies, the FDA may later decide that such product candidates no longer meet the conditions for qualification.

We may seek priority review designation for one or more of our other product candidates, but we might not receive such designation, and even if we do, such designation may not lead to a faster regulatory review or approval process.

If the FDA determines that a product candidate offers a treatment for a serious condition and, if approved, the product would provide a significant improvement in safety or effectiveness, the FDA may designate the application for such product candidate for priority review. A priority review designation means that the goal for the FDA to review an application is six months, rather than the standard review period of ten months. We may request priority review of any future BLA we submit for pegzilarginase and for applications for our other product candidates. The FDA has broad discretion with respect to whether or not to grant priority review designation to an application, so even if we believe an application for a particular product candidate is eligible for such designation, the FDA may decide not to grant it. Moreover, a priority review designation does not necessarily result in an expedited regulatory review or approval process or confer any advantage with respect to approval compared to conventional FDA procedures. Receiving priority review from the FDA does not guarantee approval within the six-month review cycle or at all.

Any product candidate for which we obtain marketing approval will be subject to extensive post-approval marketing regulatory requirements and could be subject to post-approval marketing restrictions or withdrawal from the market, and we may be subject to penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with our product candidates, when and if any of them are approved.

Our product candidates and the activities associated with their development and commercialization, including their testing, manufacture, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, are subject to comprehensive regulation by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, cGMP, requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, including periodic inspections by the FDA and other regulatory authorities, requirements regarding the distribution of samples to physicians and recordkeeping.

The FDA closely regulates the post-approval marketing and promotion of drugs and biologics to ensure drugs and biologics are marketed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA imposes stringent restrictions on manufacturers' communications regarding use of their products and if we promote our product candidates beyond their approved indications, we may be subject to enforcement action for off-label promotion. Violations of the Federal Food, Drug, and Cosmetic Act relating to the promotion of prescription drugs may lead to investigations alleging violations of federal and state healthcare fraud and abuse laws, as well as state consumer protection laws.

The FDA may also impose requirements for costly post-approval marketing studies or clinical trials and surveillance to monitor the safety or efficacy of any approved product. In particular, certain of our product candidates, if approved, are expected to be dosed chronically, and therefore could require follow-up studies and close monitoring of our patients after regulatory approval has been granted, to establish broader, longer-term understanding of potential for adverse effects than is plausible for clinical research. These studies may be expensive and time-consuming to conduct and may reveal side effects or other harmful effects in patients that use our therapeutic products after they are on the market, which may result

in the limitation or withdrawal of our drugs from the market. Alternatively, we may not be able to conduct such additional clinical trials, which might force us to abandon our efforts to develop or commercialize certain product candidates. Even if post-approval studies are not requested or required, after our products are approved and on the market, there might be safety issues that emerge over time that require a change in product labeling or that require withdrawal of the product from the market, which would cause our revenue to decline. If we fail to comply with any such post-approval regulatory requirements, approval for our products may be withdrawn, and product sales may be suspended. We may not be able to regain compliance, or we may only be able to regain compliance after a lengthy delay, significant expense, lost revenues and damage to our reputation.

In addition, later discovery of previously unknown adverse events or other problems with our product candidates, manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may yield various results, including:

- restrictions on such product candidates, manufacturers or manufacturing processes;
- restrictions on the labeling or marketing of a product;
- restrictions on product distribution or use;
- requirements to conduct post-marketing studies or clinical trials;
- warning or untitled letters;
- withdrawal of any approved product from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of product candidates;
- fines, restitution or disgorgement of profits or revenues;
- suspension or withdrawal of marketing approvals;
- refusal to permit the import or export of our product candidates;
- product seizure; or
- injunctions or the imposition of civil or criminal penalties.

Non-compliance with European requirements regarding safety monitoring or pharmacovigilance, and with requirements related to the development of products for the pediatric population, can also result in significant financial penalties. Similarly, failure to comply with Europe's and certain U.S state's requirements regarding the protection of personal information can also lead to significant penalties and sanctions.

Our relationships with customers and third-party payors will be subject to applicable anti-kickback, fraud and abuse and other healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings.

Healthcare providers, physicians and third-party payors will play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our future arrangements with third-party payors and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute any product candidates for which we obtain marketing approval. Restrictions under applicable U.S. federal and state healthcare laws and regulations include the following:

- the federal Anti-Kickback Statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made under a federal healthcare program such as Medicare and Medicaid;
- the federal False Claims Act imposes criminal and civil penalties, including civil whistleblower or *qui tam* actions, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;
- federal law requires applicable manufacturers of covered drugs to report payments and other transfers of value to physicians and teaching hospitals, which includes annual data collection and reporting obligations, with reported information disclosed on a searchable website on an annual basis; and
- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers.

Some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government and may require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures. Other states require reporting of pricing information, including price increases. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, imprisonment, exclusion of product candidates from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any of the physicians or other healthcare providers or entities with whom we expect to do business is found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

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.

In the United States, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the MMA, changed the way Medicare covers and pays for pharmaceutical products. The legislation expanded Medicare coverage for drug purchases by the elderly and introduced a new reimbursement methodology based on average sales prices for physician-administered drugs. In addition, this legislation provided authority for limiting the number of drugs that will be covered in any therapeutic class. Cost reduction initiatives and other provisions of this legislation could decrease the coverage and price that we receive for any approved product candidates. While the MMA only applies to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own reimbursement rates. Therefore, any reduction in reimbursement that results from the MMA may result in a similar reduction in payments from private payors.

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 2031, with the exception of a temporary suspension implemented under various COVID-19 relief legislation from May 1, 2020 through March 31, 2022 and a 1% reduction from April 1, 2022 through June 30, 2022, unless additional Congressional action is

taken. Under current legislation, the actual reduction in Medicare payments will vary from 1% in 2022 to up to 4% in the final fiscal year of this sequester. 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 to initiate 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 instructs 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, which will first become effective in 2026, will be capped at a statutory ceiling price 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. 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. 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.

Comprehensive tax reform bills could increase the tax burden on our orphan drug programs and adversely affect our business and financial condition.

New income, sales, use or other tax laws, statutes, rules, regulations or ordinances could be enacted at any time, which could adversely affect our business and financial condition. Further, existing tax laws, statutes, rules, regulations or ordinances could be interpreted, changed, modified or applied adversely to us. For example, the 2017 Tax Cuts and Jobs Act, among others, reduced the orphan drug credit from 50% to 25% of qualifying expenditures. When and if we become profitable, this reduction in tax credits may result in an increased federal income tax burden on our orphan drug programs. On March 27, 2020, the Coronavirus Aid, Relief and Economic Security, or CARES Act, was enacted and modified certain portions of the 2017 Tax Cuts and Jobs Act, including with respect to the carryforward of net operating losses. Future changes in corporate tax rates, rules relating to the realization of net deferred tax assets, and other tax legislation could

have a material impact on the value of our deferred tax assets, could result in a significant one-time charges, and could increase our future U.S. tax expense.

Risks Related to Our Intellectual Property

If we are unable to obtain and maintain intellectual property protection for our technology and product candidates, or if the scope of the intellectual property protection obtained is not sufficiently broad, our competitors could develop and commercialize technology and product candidates similar or identical to ours, and our ability to successfully commercialize our technology and product candidates may be impaired.

We rely upon a combination of patents, trade secret protection and confidentiality agreements to protect the intellectual property related to our technology and product candidates.

In particular, our success depends in large part on our ability, and our licensors' ability, to obtain and maintain patent protection in the United States and other countries with respect to our proprietary technology and product candidates, including any diagnostic developed by us or a third-party strategic partner. We seek to protect our proprietary position by filing patent applications in the United States and abroad related to our novel technologies and product candidates and rely on our licensors to obtain patent protection for our licensed intellectual property. Our patent portfolio includes patents and patent applications we own or we exclusively license from the University of Texas at Austin. This patent portfolio includes issued patents and pending patent applications covering compositions of matter and methods of use.

The patent prosecution process is expensive and time-consuming, and we may not be able to file, prosecute, maintain, enforce or license all necessary or desirable patent applications at a reasonable cost or in a timely manner, or in all jurisdictions. We may choose not to seek patent protection for certain innovations and may choose not to pursue patent protection in certain jurisdictions, and under the laws of certain jurisdictions, patents or other intellectual property rights may be unavailable or limited in scope. It is also possible that we will fail to identify patentable aspects of our discovery and nonclinical and clinical development output before it is too late to obtain patent protection. Moreover, the risks pertaining to our patents and intellectual property rights also apply to the intellectual property rights that we license from third parties. In some circumstances, we do not have the right to control the preparation, filing and prosecution of patent applications, or to maintain the patents, covering technology that we license from third parties. We may also require the cooperation of our licensors in order to enforce the licensed patent rights, and such cooperation may not be provided. Therefore, these patents and applications may not be prosecuted and enforced in a manner consistent with the best interests of our business and the rights we have licensed may be reduced or eliminated.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation. The U.S. Patent and Trademark Office, or U.S. PTO, has not established a consistent policy regarding the breadth of claims that it will allow in biotechnology patents. In addition, the laws of foreign jurisdictions may not protect our rights to the same extent as the laws of the United States. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot know with certainty whether we were the first to make the inventions claimed in our owned or licensed patents or pending patent applications, or that we were the first to file for patent protection of such inventions, nor can we know whether those from whom we license patents were the first to make the inventions claimed or were the first to file. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our pending and future patent applications may not result in patents being issued that protect our technology or product candidates, in whole or in part, or which effectively prevent others from commercializing competitive technologies and product candidates. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection. In addition, during prosecution of any patent application, the issuance of any patents based on an application may depend upon our ability to generate additional nonclinical or clinical data that supports the patentability of our proposed claims. We may not be able to generate such data on a timely basis, to the satisfaction of the U.S. PTO, or at all.

Moreover, we may be subject to a third-party preissuance submission of prior art to the U.S. PTO or patent offices in foreign jurisdictions, or become involved in opposition, derivation, reexamination, inter partes review, post-grant review or interference proceedings challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or product candidates and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize product candidates without infringing third-party patent rights. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates.

Even if our owned and licensed patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive

advantage. Our competitors may be able to circumvent our owned or licensed patents by developing similar or alternative technologies or product candidates in a non-infringing manner.

The issuance of a patent, while given the presumption of validity under the law, is not conclusive as to its inventorship, scope, validity or enforceability, and our owned and licensed patents may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in loss of exclusivity or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and product candidates, or limit the duration of the patent protection of our technology and product candidates. In addition, patents have a limited lifespan. In the United States, the natural expiration of a patent is generally 20 years after the first non-provisional filing in the patent family. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing product candidates similar or identical to ours.

Any inability on our part to adequately protect our intellectual property may have a material adverse effect on our business, operating results and financial position.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

Periodic maintenance fees, renewal fees, annuity fees and various other governmental fees on patents and/or applications will be due to be paid to the U.S. PTO and various governmental patent agencies outside the United States in several stages over the lifetime of the patents and/or applications. We have systems in place to remind us to pay these fees, and we employ an outside firm and rely on our outside counsel to pay these fees. The U.S. PTO and various non-U.S. governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. We employ reputable law firms and other professionals to help us comply, and in some cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. However, we also rely on licensors to effect such payments with respect to the patents and patent applications that we in-license. Moreover, there are situations in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, our competitors might be able to enter the market and this circumstance would have a material adverse effect on our business.

Third parties may initiate legal proceedings alleging that we are infringing their intellectual property rights, the outcome of which would be uncertain and could have a material adverse effect on the success of our business.

Our commercial success depends upon our ability, and the ability of our collaborators, to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing the proprietary rights of third parties. There is considerable intellectual property litigation in the biotechnology and pharmaceutical industries. We may become party to, or threatened with, future adversarial proceedings or litigation regarding intellectual property rights with respect to our product candidates and technology, including interference or derivation proceedings before the U.S. PTO and similar bodies in other jurisdictions. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future. We may also institute proceedings in courts or patent offices seeking decisions regarding the validity or scope of patents owned by third parties. For example, we have filed nullity actions in the Federal Patent Court in Germany regarding two German patents relating to arginases.

It is also possible that we have failed to identify relevant third-party patents or applications. For example, applications filed before November 29, 2000 and certain applications filed after that date that will not be filed outside the United States remain confidential until patents issue. Moreover, it is difficult for industry participants, including us, to identify all third-party patent rights that may be relevant to our product candidates and technologies because patent searching is imperfect due to differences in terminology among patents, incomplete databases and the difficulty in assessing the meaning of patent claims. We may fail to identify relevant patents or patent applications or may identify pending patent applications of potential interest but incorrectly predict the likelihood that such patent applications may issue with claims of relevance to our technology. In addition, we may be unaware of one or more issued patents that would be infringed by the manufacture, sale or use of a current or future product candidate, or we may incorrectly conclude that a third-party patent is invalid, unenforceable or not infringed by our activities. Additionally, pending patent applications that have been published can, subject to certain limitations, be later amended in a manner that could cover our technologies, our products or the use of our products.

If we are found to infringe a third party's intellectual property rights, we could be required to obtain a license from such third party to continue developing and marketing our product candidates and technology. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. We could be forced, including by court order, to cease commercializing the infringing technology or product. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees, if we are found to have willfully infringed a patent. A finding of infringement could prevent us from commercializing our product candidates or force us to cease some of our business operations, which could materially harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business.

We may be subject to claims that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information or trade secrets of third parties or that our employees, consultants or independent contractors have wrongfully used or disclosed alleged trade secrets of former or other employers.

Many of our employees, independent contractors and consultants, including our senior management, have been previously employed or retained by universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Further, many of our consultants are currently retained by other biotechnology or pharmaceutical companies and may be subject to conflicting obligations to these third parties. Although we try to ensure that our employees, consultants and independent contractors do not use the proprietary information or know-how of third parties in their work for us, and do not perform work for us that is in conflict with their obligations to another employer or any other entity, we may be subject to claims that we or our employees, consultants or independent contractors have inadvertently or otherwise improperly used or disclosed confidential information, including trade secrets or other proprietary information, of a former employer or other third parties. We may also be subject to claims that an employee, advisor, consultant, or independent contractor performed work for us that conflicts with that person's obligations to a third party, such as an employer, and thus, that the third party has an ownership interest in the intellectual property arising out of work performed for us. We are not aware of any threatened or pending claims related to these matters, but in the future litigation may be necessary to defend against such claims.

In addition, while it is our policy to require our employees, independent contractors and consultants who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in timely obtaining such an agreement with each party who in fact develops intellectual property that we regard as our own. Even if timely obtained, such agreements may be breached, and we may be forced to bring claims against third parties, or defend claims they may bring against us, to determine the ownership of what we regard as our intellectual property.

If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable personnel or intellectual property rights, such as exclusive ownership of, or right to use, valuable intellectual property. As a result, we may also elect to enter into license agreements in order to settle patent infringement claims or to resolve disputes prior to litigation, and any such license agreements may require us to pay royalties and other fees that could be significant. Such an outcome could have a material adverse effect on our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management.

The illegal distribution and sale by third parties of counterfeit versions of our products or stolen products could have a negative impact on our reputation and business.

Third parties might illegally distribute and sell counterfeit or unfit versions of our approved products, if any, which do not meet our rigorous manufacturing and testing standards. A patient who receives a counterfeit or unfit drug may be at risk for a number of dangerous health consequences. Our reputation and business could suffer harm as a result of counterfeit or unfit drugs sold under our brand name. In addition, thefts of inventory at warehouses, plants or while in-transit, which are not properly stored and which are sold through unauthorized channels, could adversely impact patient safety, our reputation and our business.

Any lawsuits relating to infringement of intellectual property rights necessary to defend ourselves or enforce our rights will be costly and time consuming, and could be unsuccessful.

Because competition in our industry is intense, competitors may infringe or otherwise violate our issued patents, patents of our licensors or other intellectual property. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming. Any claims we assert against perceived infringers

could provoke these parties to assert counterclaims against us alleging, among other claims, that we infringe their patents. In addition, in a patent infringement proceeding there are many grounds upon which a party may assert invalidity or unenforceability of a patent, and a court may decide that a patent of ours is invalid or unenforceable, in whole or in part, construe the patent's claims narrowly or refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. Litigation is uncertain and we cannot predict whether we would be successful in any such litigation. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities. We may not have sufficient financial, managerial or other resources to adequately conduct such litigation or proceedings. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial, managerial and other resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our business. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure.

Intellectual property disputes could cause us to spend substantial resources and distract our personnel from their normal responsibilities.

Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses and could distract our technical and/or management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the market price of our common stock. In some cases, we may choose not to pursue litigation against those that have infringed on our patents, or used them without authorization, due to the associated expenses and time commitment of monitoring these activities. If we fail to protect or to enforce our intellectual property rights successfully, our competitive position could suffer, which could harm our results of operations.

We may not be successful in obtaining or maintaining necessary rights for our development pipeline through acquisitions and in-licenses.

Presently we have rights to intellectual property to develop our product candidates, including patents and patent applications we own or exclusively license from the University of Texas at Austin. Because our programs may involve additional product candidates that may require the use of proprietary rights held by third parties, the growth of our business may depend in part on our ability to acquire, in-license or use these proprietary rights. We may be unable to acquire or in-license any compositions, methods of use, processes or other third-party intellectual property rights from third parties that we identify as necessary for our product candidates. The licensing and acquisition of third-party intellectual property rights is a competitive area, and a number of more established companies are also pursuing strategies to license or acquire third-party intellectual property rights that we may consider attractive. These established companies may have a competitive advantage over us due to their size, cash resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third-party intellectual property rights on terms that would allow us to make an appropriate return on our investment. If we are unable to successfully obtain rights to required third-party intellectual property rights, our business, financial condition and prospects for growth could suffer.

If we are not able to prevent disclosure of our trade secrets and other proprietary information, the value of our technology and product candidates could be significantly diminished.

We rely on trade secret protection to protect our interests in proprietary know-how and in processes that are unpatentable or for which patents are difficult to obtain or enforce. We may not be able to protect our trade secrets adequately. We have a policy of requiring our consultants, advisors and strategic partners to enter into confidentiality agreements and our employees to enter into invention, non-disclosure and non-compete agreements. However, no assurance can be given that we have entered into appropriate agreements with all parties that have had access to our trade secrets, know-how or other proprietary information, or that such agreements will provide for a meaningful protection of our trade secrets, know-how or other proprietary information in the event of any unauthorized use or disclosure of information. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. Even if we are successful in prosecuting such claims, any remedy awarded may be insufficient to fully compensate us for the improper disclosure or misappropriation. Furthermore, although we seek to preserve the integrity and confidentiality of our data, trade secrets and know-how by maintaining physical security of our premises and physical and electronic security of our information technology systems, it is also possible that our trade

secrets, know-how or other proprietary information could be obtained by third parties as a result of breaches of such systems.

Any disclosure of confidential information into the public domain or to third parties could allow our competitors to learn our trade secrets and use the information in competition against us. In addition, others may independently discover or develop our trade secrets and proprietary information or substantially equivalent techniques. Any action to enforce our rights is likely to be time consuming and expensive, and may ultimately be unsuccessful, or may result in a remedy that is not commercially valuable. These risks are accentuated in foreign countries where laws or law enforcement practices may not protect proprietary rights as fully as in the United States or Europe. Any unauthorized disclosure of our trade secrets or confidential information could harm our competitive position.

We may not be able to protect our intellectual property rights throughout the world.

Filing, prosecuting and defending patents on all of our product candidates throughout the world would be prohibitively expensive, and our patent rights in some countries outside the United States can be less extensive than those in the United States. The requirements for patentability may differ in certain countries, particularly developing countries. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions.

As part of ordinary course prosecution and maintenance activities, we determine whether to seek patent protection outside the United States and in which countries. This also applies to patents we have acquired or in-licensed from third parties. In some cases, this means that we, or our predecessors in interest or licensors of patents within our portfolio, have sought patent protection in a limited number of countries for patents covering our product candidates. Competitors may use our technologies in jurisdictions where we have not pursued and obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection but where enforcement is not as strong as in the United States. These products may compete with our products in jurisdictions where we do not have any issued patents and, even in jurisdictions where we have or are able to obtain issued patents, our patent claims or other intellectual property rights may not be effective or sufficient to prevent them from so competing. Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents and other intellectual property protection, particularly those relating to biopharmaceuticals, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial cost and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. In addition, certain countries have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties. In those countries, we may have limited remedies if our patents are infringed or if we are compelled to grant a license to our patents to a third party, which could materially diminish the value of those patents. In addition, there may be patent law reforms in foreign jurisdictions that could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents in those foreign jurisdictions. This could limit our potential revenue opportunities.

Accordingly, our efforts to obtain, register, and enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we own or license. Moreover, patent protection must ultimately be sought on a country-by-country basis, which is an expensive and time-consuming process with uncertain outcomes. Accordingly, we may choose not to seek patent protection in certain countries, and we will not have the benefit of patent protection in such countries.

If we breach any of the agreements under which we license patent rights to use, develop and commercialize our product candidates or our technologies from third parties or, in certain cases, we fail to meet certain development deadlines, we could lose license rights that are important to our business.

We are a party to license agreements under which we are granted rights to intellectual property that are important to our business and we expect that we may need to enter into additional license agreements in the future.

In December 2013, our wholly owned subsidiaries AECase, Inc. and AEMase, Inc. each entered into an exclusive, worldwide license agreement, including the right to grant sublicenses, with the University of Texas at Austin for certain intellectual property owned by the University of Texas at Austin related to our program candidates related to cystinase and methioninase. In January 2017, we and the University of Texas at Austin entered into an Amended and Restated Patent License Agreement, or the Restated License, which consolidated the two license agreements, revised certain obligations, and licensed additional patent applications and invention disclosures to us. The Restated License was amended in August 2017, December 2017, and December 2018 to revise diligence milestones and license additional patent applications, including our program candidates under the pegtarviliase and cystinuria programs. The intellectual property licensed under the Restated License includes inventions that were made with U.S. government support. The U.S. government therefore has certain rights in such inventions under the applicable funding agreements and under applicable law. In addition, we are subject to a requirement that the products covered by the applicable patents that are sold or used in the United States must be manufactured substantially in the United States unless a written waiver is obtained in advance from the U.S. government. The Restated License obligates us to make certain payments at the achievement of certain milestones and at regular intervals throughout the life of the license. The University of Texas at Austin may terminate the Restated License under certain circumstances, including for a breach by us that is not cured within 30 or 60 days of notice (depending on the type of breach), or if we or any of our affiliates or sublicensees participate in any proceeding to challenge the licensed patent rights (unless, with respect to sublicensees, we terminate the applicable sublicense).

Licensing of intellectual property is of critical importance to our business and involves complex legal, business and scientific issues. Any other licenses or other intellectual property agreements we may enter into may impose various diligence, milestone payment, royalty and other obligations on us. If disputes arise between us and our licensor or if we fail to comply with our obligations under current or future intellectual property agreements, potentially giving our counterparties the right to terminate these agreements, we might not be able to develop, manufacture or market any product that is covered by the agreement or face other penalties under the agreement. Such an occurrence could materially adversely affect the value of the product candidate being developed under any such agreement. Termination of these agreements or reduction or elimination of our rights under these agreements may result in our having to negotiate new or reinstated agreements with less favorable terms, or cause us to lose our rights under these agreements, including our rights to important intellectual property or technology.

The loss of any one of our current licenses, or any other license we may acquire in the future, could prevent or impair our ability to successfully develop and commercialize the affected product candidates and thus materially harm our business, prospects, financial condition and results of operations.

Intellectual property rights do not necessarily address all potential threats to our competitive advantage.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations, and may not adequately protect our business, provide a barrier to entry against our competitors or potential competitors, or permit us to maintain our competitive advantage. Moreover, if a third party has intellectual property rights that cover the practice of our technology or product candidates, we may not be able to fully exercise or extract value from our intellectual property rights. The following examples are illustrative:

- others may be able to make compounds that are similar to our product candidates but that are not covered by the claims of the patents that we own or license;
- we or our licensors or collaborators might not have been the first to make the inventions covered by an issued patent or pending patent application that we own or license;
- we or our licensors or collaborators might not have been the first to file patent applications covering an invention;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing or misappropriating our intellectual property rights;
- pending patent applications that we own or license may not lead to issued patents;

- issued patents that we own or license may not provide us with any competitive advantages, or may be narrowly construed or held invalid or unenforceable, as a result of legal challenges by our competitors;
- our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we may not develop or in-license additional proprietary technologies that are patentable; and
- the patents of others may have an adverse effect on our business.

Any of these events could significantly harm our business, results of operations and prospects.

Changes in patent law could diminish the value of patents in general, thereby impairing our ability to protect our products, and recent patent legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents.

As is the case with other biotechnology companies, our success is heavily dependent on patents. Obtaining and enforcing patents in the biotechnology industry involve both technological and legal complexity, and is therefore costly, time-consuming and inherently uncertain. In addition, the United States has recently enacted patent reform legislation. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this has created greater uncertainty with respect to the value of patents, once obtained. Depending on decisions by the U.S. Congress, the federal courts, and the U.S. PTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

On September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The U.S. PTO has promulgated regulations and developed procedures to govern administration of the Leahy-Smith Act. The Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business and financial condition.

The Leahy-Smith Act also requires an inventor to file a patent application on their invention prior to any other bona fide independent inventor. Since patent applications in the United States and most other countries are confidential for a period of time after filing, we cannot be certain that we were the first to either (i) file any patent application related to our product candidates or (ii) invent any of the inventions claimed in our patents or patent applications.

The Leahy-Smith Act allows a third party to provide evidence in a U.S. PTO proceeding that could invalidate our patent claims. Accordingly, a third party may use the U.S. PTO procedures to invalidate our patent claims. In such an event, this circumstance could have a material adverse effect on our business.

If we do not obtain patent term extensions under the Hatch-Waxman Act and similar legislation, thereby not extending the term of our marketing exclusivity for our product candidates, our business may be materially harmed.

Depending upon the timing, duration and specifics of FDA marketing approval of our product candidates, if any, one of the U.S. patents covering each of such approved product(s) or the use thereof may be eligible for up to five years of patent term restoration. Patent term extension allows a maximum of one patent to be extended per FDA-approved product. Patent term extension also may be available in certain foreign countries upon regulatory approval of our product candidates, if any. Nevertheless, we may not be granted patent term extension either in the United States or in any foreign country because of, for example, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents or otherwise failing to satisfy applicable requirements. Moreover, the term of extension, as well as the scope of patent protection during any such extension, afforded by the governmental authority could be less than we request. In addition, if a patent we wish to extend is owned by another party and licensed to us, we may need to obtain approval and cooperation from our licensor to request the extension.

If we are unable to obtain patent term extension or restoration, or the term or scope of any such extension is less than we request, the period during which we will have the right to exclusively market our product will be shortened and our competitors may obtain approval of competing products following our patent expiration, and our revenue could be reduced, possibly materially.

We have not yet registered our trademarks in all of our potential markets, and failure to secure those registrations could adversely affect our business.

We attempt to protect our pharmaceutical developments, services, and products under trademark laws. However, our trademark applications may not be allowed for registration, and registered trademarks may not be maintained or enforced. During trademark registration proceedings, we may receive rejections. Although we are given an opportunity to respond to those rejections, we may be unable to overcome such rejections. In addition, in the U.S. Patent and Trademark Office and in comparable agencies in many foreign jurisdictions, third parties are given an opportunity to oppose pending trademark applications and to seek to cancel registered trademarks. Opposition or cancellation proceedings may be filed against our trademarks, and our trademarks may not survive such proceedings. If we do not secure registrations for our trademarks, we may encounter more difficulty in enforcing them against third parties than we otherwise would.

Third parties may pursue trademark infringement actions against us, potentially resulting in substantial costs and material delays.

As our activities grow, we may be subject to an increasing amount of litigation that is common in the pharmaceutical industry based on allegations of infringement or other alleged violations of trademarks. Any claims of infringement, with or without merit, could be time consuming, costly, and difficult to defend. Moreover, intellectual property litigation or claims could require us to redesign packaging and advertising materials associated with our packaging, which could result in substantial costs and material delays.

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 September 30, 2022, had 69 employees. We are 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.

Recruiting and retaining qualified scientific, clinical, manufacturing and sales and marketing personnel will also be critical to our success. 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.

Our employees may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements, which could cause significant liability for us and harm our reputation.

We are exposed to the risk of employee fraud or other misconduct, including intentional failures to (i) comply with FDA regulations or similar regulations of comparable non-U.S. regulatory authorities, (ii) provide accurate information to the FDA or comparable non-U.S. regulatory authorities, (iii) comply with manufacturing standards we have established, (iv) comply with the Foreign Corrupt Practices Act and federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable non-U.S. regulatory authorities, or (v) report financial information or data accurately or disclose unauthorized activities to us. Employee misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious

harm to our reputation. It is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws, standards or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and results of operations, including the imposition of significant fines or other sanctions.

If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of our product candidates.

We face an inherent risk of product liability as a result of testing our product candidates in clinical trials and will face an even greater risk if we commercialize any products. For example, we may be sued if our product candidates cause or are perceived to cause injury or are found to be otherwise unsuitable during clinical trials, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability or a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our product candidates. Even successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in:

- inability to bring a product candidate to the market;
- decreased demand for our products;
- injury to our reputation;
- withdrawal of clinical trial participants and inability to continue clinical trials;
- initiation of investigations by regulators;
- costs to defend the related litigation;
- diversion of management's time and our resources;
- substantial monetary awards to trial participants or patients;
- product recalls, withdrawals or labeling, marketing or promotional restrictions;
- loss of revenue;
- exhaustion of any available insurance and our capital resources;
- the inability to commercialize any product candidate; and
- decline in our share price.

Our product liability insurance policies may also have various exclusions, and we may be subject to a product liability claim for which we have no coverage. We may have to pay any amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts. Even if our agreements with any future corporate collaborators entitle us to indemnification against losses, such indemnification may not be available or adequate should any claim arise.

Our ability to use our net operating loss carryforwards and certain other tax attributes may be limited.

Under Section 382 of the Internal Revenue Code of 1986, as amended, if a corporation undergoes an “ownership change,” generally defined as a greater than 50% change (by value) in its equity ownership over a three-year period, the corporation’s ability to use its pre-change net operating loss carryforwards, or NOLs, and other pre-change tax attributes (such as research tax credits) to offset its post-change income or taxes may be limited. It is possible that we may have triggered an “ownership change” limitation. We may also experience ownership changes in the future as a result of subsequent shifts in our stock ownership (some of which are outside of our control). As a result, if we earn net taxable income, our ability to use our pre-change NOLs and other pre-change tax attributes to offset U.S. federal taxable income or taxes may be subject to limitations, which could potentially result in increased future tax liability to us. Our NOLs and other tax attributes arising before our conversion from a Delaware limited liability company to a Delaware corporation in 2015 also may be limited by the Separate Return Limitation Year rule, which could increase our U.S. federal tax liability. In addition, at the state level, there may be periods during which the use of NOLs is suspended or otherwise limited, which could accelerate or permanently increase state taxes owed.

Risks Related to Our Common Stock

Our executive officers, directors and principal stockholders, if they choose to act together, may continue to have the ability to control all matters submitted to stockholders for approval.

We have a concentrated stockholder base and our executive officers and directors, combined with our stockholders who, to our knowledge, each owned more than 5% of our outstanding common stock, in the aggregate, beneficially own shares representing a substantial number of our capital stock as of September 30, 2022. As a result, if these stockholders were to choose to act together, they may be able to control all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these persons, if they choose to act together, would likely control the election of directors and approval of any merger, consolidation or sale of all or substantially all of our assets. This concentration of ownership control may:

- delay, defer or prevent a change in control;
- entrench our management and the board of directors; or
- impede a merger, consolidation, takeover or other business combination involving us that other stockholders may desire or may result in you obtaining a premium for your shares.

Failure to achieve and maintain effective internal control over financial reporting in accordance with Section 404 of the Sarbanes-Oxley Act could have a material adverse effect on our business and stock price.

Pursuant to Section 404, we have been required to furnish a report by our management on our internal control over financial reporting. However, while we remain a non-accelerated filer, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. Internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements in accordance with generally accepted accounting principles in the United States. We may encounter problems or delays in implementing any changes necessary to make a favorable assessment of our internal control over financial reporting. If we cannot favorably assess the effectiveness of our internal control over financial reporting, or if our independent registered public accounting firm is unable to provide an unqualified attestation report on our internal controls when required, investors could lose confidence in our financial information and the price of our common stock could decline.

Additionally, the existence of any material weakness or significant deficiency would require management to devote significant time and incur significant expense to remediate any such material weaknesses or significant deficiencies and management may not be able to remediate any such material weaknesses or significant deficiencies in a timely manner. The existence of any material weakness in our internal control over financial reporting could also result in errors in our financial statements that could require us to restate our financial statements causing us to fail to meet our reporting obligations and cause stockholders to lose confidence in our reported financial information, all of which could materially and adversely affect us.

Provisions in our corporate charter documents and under Delaware law could make an acquisition of our company, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management.

Provisions in our certificate of incorporation and our bylaws may discourage, delay or prevent a merger, acquisition or other change in control of our company that stockholders may consider favorable, including transactions in which you might otherwise receive a premium for your shares. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, because our board of directors is responsible for appointing the members of our management team, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Among other things, these provisions:

- establish a classified board of directors such that only one of three classes of directors is elected each year;
- allow the authorized number of our directors to be changed only by resolution of our board of directors;
- limit the manner in which stockholders can remove directors from our board of directors;
- establish advance notice requirements for stockholder proposals that can be acted on at stockholder meetings and nominations to our board of directors;
- require that stockholder actions must be effected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent;

- limit who may call stockholder meetings;
- authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a “poison pill” that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board of directors; and
- require the approval of the holders of at least two-thirds of the votes that all our stockholders would be entitled to cast to amend or repeal specified provisions of our certificate of incorporation or bylaws.

Moreover, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner.

Any of these provisions of our charter documents or Delaware law could, under certain circumstances, depress the market price of our common stock.

Our amended and restated certificate of incorporation designates the Court of Chancery of the State of Delaware as the sole and exclusive forum for certain types of actions and proceedings that may be initiated by our stockholders, and our amended and restated bylaws designates the federal courts of the United States as the exclusive forum for actions arising under the Securities Act, each of which could limit our stockholders’ ability to obtain a favorable judicial forum for disputes with us or our directors, officers, employees or agents.

Our amended and restated certificate of incorporation provides that, unless we consent in writing to an alternative forum, the Court of Chancery of the State of Delaware will be the sole and exclusive forum for any derivative action or proceeding brought on our behalf, any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers, employees or agents to us or our stockholders, any action asserting a claim arising pursuant to any provision of the DGCL, our amended and restated certificate of incorporation or our amended and restated bylaws or any action asserting a claim that is governed by the internal affairs doctrine, in each case subject to the Court of Chancery having personal jurisdiction over the indispensable parties named as defendants therein and the claim not being one which is vested in the exclusive jurisdiction of a court or forum other than the Court of Chancery or for which the Court of Chancery does not have subject matter jurisdiction. Any person purchasing or otherwise acquiring any interest in any shares of our capital stock shall be deemed to have notice of and to have consented to this provision of our amended and restated certificate of incorporation.

In March 2020, we amended and restated our restated bylaws to provide that the federal district courts of the United States of America will, to the fullest extent permitted by law, be the exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act (a Federal Forum Provision). Our decision to adopt a Federal Forum Provision followed a decision by the Supreme Court of the State of Delaware holding that such provisions are facially valid under Delaware law. While there can be no assurance that federal or state courts will follow the holding of the Delaware Supreme Court or determine that the Federal Forum Provision should be enforced in a particular case, application of the Federal Forum Provision means that suits brought by our stockholders to enforce any duty or liability created by the Securities Act must be brought in federal court and cannot be brought in state court.

These choice of forum provisions may limit our stockholders’ ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers, employees or agents, which may discourage such lawsuits against us and our directors, officers, employees and agents even though an action, if successful, might benefit our stockholders. Stockholders who do bring a claim in the specified courts could face additional litigation costs in pursuing any such claim. The specified courts may also reach different judgments or results than would other courts, including courts where a stockholder considering an action may be located or would otherwise choose to bring the action, and such judgments or results may be more favorable to us than to our stockholders. Alternatively, if a court were to find these provisions of our governance documents inapplicable to, or unenforceable in respect of, one or more of the specified types of actions or proceedings, we may incur additional costs associated with resolving such matters in other jurisdictions, which could have a material adverse effect on our business, financial condition or results of operations.

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 competitive products or technologies;
- results of ongoing or planned 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 and the economic impact of the war in Ukraine and the ongoing COVID-19 pandemic; and
- the other factors described in this “Risk Factors” section.

We have broad discretion in the use of the net proceeds from our public offerings and may not use them effectively.

Our management has broad discretion in the application of the net proceeds from our public offerings, and you will not have the opportunity as part of your investment decision to assess whether the net proceeds are being used appropriately. Our management could spend the net proceeds from our public offerings in ways that do not improve our results of operations or enhance the value of our common stock. The failure by our management to apply these funds effectively could result in financial losses that could have a material adverse effect on our business, cause the price of our common stock to decline and delay the development of our product candidates. Pending their use, we may invest the net proceeds from our public offerings in a manner that does not produce income or that loses value.

Future sales of our common stock in the public market could cause the market price of our common stock to drop significantly, even if our business is doing well.

Sales of a substantial number of shares of our common stock in the public market, or the perception in the market that the holders of a large number of shares intend to sell shares, could reduce the market price of our common stock and make it more difficult for you to sell your common stock at a time and price that you deem appropriate.

Moreover, we have also registered under the Securities Act shares of common stock that we may issue under our equity compensation plans.

In July 2020, we filed a new shelf registration statement on Form S-3 that was declared effective in July 2020 by the SEC 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. If we sell common stock, preferred stock, convertible securities and other equity securities in other transactions pursuant to our shelf registration statements on Form S-3, existing investors may be materially diluted by such subsequent sales and new investors could gain rights superior to our existing stockholders. In May 2021, we filed a shelf registration statement on Form S-3, that was declared effective on June 8, 2021 by the SEC, registering up to 19,020,434 shares of our common stock held by 667, L.P., or 667, and Baker Brothers Life

Sciences, L.P., or Life Sciences, and together with 667, the Baker Funds, which includes 15,610,328 shares of common stock issuable upon the exercise of pre-funded warrants held by the Baker Funds, for resale or other disposition from time to time as described in the registration statement.

In May 2022, we entered into a securities purchase agreement with certain institutional investors providing for the purchase and sale of our common stock and pre-funded warrants to purchase shares of common stock in a registered direct offering for gross proceeds to us of approximately $45.0 million prior to deducting placement agent fees and estimated offering expenses. The financing included the issuance and sale of 10,752,688 shares of our common stock and pre-funded warrants to purchase 17,372,397 shares of our common stock.

In May 2022, we entered into an “at-the-market” offering of our common stock pursuant to a sales agreement between us and JonesTrading Institutional Services LLC, or JonesTrading, under a shelf registration statement on Form S-3. Subject to certain limitations in the sales agreement and compliance with applicable law, we have the discretion to deliver a placement notice to JonesTrading at any time throughout the term of the sales agreement, which has a term equal to the term of the registration statement on Form S-3 unless otherwise terminated earlier by us or JonesTrading pursuant to the terms of the sales agreement. The number of shares that are sold by JonesTrading after delivering a placement notice will fluctuate based on the market price of our common stock during the sales period and limits we set with JonesTrading. Because the price per share of each share sold pursuant to the sales agreement will fluctuate based on the market price of our common stock during the sales period, it is not possible at this stage to predict the number of shares that will be ultimately issued. Issuances of any shares sold pursuant to the sales agreement will have a dilutive effect on our existing stockholders.

In addition, in the future, we may issue additional shares of common stock or other equity or debt securities convertible into common stock in connection with a financing, acquisition, litigation settlement, employee arrangements or otherwise, including upon exercise of our pre-funded warrants. Any such issuance could result in substantial dilution to our existing stockholders and could cause our stock price to decline.

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 September 30, 2022, we have issued pre-funded warrants to purchase a total of 34,982,640 shares of our common stock, of which 2,251,512 have been exercised and 32,731,128 are 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.

There is no public market for our pre-funded warrants.

There is no public trading market for our pre-funded warrants issued in the February 2019, April 2020 and May 2022 public offerings, and we do not expect a market to develop. In addition, we do not intend to apply to list the pre-funded warrants on any securities exchange or nationally recognized trading system, including the Nasdaq Global Market. Without an active market, the liquidity of the pre-funded warrants will be limited and their value may be adversely impacted.

Additionally, each holder of pre-funded warrants will not be entitled to exercise any portion of any pre-funded warrant, which, upon giving effect to such exercise, would cause (i) the aggregate number of shares of our common stock beneficially owned by the holder (together with its affiliates) to exceed 4.99%, or 9.99% for certain holders, of the number of shares of our common stock outstanding immediately after giving effect to the exercise, or (ii) the combined voting power of our securities beneficially owned by the holder (together with its affiliates) to exceed 4.99%, or 9.99% for certain holders, of the combined voting power of all of our securities then outstanding immediately after giving effect to the exercise. However, any holder may increase or decrease such percentage to any other percentage (not in excess of 19.99% for the majority of such warrants) upon at least 61 days’ prior notice from the holder to us.

We are a "smaller reporting company," and the reduced disclosure requirements applicable to smaller reporting companies may make our common stock less attractive to investors.

We are a "smaller reporting company" under the Exchange Act. For so long as we remain a smaller reporting company, we are permitted and intend to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not smaller reporting companies. These exemptions include:

- being permitted to provide only two years of audited financial statements, in addition to any required unaudited interim financial statements, with correspondingly reduced "Management's Discussion and Analysis of Financial Condition and Results of Operations" disclosure;
- not being required to comply with the auditor attestation requirements in the assessment of our internal control over financial reporting of Section 404(b) of the Sarbanes-Oxley Act; and
- reduced disclosure obligations regarding executive compensation.

We may continue to take advantage of these exemptions until we are no longer a smaller reporting company. We will remain a smaller reporting company if we have either (i) less than $250 million in market value of our shares held by non-affiliates as of the last business day of our second fiscal quarter or (ii) less than $100 million of annual revenues in our most recent fiscal year and a market value of our shares held by non-affiliates less than $700 million as of the last business day of our second fiscal quarter. We may choose to take advantage of some but not all of these scaled disclosure requirements. Therefore, the information that we provide stockholders may be different than one might get from other public companies. Further, if some investors find our shares of common stock less attractive as a result, there may be a less active trading market for our shares of common stock and the market price of such shares of common stock may be more volatile.

We will continue to incur increased costs as a result of operating as a public company, and our management will be required to devote substantial time to new compliance initiatives and corporate governance practices.

As a public company, and particularly now that we are no longer an emerging growth company, we incur significant legal, accounting and other expenses that we did not incur as a private company. The Sarbanes-Oxley Act of 2002, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of The Nasdaq Global Market and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel will need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will continue to increase our legal and financial compliance costs and will make some activities more time-consuming and costly. For example, we expect that these rules and regulations may make it more difficult and more expensive for us to obtain and maintain director and officer liability insurance, which in turn could make it more difficult for us to attract and retain qualified members of our board of directors.

We are evaluating these rules and regulations, and cannot predict or estimate the amount of additional costs we may incur or the timing of such costs. These rules and regulations are often subject to varying interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. This could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices.

Pursuant to Section 404, we are required to furnish a report by our management on our internal control over financial reporting. As discussed above, if we cease to be a non-accelerated filer, we will be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm as required by Section 404(b). To achieve compliance with Section 404 within the prescribed period, we will be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that we will not be able to conclude, within the prescribed timeframe or at all, that our internal control over financial reporting is effective as required by Section 404. If we identify one or more material weaknesses, it could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our consolidated financial statements.

Since we do not anticipate paying any cash dividends on our capital stock in the foreseeable future, stock price appreciation, if any, will be your sole source of gain.

We have never declared or paid cash dividends on our capital stock. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business. In addition, the terms of any future debt agreements

may preclude us from paying dividends. As a result, appreciation, if any, in the market price of our common stock will be your sole source of gain for the foreseeable future.

The price of our common stock does not meet the requirements for continued listing on Nasdaq. If we fail to regain compliance with the minimum listing requirements, our common stock will be subject to delisting. Our ability to publicly or privately sell equity securities and the liquidity of our common stock could be adversely affected if our common stock is delisted.

The continued listing standards of Nasdaq require, among other things, that the minimum bid price of a listed company's stock be at or above $1.00. If the closing minimum bid price is below $1.00 for a period of more than 30 consecutive trading days, the listed company will fail to be in compliance with Nasdaq's listing rules and, if it does not regain compliance within the grace period, will be subject to delisting. As previously reported, on July18, 2022, we received a notice from the Nasdaq Listing Qualifications Department notifying us that for 30 consecutive trading days, the bid price of our common stock had closed below the minimum $1.00 per share requirement. In accordance with Nasdaq's listing rules, we were afforded a grace period of 180 calendar days, or until January 16, 2023, to regain compliance with the bid price requirement. In order to regain compliance, the bid price of our common stock must close at a price of at least $1.00 per share for a minimum of 10 consecutive trading days.

If we fail to regain compliance by January 16, 2023, we may be eligible for a second 180 day compliance period if we elect to transfer to The Nasdaq Capital market, provided that, on such date, we meet the continued listing requirement for market value of publicly held shares and all other applicable Nasdaq listing requirements (other than the minimum closing bid price requirement) and we provide written notice to Nasdaq of our intention to cure the deficiency during the second compliance period, by effecting a reverse stock split, if necessary. Such extension of the grace period would be subject to Nasdaq's discretion, and there can be no guarantee that we would be granted an extension.

We cannot provide any guarantee that we will regain compliance during the grace period or be able to maintain compliance with Nasdaq's listing requirements in the future. If we are not able to regain compliance during the grace period, or any extension of the grace period for which we may be eligible, our common stock will be subject to delisting. Delisting from Nasdaq could adversely affect our ability to raise additional financing through the public or private sale of equity securities, would significantly affect the ability of investors to trade our securities and would negatively affect the value and liquidity of our common stock. Delisting could also have other negative results, including the potential loss of confidence by employees, the loss of institutional investor interest and fewer business development opportunities.

General Risk Factors

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could harm our business.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties for failure to comply with such laws and regulations.

Although we maintain workers' compensation insurance that we believe is consistent with industry norms to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, we cannot assure you that it will be sufficient to cover our liability in such cases. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological, hazardous or radioactive materials.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our discovery, nonclinical and clinical development or production efforts. Our failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Our information technology systems, or those used by our CROs, third-party vendors, contractors or consultants, may fail or suffer security breaches, cyber-attacks, and loss of data, which could harm our business, reputation, financial condition, and operations.

Cyber-attacks are increasing in their frequency, sophistication and intensity, and have become increasingly difficult to detect. Despite the implementation of security measures, our information technology systems and those of our strategic partners and third parties on whom we rely are vulnerable to cyber-attacks, security breaches, damage from computer

viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. Cyber-attacks could include the deployment of harmful malware, ransomware, denial-of-service attacks, social engineering and other means to affect service reliability and threaten the confidentiality, integrity and availability of information. Cyber-attacks also could include phishing attempts or e-mail fraud to cause payments or information to be transmitted to an unintended recipient. Furthermore, we have little or no control over the security measures and computer systems of third parties including any CROs we may work with in the future. While we and, to our knowledge, our third-party strategic partners have not experienced any such material system failure, accident or security breach to date, if such an event were to occur, it could result in material negative consequences for us including interruptions in our operations, the operations of our strategic partners, or our manufacturers or suppliers, misappropriation of confidential business information and trade secrets, disclosure of corporate strategic plans, and result in material disruptions of our product candidate development programs. Additionally, the costs to us or our CROs, third-party vendors, or other contractors or consultants we may utilize to mitigate network security problems, bugs, viruses, worms, malicious software programs and security vulnerabilities could be significant, and while we have implemented security measures to protect our data security and information technology systems, our efforts to address these problems may not be successful, and these problems could result in unexpected system failures, interruptions, delays, cessation of service and other harm to our business and our competitive position. For example, the loss of clinical trial data from completed or ongoing or planned clinical trials could result in delays in our regulatory approval efforts, and we may incur substantial costs to attempt to recover or reproduce the data. If any disruption or security breach resulted in a loss of or damage to our data or applications, or inappropriate disclosure of confidential or proprietary information, including personal information or health information, we could incur liability, or the further development of our product candidates could be delayed.

Moreover, if a security breach affects our systems or results in the unauthorized access, use or disclosure of personal information, our reputation could be materially damaged. In addition, such a breach may require notification to governmental agencies, the media and/or affected individuals pursuant to various federal, state and international privacy and security laws, if applicable, including HIPAA or HITECH and its implementing rules and regulations, as well as regulations promulgated by the Federal Trade Commission and state breach notification laws. We would also be exposed to a risk of loss or litigation and potential liability under laws, regulations and contracts that protect the privacy and security of personal information. For example, the California Consumer Privacy Act, or the CCPA, imposes a private right of action for security breaches that could lead to some form of remedy including regulatory scrutiny, fines, private right of action settlements, and other consequences. Additional states, including Virginia, Colorado, and Utah, have recently enacted privacy-related laws, and legislation is pending in many other states. The financial exposure from the events referenced above could either not be insured against or not be fully covered through any insurance that we may maintain, and there can be no assurance that the limitations of liability in any of our contracts would be enforceable or adequate or would otherwise protect us from liabilities or damages as a result of the events referenced above. Any of the foregoing could have a material adverse effect on our business, reputation, results of operations, financial condition and prospects.

We depend on our information technology and infrastructure, and disruptions could compromise sensitive information related to our business or other personal information or prevent us from accessing critical information, which could adversely affect our business, reputation, results of operations, financial condition and prospects.

We rely on the efficient and uninterrupted operation of information technology systems to manage our operations, to process, transmit, and store electronic and financial information, and to comply with regulatory, legal and tax requirements. We also depend on our information technology infrastructure for communications among our personnel, contractors, consultants and suppliers. System failures or outages could materially compromise our ability to perform these functions in a timely manner, which could harm our ability to conduct business or delay our financial reporting, and could otherwise compromise the security of sensitive information, including personal information and health information. In addition, our remediation efforts for system failures, outages, or security breaches may not be successful. If we do not allocate and effectively manage the resources necessary to build and sustain the proper technology and cybersecurity infrastructure, we could suffer significant business disruption, including transaction errors, supply chain or manufacturing interruptions, processing inefficiencies, data loss or the loss of or damage to intellectual property or other proprietary information, including personal information and health information. In addition, we depend on third parties to operate and support our information technology systems. Failure by these providers to adequately deliver the contracted services could have an adverse effect on our business, which in turn may materially adversely affect our operating results and financial condition.

We are subject to a variety of stringent and changing privacy and data security laws, regulations and standards, as well as contractual obligations related to data privacy and security, and our actual or perceived failure to comply with them could harm our business and reputation and subject us to significant fines and liability.

We maintain a quantity of sensitive information, including confidential business and patient health information in connection with our clinical trials, and are subject to laws and regulations governing the privacy and security of such information. In the United States, there are numerous federal and state privacy and data security laws and regulations governing the collection, use, disclosure and protection of personal information, including federal and state health information privacy laws, federal and state security breach notification laws, and federal and state consumer protection laws. Each of these laws is subject to varying interpretations and constantly evolving. In May 2018, a new privacy regime, the General Data Protection Regulation, or GDPR, took effect in the European Economic Area, or EEA. The GDPR increases our obligation with respect to clinical trials conducted in the EEA by expanding the definition of "personal data" and requiring changes to informed consent practices, as well as more detailed notices for clinical trial subjects and investigators. The GDPR authorizes fines for certain violations of up to 4% of global annual revenue or €20 million, whichever is greater, and other administrative penalties. In addition, the GDPR increases the scrutiny of transfers of personal information from clinical trial sites located in the EEA to the United States. For example, on July 16, 2020, the Court of Justice of the European Union (the Court of Justice) invalidated the European Union-United States (EU-U.S.) Privacy Shield on the grounds that the EU-U.S. Privacy Shield failed to offer adequate protections to EU personal information transferred to the United States. While the Court of Justice upheld the use of other data transfer mechanisms, such as the Standard Contractual Clauses, or SCCs, the decision has led to some uncertainty regarding the use of such mechanisms for data transfers to the United States, and the court made clear that reliance on SCCs alone may not necessarily be sufficient in all circumstances. The use of SCCs for the transfer of personal information specifically to the United States also remains under review by a number of European data protection supervisory authorities. For example, German and Irish supervisory authorities have indicated that the SCCs alone provide inadequate protection for EU-U.S. data transfers. Use of the data transfer mechanisms must now be assessed on a case-by-case basis taking into account the legal regime applicable in the destination country, in particular applicable surveillance laws and rights of individuals. The European Data Protection Board, or the EDPB, issued additional guidance regarding the Court of Justice's decision on November 11, 2020 which imposes higher burdens on the use of data transfer mechanisms, such as the SCCs, for cross-border data transfers. To comply with this guidance, we may need to implement additional safeguards to further enhance the security of data transferred out of the EEA, which could increase our compliance costs, expose us to further regulatory scrutiny and liability, and adversely affect our business. Further, the European Commission adopted two new sets of SCCs on June 4, 2021 and set timelines for when they became effective. These obligations may be interpreted and applied in a manner that is inconsistent from one jurisdiction to another and may conflict with other requirements or our practices.

Furthermore, Brexit has caused some uncertainty in this regulatory framework. For example, since the transition period for Brexit ended December 31, 2020, there remains some uncertainty regarding cross-border data transfers from the EEA to the United Kingdom. With respect to transfers of personal data from the EEA to the United Kingdom, on June 28, 2021, the European Commission issued an adequacy decision in respect of the United Kingdom's data protection framework, enabling data transfers from EU member states to the United Kingdom to continue without requiring organizations to put in place contractual or other measures in order to lawfully transfer personal data between the territories. While it is intended to last for at least four years, the European Commission may unilaterally revoke the adequacy decision at any point, and if this occurs it could lead to additional costs and increase our overall risk exposure. Additionally, the United Kingdom implemented the Data Protection Act effective in May 2018 and statutorily amended in 2019, that substantially implements the GDPR and contains provisions, including United Kingdom-specific derogations, for how GDPR is applied in the United Kingdom. Since the end of the Brexit transition period ended, we have to continue to comply with the GDPR and also the Data Protection Act, with each regime having the ability to fine up to the greater of €20 million (£17 million) or 4% of global turnover. Compliance with these privacy and data security laws and regulations is a rigorous and time-intensive process and if we fail to comply with any such laws or regulations, we may face significant fines and penalties that could adversely affect our business, financial condition and results of operations.

In the United States, in addition to HIPAA, various federal and state regulators have adopted, or are considering adopting, laws and regulations concerning personal information and data security. Certain state laws may be more stringent or broader in scope, or offer greater individual rights, with respect to personal information than federal, international or other state laws, and such laws may differ from each other, all of which may complicate compliance efforts. For example, the CCPA, which increases privacy rights for California residents and imposes obligations on companies that process their personal information, came into effect on January 1, 2020, and became enforceable by the California Attorney General on July 1, 2020, along with related regulations which came into force on August 14, 2020. Additionally, although not effective until January 1, 2023, the California Privacy Rights Act, or the CPRA, which expands upon the CCPA, was passed in the recent election on November 3, 2020. Among other things, the CCPA requires covered companies to provide new

disclosures to California consumers about their data collection, use and sharing practices and provide such consumers new data protection and privacy rights, including the ability to opt out of certain sales of personal information, right to request correction, access, and deletion of their personal information, the right to opt out of certain personal information sharing, and the right to receive detailed information about how their personal information is processed. The CCPA provides for civil penalties for violations, as well as a private right of action for data breaches that result in the loss of personal information, as mentioned above. This private right of action may increase the likelihood of, and risks associated with, data breach litigation. The CPRA significantly modifies the CCPA, including by expanding consumers' rights with respect to certain personal information and creating a new state agency to oversee implementation and enforcement efforts. The CCPA and CPRA may increase our compliance costs and potential liability, particularly in the event of a data breach, and could have a material adverse effect on our business, including how we use personal information, our financial condition, the results of our operations or prospects. State laws are changing rapidly. For example, several states, including Virginia, Colorado, and Utah, have recently enacted privacy-related laws, and legislation is pending in many other states. There is also discussion in the U.S. of a new comprehensive federal data privacy law to which we would become subject if it is enacted.

All of these evolving compliance and operational requirements impose significant costs, such as costs related to organizational changes, implementing additional protection technologies, training employees and engaging consultants, which are likely to increase over time. In addition, such requirements may require us to modify our data processing practices and policies, distract management or divert resources from other initiatives and projects, all of which could have a material adverse effect on our business, financial condition, results of operations and prospects. Any failure or perceived failure by us to comply with any applicable federal, state or similar foreign laws and regulations relating to data privacy and security could result in damage to our reputation, as well as proceedings or litigation by governmental agencies or other third parties, including class action privacy litigation in certain jurisdictions, which would subject us to significant fines, sanctions, awards, injunctions, penalties or judgments. Any of the foregoing could have a material adverse effect on our business, results of operations, financial condition and prospects.

We and our strategic partners that we rely on may be adversely affected by natural disasters, and our business continuity and disaster recovery plans may not adequately protect us from a serious disaster.

Natural disasters could severely disrupt our operations or the operations of our third party manufacturers' facilities and have a material adverse effect on our business, financial condition, results of operations and prospects. If a natural disaster, power outage, global epidemic, pandemic or contagious disease, or other event occurred that prevented us from using all or a significant portion of our headquarters or research laboratory, that damaged critical infrastructure, such as our third party manufacturers' facilities, or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. The disaster recovery and business continuity plans we have in place currently are limited and may not prove adequate in the event of a serious disaster or similar event. Substantially all of our current supply of product candidates are located at a single third party manufacturer's facilities, and we do not have any existing back-up facilities in place or plans for such back-up facilities. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

We may be subject to securities litigation, which is expensive and could divert management attention.

Our stock price is volatile, and in the past companies that have experienced volatility in the market price of their stock have been subject to an increased incidence of securities class action litigation. We may be the target of this type of litigation in the future. Securities litigation against us could result in substantial costs and divert our management's attention from other business concerns, which could seriously harm our business.

If securities or industry analysts do not publish research or reports about our business, or publish negative reports about our business, our stock price and trading volume could decline.

The trading market for our common stock will depend in part on the research and reports that securities or industry analysts publish about us or our business. We do not have any control over these analysts. There can be no assurance that analysts will cover us or provide favorable coverage. If one or more of the analysts who cover us downgrade our stock or change their opinion of our stock, our stock price would likely decline. If one or more of these analysts cease coverage of our company or fail to regularly publish reports on us, we could lose visibility in the financial markets, which could cause our stock price or trading volume 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
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 September 30, 2022, 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: November 3, 2022

AEGLEA BIOTHERAPEUTICS, INC.

By: /s/ James Kastenmayer
James Kastenmayer
Interim Chief Executive Officer and General Counsel
(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: November 3, 2022

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, James Kastenmayer, 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: November 3, 2022

/s/ James Kastenmayer
James Kastenmayer
Interim Chief Executive Officer and General Counsel
(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: November 3, 2022

/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 September 30, 2022, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, James Kastenmayer, Interim 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: November 3, 2022

/s/ James Kastenmayer
James Kastenmayer
Interim Chief Executive Officer and General Counsel
(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 September 30, 2022 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: November 3, 2022

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