

Aeglea BioTherapeutics, Inc.  
Form 10-Q  
May 08, 2018

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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, DC 20549

FORM 10-Q

(Mark One)

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

For the quarterly period ended March 31, 2018

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 (I.R.S. Employer

incorporation or organization) Identification No.)  
901 S. MoPac Expressway

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Barton Oaks Plaza One

Suite 250

Austin, TX 78746

(Address of principal executive offices including  
zip code)

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

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 and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted 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 and post 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	(Do not check if a smaller reporting company)
Smaller reporting company	Emerging growth company

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

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

As of May 4, 2018, the registrant had 21,858,874 shares of common stock, \$0.0001 par value per share, outstanding.

AEGLEA BIOTHERAPEUTICS, INC.

QUARTERLY REPORT ON FORM 10-Q

FOR THE QUARTER ENDED MARCH 31, 2018

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## NOTE ABOUT FORWARD-LOOKING STATEMENTS

This quarterly report contains forward-looking statements. All statements other than statements of historical fact are “forward-looking statements” for purposes of this Quarterly Report on Form 10-Q. These forward-looking statements may include, but are not limited to, statements regarding our future results of operations and financial position, business strategy, market size, potential growth opportunities, clinical development activities, efficacy and safety profile of our product candidates, our ability to maintain and recognize the benefits of certain designations received by product candidates, the timing and results of clinical trials and potential regulatory approval and commercialization of product candidates. The words “believe,” “may,” “will,” “potentially,” “estimate,” “continue,” “anticipate,” “predict,” “target,” “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 “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.

As used in this Quarterly Report on Form 10-Q, the terms “Aeglea,” “the Company,” “we,” “us,” and “our” refer to Aeglea BioTherapeutics, Inc. and, where appropriate, its consolidated subsidiaries, unless the context indicates otherwise.

## PART I. – FINANCIAL INFORMATION

Item 1. Financial Statements  
Aeglea BioTherapeutics, Inc.

## Condensed Consolidated Balance Sheets

(Unaudited)

(In thousands, except share and per share amounts)

	March 31, 2018	December 31, 2017
<b>ASSETS</b>		
<b>CURRENT ASSETS</b>		
Cash and cash equivalents	\$ 10,760	\$ 12,817
Marketable securities	32,715	37,482
Accounts receivable - grant	3,373	3,078
Prepaid expenses and other current assets	1,995	1,614
Total current assets	48,843	54,991
Property and equipment, net	810	854
Other non-current assets	133	232
<b>TOTAL ASSETS</b>	<b>\$ 49,786</b>	<b>\$ 56,077</b>
<b>LIABILITIES AND STOCKHOLDERS' EQUITY</b>		
<b>CURRENT LIABILITIES</b>		
Accounts payable	\$ 763	\$ 389
Deferred revenue	—	\$ 20
Accrued and other current liabilities	5,002	5,220
Total current liabilities	5,765	5,629
Other non-current liabilities	101	111
<b>TOTAL LIABILITIES</b>	<b>5,866</b>	<b>5,740</b>
Commitments and Contingencies (Note 9)		
<b>STOCKHOLDERS' EQUITY</b>		
Preferred stock, \$0.0001 par value; 10,000,000 shares authorized as of		
March 31, 2018 and December 31, 2017; no shares issued and		
outstanding as of March 31, 2018 and December 31, 2017		
	—	—
Common stock, \$0.0001 par value; 500,000,000 shares authorized as of		
March 31, 2018 and December 31, 2017; 16,809,669 shares and		
16,670,188 shares issued and outstanding as of March 31, 2018 and		

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December 31, 2017, respectively

Additional paid-in capital	124,648	122,950
Accumulated other comprehensive loss	(98 )	(102 )
Accumulated deficit	(80,632 )	(72,513 )
TOTAL STOCKHOLDERS' EQUITY	43,920	50,337
TOTAL LIABILITIES AND STOCKHOLDERS' EQUITY	\$49,786	\$56,077

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

Aeglea BioTherapeutics, Inc.

Condensed Consolidated Statements of Operations

(Unaudited)

(In thousands, except share and per share amounts)

	Three Months Ended March 31,	
	2018	2017
<b>Revenues:</b>		
Grant	\$1,510	\$982
<b>Operating expenses:</b>		
Research and development	\$6,870	\$4,949
General and administrative	2,885	2,364
Total operating expenses	9,755	7,313
Loss from operations	(8,245 )	(6,331 )
<b>Other income (expense):</b>		
Interest income	143	95
Other expense	(17 )	(11 )
Total other income	126	84
Net loss	\$(8,119 )	\$(6,247 )
Net loss per share, basic and diluted	\$(0.49 )	\$(0.47 )
Weighted-average common shares outstanding, basic and diluted	16,672,125	13,365,823

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



Aeglea BioTherapeutics, Inc.

Condensed Consolidated Statements of Comprehensive Loss

(Unaudited)

(In thousands)

	Three Months Ended March 31,	
	2018	2017
Net loss	\$(8,119)	\$(6,247)
Other comprehensive income (loss):		
Unrealized gain (loss) on marketable securities	4	(33 )
Total comprehensive loss	\$(8,115)	\$(6,280)

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

Aeglea BioTherapeutics, Inc.

Condensed Consolidated Statements of Cash Flows

(Unaudited)

(In thousands)

	Three Months Ended March 31,	
	2018	2017
<b>CASH FLOWS FROM OPERATING ACTIVITIES</b>		
Net loss	\$(8,119 )	\$(6,247 )
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	70	52
Purchase net premium on marketable securities	—	(55 )
Net (accretion of discount) amortization of premium on marketable securities	(14 )	49
Stock-based compensation	835	401
Research and development services settled with stock	30	—
Other, net	(11 )	(5 )
Changes in operating assets and liabilities:		
Accounts receivable-grant	(295 )	234
Prepaid expenses and other assets	(102 )	151
Accounts payable	396	95
Deferred revenue	(20 )	(20 )
Accrued and other liabilities	(217 )	(87 )
Net cash used in operating activities	(7,447 )	(5,432 )
<b>CASH FLOWS FROM INVESTING ACTIVITIES</b>		
Purchases of property and equipment	(83 )	(271 )
Purchases of marketable securities	—	(32,780)
Proceeds from maturities of marketable securities	4,785	7,440
Net cash provided by (used in) investing activities	4,702	(25,611)
<b>CASH FLOWS FROM FINANCING ACTIVITIES</b>		
Proceeds from employee stock plan purchases and stock option exercises	688	96
Net cash provided by financing activities	688	96
<b>NET DECREASE IN CASH AND CASH EQUIVALENTS</b>	<b>(2,057 )</b>	<b>(30,947)</b>
<b>CASH AND CASH EQUIVALENTS</b>		
Beginning of period	12,817	47,748
End of period	\$10,760	\$16,801
Supplemental Disclosure of Non-Cash Investing and Financing Information:		
Unpaid amounts related to purchase of property and equipment	\$—	\$4

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



Aeglea BioTherapeutics, Inc.

Notes to Condensed Consolidated Financial Statements

## 1. The Company and Basis of Presentation

Aeglea BioTherapeutics, Inc. (“Aeglea” or the “Company”) is a clinical-stage biotechnology company committed to developing enzyme-based therapeutics in the field of amino acid metabolism to treat rare genetic diseases and cancer. 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 (the “LLC Conversion”) on March 10, 2015. The Company operates in one segment and has its principal offices in Austin, Texas.

### Stock Offering

In April 2018, the Company issued and sold 5,046,510 shares of common stock in an underwritten public offering (“2018 Stock Offering”) pursuant to a shelf registration statement on Form S-3 at a public offering price of \$8.00 per share, including 546,510 shares of common stock issued upon the partial exercise by the underwriters of their option to purchase additional shares. The net proceeds to the Company from this public offering were approximately \$37.7 million, after deducting underwriting discounts and commissions of \$2.4 million and estimated offering costs of \$280,000.

### Liquidity

As of March 31, 2018, the Company had working capital of \$43.1 million, an accumulated deficit of \$80.6 million, and cash, cash equivalents, and marketable securities of \$43.5 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 and development 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.

Based upon the Company’s cash, cash equivalents, and marketable securities, in conjunction with the proceeds received in connection with its 2018 Stock Offering, the Company believes that it has sufficient resources to fund operations through the middle of 2020 with its existing cash, cash equivalents, and marketable securities. The Company will need to secure additional funding in the future, in order to carry out all of its planned research and development activities. If the Company is unable to obtain additional financing or generate license or product revenue, the lack of liquidity could have a material adverse effect on the Company’s future prospects.

### Unaudited Interim Financial Information

The interim condensed consolidated financial statements included in this document are unaudited. The unaudited interim financial statements have been prepared on the same basis as the annual financial statements and reflect, in the opinion of management, all adjustments of a normal and recurring nature that are necessary for a fair statement of the Company's financial position as of March 31, 2018, and its results of operations for the three months ended March 31, 2018 and 2017, and cash flows for the three months ended March 31, 2018 and 2017. The results of operations for three months ended March 31, 2018 are not necessarily indicative of the results to be expected for the year ending December 31, 2018 or for any other future annual or interim period. The December 31, 2017 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, 2017 as filed with the SEC.

## 2. Summary of Significant Accounting Policies

### 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 consolidated financial statements and accompanying notes. Such management estimates include those related to accruals of research and development related costs, stock-based compensation, and certain company income tax related items. 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. Actual results could differ significantly from those estimates.

### Cash and Cash Equivalents

The Company considers all highly liquid investments with original maturities of three months or less from the date of purchase to be cash equivalents. Cash equivalents consist of money market funds and debt securities and are stated at fair value.

### Marketable Securities

All investments have been classified as available-for-sale and are carried at estimated fair value as determined based upon quoted market prices or pricing models for similar securities. Management determines the appropriate classification of its investments in debt securities at the time of purchase. The Company may or may not hold securities with stated maturities greater than one year until maturity. All available-for-sale securities are considered available to support current operations and are classified as current assets.

Unrealized gains and losses are excluded from earnings and are reported as a component of accumulated comprehensive loss. Realized gains and losses and declines in fair value judged to be other than temporary, if any, on available-for-sale securities are included in other income (expense). The cost of securities sold is based on the specific-identification method. There were no realized gains or losses on marketable securities for the three months ended March 31, 2018 and 2017. Interest on marketable securities is included in interest income.

### Concentration of Credit Risk

Financial instruments that potentially subject the Company to a concentration of credit risk consist of cash, cash equivalents, and marketable securities. The Company's investment policy limits investments to high credit quality securities issued by the U.S. government, U.S. government-sponsored agencies and highly rated banks, subject to certain concentration limits and restrictions on maturities. The Company's cash, cash equivalents, and marketable securities are held by financial institutions in the United States that management believes are of high credit quality. Amounts on deposit may at times exceed federally insured limits. The Company has not experienced any losses on its deposits of cash and cash equivalents and its accounts are monitored by management to mitigate risk. The Company is exposed to credit risk in the event of default by the financial institutions holding its cash and cash equivalents and bond issuers.

### Property and Equipment

Property and equipment are stated at cost, net of accumulated depreciation and amortization. Depreciation and amortization are computed using the straight-line method over the estimated useful lives of the assets. Repairs and maintenance that do not extend the life or improve an asset are expensed as incurred. Upon retirement or sale, the cost of disposed assets and their related accumulated depreciation and amortization are removed from the balance sheet. Any gain or loss is credited or charged to operations.

The useful lives of the property and equipment are as follows:

Laboratory equipment	5 years
Furniture and office equipment	5 years
Computer equipment	3 years
Software	3 years
Leasehold improvements	Shorter of remaining lease term or estimated useful life

#### Impairment of Long-Lived Assets

Long-lived assets are reviewed for indications of possible impairment whenever events or changes in circumstances indicate that the carrying amount of an asset may not be recoverable. Recoverability is measured by comparison of the carrying amounts to the future undiscounted cash flows attributable to these assets. An impairment loss is recognized to the extent an asset group is not recoverable, and the carrying amount exceeds the projected discounted future cash flows arising from these assets. There were no impairments of long-lived assets for the three months ended March 31, 2018 and 2017.

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### Accrued Research and Development Costs

The Company records the costs associated with research nonclinical studies, clinical trials, and manufacturing development as incurred. These costs are a significant component of the Company's research and development expenses, with a substantial portion of the Company's on-going research and development activities conducted by third-party service providers, including contract research and manufacturing organizations.

The Company accrues for expenses resulting from obligations under agreements with contract research organizations ("CROs"), contract manufacturing organizations ("CMOs"), and other outside service providers for which payment flows do not match the periods over which materials or services are provided to the Company. Accruals are recorded based on estimates of services received and efforts expended pursuant to agreements established with CROs, CMOs, and other outside service providers. These estimates are typically based on contracted amounts applied to the proportion of work performed and determined through analysis with internal personnel and external service providers as to the progress or stage of completion of the services. The Company makes significant judgments and estimates in determining the accrual balance in each reporting period. In the event advance payments are made to a CRO, CMO, or outside service provider, the payments will be recorded as a prepaid asset which will be amortized as the contracted services are performed. As actual costs become known, the Company adjusts its accruals. Inputs, such as the services performed, the number of patients enrolled, or the study duration, may vary from the Company's estimates, resulting in adjustments to research and development expense in future periods. Changes in these estimates that result in material changes to the Company's accruals could materially affect the Company's results of operations. The Company has not experienced any material deviations between accrued and actual research and development expenses.

### Leases

The Company entered into lease agreements for its office and laboratory facilities. The leases are classified as operating leases. The Company records rent expense on a straight-line basis over the term of the leases and, accordingly records the difference between cash rent payments and the recognition of rent expense as a deferred rent liability. Incentives granted under the Company's facilities leases, including allowances to fund leasehold improvements, are deferred and are recognized as adjustments to rental expense on a straight-line basis over the term of the lease.

### Fair Value of Financial Instruments

The Company uses fair value measurements to record fair value adjustments to certain financial and non-financial assets and liabilities and to determine fair value disclosures. The accounting standards define fair value, establish a framework for measuring fair value, and require disclosures about fair value measurements. Fair value is defined as the price that would be received from selling an asset or paid to transfer a liability in an orderly transaction between market participants at the measurement date. When determining the fair value measurements for assets and liabilities required to be recorded at fair value, the principal or most advantageous market in which the Company would transact are considered along with assumptions that market participants would use when pricing the asset or liability, such as inherent risk, transfer restrictions, and risk of nonperformance.

The accounting standard for fair value establishes a fair value hierarchy based on three levels of inputs, the first two of which are considered observable and the last unobservable, that requires an entity to maximize the use of observable inputs and minimize the use of unobservable inputs when measuring fair value. A financial instrument's categorization within the fair value hierarchy is based upon the lowest level of input that is significant to the fair value measurement.

The three levels of inputs that may be used to measure fair value are as follows:



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Level 1: Observable inputs, such as quoted prices in active markets for identical assets or liabilities.

Level 2: Observable inputs other than Level 1 prices, such as quoted prices for similar assets or liabilities, or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the assets or liabilities.

Level 3: Valuations based on unobservable inputs to the valuation methodology and including data about assumptions that market participants would use in pricing the asset or liability based on the best information available under the circumstances.

Financial instruments carried at fair value include cash, cash equivalents, and marketable securities. The carrying amount of accounts receivable, accounts payable and accrued liabilities approximate fair value due to their relatively short maturities.

## Revenue Recognition

The Company's sole source of revenue is grant revenue related to a \$19.8 million research grant received from the Cancer Prevention and Research Institute of Texas ("CPRIT"), covering a four-year period from June 1, 2014 through May 31, 2018. Grant revenue is recognized when qualifying costs are incurred and there is reasonable assurance that the conditions of the award have been met for collection. Proceeds received prior to the costs being incurred or the conditions of the award being met are recognized as deferred revenue until the services are performed and the conditions of the award are met (see Note 5).

## Research and Development Costs

Research and development costs are expensed as incurred. Research and development costs include, but are not limited to, salaries, benefits, travel, stock-based compensation, consulting costs, contract research service costs, laboratory supplies and facilities, contract manufacturing costs, and costs paid to other third parties that conduct research and development activities on the Company's behalf. Amounts incurred in connection with license agreements are also included in research and development expense.

Certain research and development costs incurred were settled contractually by the Company issuing a variable number of the Company's shares determined by dividing the fixed monetary amount of costs incurred by the issuance-date fair value of the issuable shares. The Company recorded research and development expense for these costs and accrued for the fixed monetary amount as an accrued liability as the services were rendered until the amount was settled. In June 2015, the remaining Company obligation to settle these costs with Company shares was converted to a cash-based payment through a contract amendment with the service provider.

Advance payments for goods or services to be rendered in the future for use in research and development activities are recorded as a prepaid asset and expensed as the related goods are delivered or the services are performed.

## Stock-Based Compensation

The Company recognizes the cost of stock-based awards granted to employees based on the estimated grant-date fair values of the awards. The value of the award is recognized as compensation expense on a straight-line basis over the requisite service period. Forfeitures are recognized when they occur, which may result in the reversal of compensation costs in subsequent periods as the forfeitures arise. The Company recognizes the cost of stock-based awards granted to nonemployees at their then-current fair values as services are performed, and are remeasured through the counterparty performance date.

## Income Taxes

The Company and its seven wholly-owned subsidiary corporations use the asset and liability method of accounting for income taxes. Under this method, deferred tax assets and liabilities are recognized for the expected future tax consequences of temporary differences between the financial statements and the tax bases of assets and liabilities. Additionally, any changes in income tax laws are immediately recognized in the year of enactment.

A valuation allowance is established against the deferred tax assets to reduce their carrying value to an amount that is more likely than not to be realized. The deferred tax assets and liabilities are classified as noncurrent along with the related valuation allowance. Due to a lack of earnings history, the net deferred tax assets have been fully offset by a valuation allowance.

The Company recognizes benefits of uncertain tax positions if it is more likely than not that such positions will be sustained upon examination based solely on the technical merits, as the largest amount of benefits that is more likely than not to be realized upon the ultimate settlement. The Company's policy is to recognize interest and penalties related to the unrecognized tax benefits as a component of income tax expense.

#### Comprehensive Loss

Comprehensive loss is the change in stockholders' equity from transactions and other events and circumstances other than those resulting from investments by stockholders and distributions to stockholders. The Company's other comprehensive income (loss) is currently comprised of changes in unrealized gains and losses on available-for-sale securities.

## Reclassification

Certain reclassifications have been made to prior period amounts to conform to current period presentation. These reclassifications did not have an impact on the Company's results of operations or financial position as of March 31, 2018 and December 31, 2017.

## Recent Accounting Pronouncements

In February 2016, the FASB issued ASU No. 2016-02, Leases (Topic 842), which establishes a comprehensive new lease accounting model. The new standard: (a) clarifies the definition of a lease; (b) requires a dual approach to lease classification similar to current lease classifications; and, (c) causes lessees to recognize leases on the balance sheet as a lease liability with a corresponding right-of-use asset for leases with a lease-term of more than twelve months. The new standard is effective for fiscal years and interim periods beginning after December 15, 2018 and requires modified retrospective application. Early adoption is permitted. The Company is currently evaluating the impact that the adoption of ASU 2016-02 will have on its consolidated financial statements, but expect the impact to be limited to the operating lease agreements for the office and laboratory spaces in Austin, Texas.

## 3. Cash Equivalents and Marketable Securities

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

	March 31, 2018		Gross		Estimated
	Amortized	Unrealized	Unrealized		Fair
	Cost	Gains	Losses		Value
<b>Cash equivalents:</b>					
Money market funds	\$ 1,370	\$ —	\$ —		\$ 1,370
Reverse repurchase agreements	6,250	—	—		6,250
Total cash equivalents	7,620	—	—		7,620
<b>Marketable securities:</b>					
U.S. government securities	32,813	—	(98 )		32,715
Total marketable securities	\$ 32,813	\$ —	\$ (98 )		\$ 32,715

	December 31, 2017		Gross		Estimated
	Amortized	Unrealized	Unrealized		Fair
	Cost	Gains	Losses		Value
<b>Cash equivalents:</b>					

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Money market funds	\$1,674	\$	—	\$	—	\$ 1,674
Reverse repurchase agreements	7,250		—		—	7,250
Total cash equivalents	8,924		—		—	8,924
Marketable securities:						
U.S. treasury securities	1,502		—	(1	)	1,501
U.S. government securities	36,082		—	(101	)	35,981
Total marketable securities	\$37,584	\$	—	\$	(102	) \$ 37,482

The reverse repurchase agreements are settled in cash nightly, and as such are classified as cash equivalents.

As of March 31, 2018 and December 31, 2017, all debt securities with an unrealized loss position have been in a loss position for less than one year. The aggregate fair value of debt securities in an unrealized loss position as of March 31, 2018 and December 31, 2017 were \$32.7 million and \$37.5 million, respectively, with no individual securities in a significant unrealized loss position. The Company evaluated its securities for other-than-temporary impairment and considered the decline in market value for the securities to be primarily attributable to current economic and market conditions and would not be required to sell the securities before recovery of the amortized cost basis. Based on this analysis, these marketable securities were not considered to be other-than-temporarily impaired as of March 31, 2018 and December 31, 2017.

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

	March 31, 2018	December 31, 2017
Due in one year or less	\$ 32,715	\$ 34,498
Due in 1 - 2 years	—	2,984
Total marketable securities	\$ 32,715	\$ 37,482

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.

#### 4. Accrued and Other Current Liabilities

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

	March 31, 2018	December 31, 2017
Accrued compensation	\$ 1,001	\$ 1,837
Accrued contracted research and development costs	3,379	2,552
Accrued professional and consulting fees	512	672
Accrued other and other current liabilities	110	159
Total accrued and other current liabilities	\$ 5,002	\$ 5,220

#### 5. Grant Revenues

In June 2015, the Company entered into a Cancer Research Grant Contract ("Grant Contract") with CPRIT, under which CPRIT awarded a grant not to exceed \$19.8 million for use in developing cancer treatments by exploiting the metabolism of cancer cells. The Grant Contract covers a four-year period from June 1, 2014 through May 31, 2018.

Upon commercialization of the product, the terms of the Grant Contract require the Company to pay tiered royalties in the low to mid-single digit percentages. Such royalties reduce to less than one percent after a mid-single-digit multiple of the grant funds have been paid to CPRIT as royalties.

The Company recognized grant revenue of \$1.5 million and \$1.0 million in the three months ended March 31, 2018 and 2017, respectively, for qualified expenditures under the grant. As of March 31, 2018 and December 31, 2017, the

Company had outstanding grant receivables of \$3.4 million and \$3.1 million, respectively, for the grant expenditures that were paid but had not been reimbursed and deferred revenue of \$0 and \$20,000, respectively, for proceeds received but for which the costs had not been incurred or the conditions of the award had not been met.

## 6. Stock-Based Compensation

On February 20, 2018, the Board of Directors approved and adopted the 2018 Equity Inducement Plan (“2018 Plan”) which became effective on the same date. The Board of Directors approved an initial reserve of 1,100,000 shares of common stock to be used exclusively for individuals who were not previously employees or directors, or following a bona fide period of non-employment, as an inducement material to the individual entering into employment with the Company. Nonqualified stock options or restricted stock units may be granted under the 2018 Plan at the discretion of the Compensation Committee or the Board of Directors. The Company did not seek stockholder approval of the 2018 Plan pursuant to Nasdaq Rule 5635(c)(4). As of March 31, 2018, no grants had been awarded under the 2018 Plan.

The 2016 Equity Incentive Plan (“2016 Plan”) provides for an annual increase in the number of shares available for issuance thereunder, to be added on the first day of each fiscal year, beginning on January 1, 2017 and continuing through 2023, up to 4% of the outstanding number of shares of the Company’s common stock on the December 31 immediately prior to the date of increase, provided that an increase is only effective if the Company’s board of directors either confirmed the increase or approved the increase of a lesser number of shares prior to January 1 of each relevant year. As a result of this provision, on January 1, 2018 and January 1, 2017, an additional 666,807 and 537,233 shares, respectively, became available for issuance under the 2016 Plan.

During the three months ended March 31, 2018 and 2017, the Company issued an aggregate of 829,500 and 772,800 options to purchase common stock, respectively, under its equity incentive plans for an aggregate fair value of \$3.9 million and \$4.2 million, respectively.

Under the Company's 2016 Employee Stock Purchase Plan ("2016 ESPP"), the Company issued and sold 30,937 shares for aggregate cash proceeds of \$78,000 during the three months ended March 31, 2018 and 18,184 shares for aggregate cash proceeds of \$78,000 during the three months ended March 31, 2017.

Total stock-based compensation expense related to the Company's equity incentive plans and 2016 ESPP was as follows (in thousands):

	Three Months Ended March 31, 2018 2017	
Research and development	\$323	\$110
General and administrative	512	291
Total stock-based compensation expense	\$835	\$401

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 equity incentive plans and the shares purchasable under the 2016 ESPP during the periods presented:

	Three Months Ended March 31, 2018 2017	
<b>Equity Incentive Plans</b>		
Expected term	6.01	5.99
Expected volatility	85 %	86 %
Risk-free interest	2.72 %	2.13 %
Dividend yield	0 %	0 %
<b>2016 ESPP</b>		
Expected term	0.49	0.50
Expected volatility	69 %	79 %
Risk-free interest	2.00 %	0.68 %
Dividend yield	0 %	0 %



## 7. Fair Value Measurements

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

	March 31, 2018			Total
	Level	Level 2	Level	
	1		3	
<b>Financial Assets</b>				
Money market funds	\$1,370	\$—	\$ —	\$1,370
Reverse repurchase agreements	—	6,250	—	6,250
U.S. government securities	—	32,715	—	32,715
<b>Total financial assets</b>	<b>\$1,370</b>	<b>\$38,965</b>	<b>\$ —</b>	<b>\$40,335</b>

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	December 31, 2017			Total
	Level 1	Level 2	Level 3	
<b>Financial Assets</b>				
Money market funds	\$1,674	\$—	\$ —	\$1,674
Reverse repurchase agreements	—	7,250	—	7,250
U.S. treasury securities	1,501	—	—	1,501
U.S. government securities	—	35,981	—	35,981
Total financial assets	\$3,175	\$43,231	\$ —	\$46,406

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 reverse repurchase agreements and U.S. government securities 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. There were no transfers between Level 1 and Level 2 during the periods presented.

## 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 outstanding during the period. For periods in which the Company generated a net loss, the Company does not include the potential impact of dilutive securities in diluted net loss per share, as the impact of these items is anti-dilutive.

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

	Three Months Ended	
	March 31, 2018	2017
Unvested restricted common stock	32,066	74,013
Options to purchase common stock	2,695,802	1,330,481

## 9. Research and License Agreements

University Research Agreement

In December 2013, the Company entered into a research agreement with the University of Texas at Austin (the “University”). Under the terms of this research agreement, the Company engaged the University to perform certain nonclinical research activities related to the systemic depletion of amino acids for cancer and rare disease therapy.

Under the research agreement, the Company was required to pay the University an annual amount not to exceed \$386,000 during the one-year term of the agreement from the effective date. Pursuant to subsequent amendments to the research agreement, the term and maximum expenditure limitation were extended and increased through August 31, 2018 for a combined amount of \$2.5 million. For each of the three months ended March 31, 2018 and 2017, the Company paid \$188,000 to the University under the research agreement.

#### License Agreements

In December 2013, two of the Company’s wholly owned subsidiaries, AECCase, Inc. (“AECCase”) and AEMase, Inc. (“AEMase”), entered into license agreements with the University under which the University granted to AECCase and AEMase exclusive, worldwide, sublicenseable licenses. The University granted the AECCase license under a patent application relating to the right to use technology related to the Company’s AEB3103 product candidate. The University granted the AEMase license under a patent relating to the right to use technology related to the Company’s AEB2109 product candidate.

In January and December 2017, the Company entered into and subsequently amended an Amended and Restated Patent License Agreement (the “Restated License”) with the University which consolidated the two license agreements, revised certain obligations, and licensed additional patent applications and invention disclosures to the Company. Pursuant to the terms of the Restated License, the Company may be required to pay the University up to \$6.4 million milestone payments based on the achievement of certain development milestones, including clinical trials and regulatory approvals, the majority of which are due upon the achievement of later development milestones, including a \$5.0 million payment due on regulatory approval of a product and a \$500,000 payment payable on final regulatory approval of a product for a second indication. In addition, the Company is required to pay the University a low single-digit royalty on worldwide-net sales of products covered under the Restated License, together with a revenue share on non-royalty consideration received from sublicensees. The rate of the revenue share ranges from 6.5% to 25% depending on the date the sublicense agreement is signed.

#### 10. Related Party Transactions

One of the founders, a non-employee member of the Company’s board of directors, entered into a consulting agreement with the Company in 2014 under which the founder would receive \$50,000 per year for a fixed number of hours of consulting and advisory services and receive equity incentive shares, which converted into 43,290 restricted stock awards and 13,852 stock options upon the LLC Conversion, with the vesting contingent on time and performance milestones being achieved. For the three months ended March 31, 2018 and 2017, there were no payments made to the Founder under the consulting agreement. As of March 31, 2018 and December 31, 2017, the Company had no outstanding liability to the related party.

#### 11. Subsequent Event

In April 2018, the Company issued and sold 5,046,510 shares of common stock in an underwritten public offering pursuant to a shelf registration statement on Form S-3 at a public offering price of \$8.00 per share, including 546,510 shares of common stock issued upon the partial exercise by the underwriters of their option to purchase additional shares. The net proceeds to the Company from this public offering were approximately \$37.7 million, after deducting underwriting discounts and commissions of \$2.4 million and estimated offering costs of \$280,000.

## 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, 2017 filed with the SEC on March 13, 2018. 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."

### Overview

We are a clinical-stage biotechnology company that designs and develops innovative human enzyme therapeutics for patients with rare genetic diseases and cancer. We believe our novel approach of utilizing human enzymes offers advantages over bacterial enzyme-based approaches including a more favorable safety profile that may provide a greater likelihood of clinical success.

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

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

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

Our lead product candidate, pegzilarginase, is engineered to degrade the amino acid arginine and is being developed to treat two extremes of arginine metabolism, including arginine excess in patients with Arginase 1 Deficiency, a rare genetic disease, as well as some cancers which have been shown to have a metabolic dependence on arginine. Pegzilarginase is currently being evaluated in three ongoing clinical trials, consisting of one Phase 1/2 clinical trial for the treatment of Arginase 1 Deficiency, one Phase 1 clinical trial for the treatment of advanced solid tumors, and one Phase 1/2 combination clinical trial of pegzilarginase with pembrolizumab for the treatment of patients with small cell lung cancer (SCLC). We are also building a pipeline of additional product candidates targeting key amino acids and other metabolites, including homocysteine (and the oxidized form homocystine), a target for another rare genetic disease as well as cysteine, and its oxidized form cystine, and methionine, for cancer indications.

Since inception, we have devoted substantially all of our efforts and resources to identifying and developing product candidates, conducting nonclinical studies, initiating and conducting clinical trials, recruiting personnel and raising capital. To date, we have financed our operations primarily through private placements of our preferred stock, the initial public offering, or IPO, of our common stock, follow-on public offerings of our common stock, and collection of a research grant.

We have incurred net losses in each year since inception. Our net losses were \$8.1 million and \$6.2 million for the three months ended March 31, 2018 and 2017, respectively, and have resulted from costs incurred in connection with our research and development programs and from general and administrative expenses associated with our operations. As of March 31, 2018, we had an accumulated deficit of \$80.6 million. We expect to continue to incur operating losses over the next several years. Our net losses may fluctuate significantly from quarter to quarter and from year to year. We anticipate that our expenses will increase significantly as we continue our clinical and diagnostic development activities for our lead 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.

## Recent Developments

### Pegzilarginase in Patients with Arginase 1 Deficiency

In April 2018, we announced initial data that confirmed the utility of standardized assessment tools in quantifying disease manifestations and that we believe demonstrates clinically relevant treatment effects with pegzilarginase in two Arginase 1 Deficiency patients after eight weeks of dosing. Additionally, baseline data in five patients indicated that clinical abnormalities in Arginase 1 Deficiency patients can be detected and quantified using standardized assessment tools. Assessment tools used in the trial include:

- Six-Minute Walk Test (6MWT) was below age and gender match norms for all five patients
- Berg Balance Scale demonstrated impaired balance in two patients
- Gross Motor Function Measure (GMFM) total and Part E subscale (walking, running, and jumping) was abnormal in four of the five patients
- Purdue Pegboard test demonstrated fine motor ability was also quantifiably impaired in all five patients
- All five patients had markedly elevated plasma arginine and plasma guanidino compounds (GC)
- All patients had evidence of growth impairment with height in the lowest 10% for age and gender and protein intakes less than the prescribed restricted amounts, which we believe likely reflects an aversion to protein caused by the disease
- One patient had abnormal baseline ammonia and hepatic transaminases, which are also potentially important disease related biochemical manifestations
- Tests of neurocognition were abnormal in all subjects indicating significant cognitive impairment

Data was available for the first two patients that we believe demonstrated clinically relevant treatment effects using standardized assessment tools:

• 6MWT demonstrated that two patients observed improvements on pegzilarginase. Patient 1 experienced a 31.4% improvement, from 102 to 134 meters, and Patient 2 experienced a 23.4% improvement, from 261 to 322 meters. Both observed improvements were well above the Minimal Clinically Important Difference (MCID) of 9% at eight weeks, with continued improvement, described above, measured at twenty weeks.

• Berg Balance Scale measured a clinically meaningful improvement in balance in Patient 1, who transitioned from a high risk to a medium risk of fall category. Patient 2 had a normal baseline assessment which precluded demonstration of any improvement.

• The GMFM–Part E subscale demonstrated clinically important improvement after the initial eight repeat doses with further improvement by twenty weeks in Patient 1. Patient 2 was at the upper end of the scale at baseline, and as expected, no significant change was observed.

• Protein intake relative to the prescribed amount improved during the initial eight weeks of repeat dosing in the first two patients. Despite the increase in protein intake, patients' plasma arginine values were better controlled with pegzilarginase as compared to baseline values with a protein restricted diet and ammonia scavengers.

We expect to report additional pediatric and adult repeat dose data in patients with Arginase 1 Deficiency in the third quarter of 2018. To date, we have identified more than 100 patients who have Arginase 1 Deficiency worldwide.

### Pegzilarginase in Patients with Advanced Solid Tumors

In the first quarter of 2018, we initiated recruitment to cohort expansions of approximately 12 patients each and dosed our first patients with SCLC, uveal melanoma and cutaneous melanoma. The primary endpoint of each cohort expansion is to assess the safety of pegzilarginase in patients with each tumor type. Secondary endpoints include the assessment of pharmacokinetics, pharmacodynamics and clinical response. We will also use the data to inform the viability of companion diagnostic development, which has the potential to enrich patient populations with the greatest likelihood of clinical success.





## Pegzilarginase with Pembrolizumab in Patients with Small Cell Lung Cancer

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

## Stock Offering

In April 2018, we sold an aggregate of 5,046,510 shares of common stock in an underwritten public offering pursuant to a shelf registration statement on Form S-3, including 546,510 shares of common stock issued upon the partial exercise by the underwriters of their option to purchase additional shares, for gross proceeds of \$40.4 million. The net proceeds to the Company from this public offering were approximately \$37.7 million after deducting underwriting discounts and commissions and estimated offering expenses.

## Components of Operating Results

### Revenue

To date, we have recognized revenue solely from a research grant from the Cancer Prevention and Research Institute of Texas, or CPRIT, and have not generated any revenue from the sale of any of our product candidates. Our ability to generate product revenues, which we do not expect will occur for several years, if ever, will depend heavily on the successful development, regulatory approval and eventual commercialization of our product candidates.

In June 2015, we entered into a grant agreement with CPRIT, or the Grant Contract, for \$19.8 million for use in developing cancer treatments by exploiting the metabolism of cancer cells. The Grant Contract covers a four-year period from June 1, 2014 through May 31, 2018. The grant allows us to receive funds in advance of costs and allowable expenses being incurred. We record the revenue as qualifying costs are incurred and there is reasonable assurance that the conditions of the award have been met for collection. Proceeds received prior to the costs being incurred or the conditions of the award being met are recognized as deferred revenue until the services are performed and the conditions of the award are met.

On a quarterly basis, we are required to submit a financial reporting package outlining the nature and extent of reimbursable costs paid and requesting reimbursement under the grant. At the end of each period, qualifying costs paid prior to reimbursement result in the recognition of a grant receivable.

### Research and development expenses

Research and development expenses consist primarily of costs incurred for the discovery and development of our product candidates, most notably, our lead product candidate pegzilarginase. Since we currently do not have internal manufacturing capabilities, we contract with external providers for manufacturing services. In addition, while we opened an internal research laboratory in February 2017, we continue to contract with external providers for nonclinical studies and clinical trials. Our research and development expenses include:

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costs from acquiring clinical trial materials and services performed for contracted services with a contract manufacturing organization;

fees paid to clinical trial sites, clinical research organizations, contract research organizations, contract manufacturing organizations, nonclinical research companies, and academic institutions; and

employee and consultant-related expenses incurred, which include salaries, benefits, travel and stock-based compensation.

Research and development costs are expensed as incurred. Advance payments for goods or services to be rendered in the future for use in research and development activities are deferred and capitalized. The capitalized amounts are expensed as the related goods are delivered or the services are performed.

Research and development expenses have historically represented the largest component of our total operating expenses. We plan to increase our research and development expenses for the foreseeable future as we continue the development of our product candidates.

Our expenditures on current and future nonclinical and clinical development programs are subject to numerous uncertainties in timing and cost to completion. The duration, costs, and timing of clinical trials and development of our product candidates will depend on a variety of factors, including:

- the scope, rate of progress, and expenses of our ongoing research activities as well as any additional clinical trials and other research and development activities;
- future clinical trial results;
- uncertainties in clinical trial enrollment rates or drop-out or discontinuation rates of patients;
- potential safety monitoring or other studies requested by regulatory agencies;
- significant and changing government regulation; and
- the timing and receipt of regulatory approvals, if any.

The process of conducting the necessary clinical research to obtain FDA and other regulatory approval is costly and time consuming and the successful development of our product candidates is highly uncertain. The risks and uncertainties associated with our research and development projects are discussed more fully in Part II, Item 1A of this Quarterly Report titled “Risk Factors.” As a result of these risks and uncertainties, we are unable to determine with any degree of certainty the duration and completion costs of our research and development projects, or if, when, or to what extent we will generate revenues from the commercialization and sale of any of our product candidates that obtain regulatory approval. We may never succeed in achieving regulatory approval for any of our product candidates.

#### General and administrative expenses

General and administrative expenses consist primarily of salaries and other related costs, including stock-based compensation, for personnel in executive, finance, accounting, operations, and human resources functions. Other significant costs include legal fees relating to corporate matters and fees for insurance, accounting, consulting, and recruiting services.

We expect that our general and administrative expenses will increase in the future to support our continued research and development activities, and the potential commercialization of our product candidates. These increases will likely include higher costs related to the hiring of additional personnel and fees to outside consultants, lawyers and accountants, among other expenses. Additionally, we have incurred and expect to continue to incur increased costs associated with being a public company, including expenses related to services associated with maintaining compliance with Nasdaq listing rules and SEC requirements, insurance, and investor relations costs.

#### Interest income

Interest income consists of interest earned on our cash, cash equivalents, and marketable securities.

#### Income taxes

We serve as a holding company for our seven wholly-owned subsidiary corporations and file consolidated corporate federal income tax returns. We use the asset and liability method of accounting for income taxes. Under this method, deferred tax assets and liabilities are recognized for the expected future tax consequences of temporary differences between the financial statements and the tax bases of assets and liabilities. A valuation allowance is established against the deferred tax assets to reduce their carrying value to an amount that is more likely than not to be realized. The deferred tax assets and liabilities are classified as noncurrent along with the related valuation allowance. Due to

our lack of earnings history, the net deferred tax assets have been fully offset by a valuation allowance.

We recognize benefits of uncertain tax positions if it is more likely than not that such positions will be sustained upon examination based solely on the technical merits, as the largest amount of benefits that is more likely than not to be realized upon the ultimate settlement. Our policy is to recognize interest and penalties related to the unrecognized tax benefits as a component of income tax expense.

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## Critical Accounting Policies and Estimates

Our condensed consolidated financial statements are prepared in accordance with generally accepted accounting principles in the United States, or GAAP. 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 and liabilities, 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 consolidated financial statements. We believe that the assumptions and estimates associated with our most critical accounting policies are those relating to accrued research and development costs and stock-based compensation.

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, 2017.

## Results of Operations

### Comparison of the Three Months Ended March 31, 2018 and 2017

The following table summarizes our results of operations for the three months ended March 31, 2018 and 2017, together with the changes in those items in dollars and as a percentage:

	Three Months Ended		Dollar Change	% Change	
	2018	2017			
	March 31,				
	(dollars in thousands)				
<b>Revenues:</b>					
Grant	\$1,510	\$982	\$528	54	%
<b>Operating expenses:</b>					
Research and development	\$6,870	\$4,949	\$1,921	39	%
General and administrative	2,885	2,364	521	22	%
Total operating expenses	9,755	7,313	2,442	33	%
Loss from operations	(8,245)	(6,331)	(1,914)	30	%
Interest income	143	95	48	51	%
Other expense	(17 )	(11 )	(6 )	55	%
Net loss	\$(8,119)	\$(6,247)	\$(1,872)	30	%

**Grant Revenues.** Grant revenues increased by \$0.5 million, or 54%, to \$1.5 million for the three months ended March 31, 2018 from \$1.0 million for the three months ended March 31, 2017. The increase was primarily due to

additional research and development costs associated with the clinical trials for pegzilarginase in cancer patients, for which we recognized grant revenue pursuant to the Grant Contract.

**Research and Development Expenses.** Research and development expenses increased by \$1.9 million, or 39%, to \$6.8 million for the three months ended March 31, 2018 from \$4.9 million for the three months ended March 31, 2017. The change in research and development expenses was primarily due to:

• Higher personnel-related expenses, which increased by \$0.7 million as a result of additional employee headcount to strengthen our management team and expand our internal regulatory, research laboratory, and clinical development capabilities;

• Higher clinical development expenses, which increased by \$1.5 million as a result of advancing our Phase 1/2 clinical trial for pegzilarginase in patients with Arginase 1 Deficiency, initiating three single agent cohort expansions for the Phase 1 trial in patients with advanced solid tumors, and initiating our Phase 1/2 combination trial in patients with small cell lung cancer; offset by

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Lower manufacturing expenses, which decreased by \$0.4 million as a result of a process scale-up for pegzilarginase and additional manufacturing activities for pipeline development in the prior year.

General and Administrative Expenses. General and administrative expenses increased by \$0.5 million, or 22%, to \$2.8 million for the three months ended March 31, 2018 from \$2.3 million for the three months ended March 31, 2017. The increase in general and administrative expenses was primarily due to additional employee headcount and compensation to strengthen our management team and support expanding research and development activities.

Interest Income. The increase in interest income to \$143,000 for the three months ended March 31, 2018 from \$95,000 for the three months ended March 31, 2017 was primarily due to increasing yield rates and purchasing investments with greater maturity terms.

## Liquidity and Capital Resources

### Sources of liquidity

We are a clinical-stage biotechnology company with a limited operating history, and due to our significant research and development expenditures, we have generated operating losses since our inception and have not generated any revenue from the sale of any products. Since our inception and through March 31, 2018, we have funded our operations primarily by raising an aggregate of \$123.7 million of gross proceeds from the sale and issuance of convertible preferred and common equity securities and collecting \$14.1 million in grant proceeds.

In May 2017, we filed a shelf registration statement on Form S-3 with the SEC for the offering, issuance and sale by us of up to \$150.0 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 April 2018, we sold an aggregate of 5,046,510 shares of common stock in an underwritten public offering pursuant to a shelf registration statement on Form S-3 for gross proceeds of \$40.4 million, resulting in net proceeds of approximately \$37.7 million after deducting underwriting discounts and commissions and estimated offering expenses.

In June 2015, we entered into the Grant Contract with CPRIT, under which CPRIT agreed to provide up to \$19.8 million in grant funding to fund our development of pegzilarginase. Through March 31, 2018, we have collected \$14.1 million in grant proceeds with \$5.7 million available for future collection under the grant contract. As of March 31, 2018, we have a grant receivable outstanding of \$3.4 million.

Our primary use of cash is to fund the development of our lead product candidate, pegzilarginase. 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 our clinical trials in pegzilarginase and expand our development efforts in our pipeline of nonclinical candidates.

### Future funding requirements and operational plan

Our operational plan for the near future is to continue clinical trials for our lead product candidate pegzilarginase in two separate indications: Arginase 1 Deficiency and advanced solid tumors, and to expand development for at least one additional product candidate. As such, we plan to increase our research and development expenditures for the foreseeable future with nonclinical studies, clinical trials, manufacturing, and an integrated biomarker strategy. We expect our principal expenditures during this time period to include expenses for the following:

- funding the continuing development of pegzilarginase;
- funding the 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 \$80.6 million as of March 31, 2018. 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, 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, and marketable securities of \$43.5 million as of March 31, 2018, in conjunction with the proceeds received from our stock offering in April 2018, we believe that we have sufficient resources to fund our operations through the middle of 2020. We have based this estimate on assumptions that may prove to be incorrect, however, and we could deplete our capital resources sooner than we expect.

#### Cash flows

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

	March 31,	
	2018	2017
Net cash and cash equivalents (used in) provided by:		
Operating activities	\$(7,447)	\$(5,432 )
Investing activities	4,702	(25,611)
Financing activities	688	96
Net decrease in cash and cash equivalents	\$(2,057)	\$(30,947)

#### Cash used in operating activities

Cash used in operating activities for the three months ended March 31, 2018 was \$7.4 million and reflected a net loss of \$8.1 million. Our net loss was offset in part by non-cash expenses of \$0.8 million for stock-based compensation and \$0.1 million for depreciation and amortization with \$0.2 million net decrease in operating assets and liabilities during the three months ended March 31, 2018.

Cash used in operating activities for the three months ended March 31, 2017 was \$5.4 million and reflected a net loss of \$6.2 million. Our net loss was offset in part by non-cash expenses of \$0.4 million for stock-based compensation and by a \$0.4 million change in operating assets and liabilities. The change in operating assets and liabilities was primarily due to the collection and recognition of \$1.2 million and \$1.0 million, respectively, in grants accounts receivable under the Grant Contract during the three months ended March 31, 2017 and increased manufacturing and clinical activities resulted in decreased prepaid expenses of \$0.2 million.

#### Cash provided by (used in) investing activities

Cash provided by investing activities for the three months ended March 31, 2018 was \$4.7 million and consisted of \$0.1 million in purchases of property and equipment offset by \$4.8 million in maturities of marketable securities.

Cash used in investing activities for the three months ended March 31, 2017 was \$25.6 million and primarily consisted of \$32.8 million in purchases of marketable securities and \$0.3 million in purchases of property and equipment to develop an internal research laboratory, offset by \$7.4 million in maturities of marketable securities.

#### Cash provided by financing activities

Cash provided by financing activities for the three months ended March 31, 2018 was \$0.7 million as a result of proceeds received from stock option exercises and the sale of common stock under our 2016 Employee Stock Purchase Plan.

Cash provided by financing activities for the three months ended March 31, 2017 was \$0.1 million and was a result of the sale of common stock under our 2016 Employee Stock Purchase Plan and the exercise of stock options.

### Contractual Obligations and Other Commitments

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 preclinical research studies and other services and products for operating purposes. These contractual obligations are cancelable at any time by us, generally upon 30 days' prior written notice to the vendor.

There have been no material changes to the contractual obligations during the three months ended March 31, 2018 as compared to those disclosed in our Annual Report on Form 10-K for the year ended December 31, 2017.

### Off-Balance Sheet Arrangements

Through March 31, 2018, we do not have any off-balance sheet arrangements, as defined by applicable SEC regulations.

### Recent Accounting Pronouncements

In February 2016, the FASB issued ASU No. 2016-02, Leases (Topic 842), which establishes a comprehensive new lease accounting model. The new standard: (a) clarifies the definition of a lease; (b) requires a dual approach to lease classification similar to current lease classifications; and, (c) causes lessees to recognize leases on the balance sheet as a lease liability with a corresponding right-of-use asset for leases with a lease-term of more than twelve months. The new standard is effective for fiscal years and interim periods beginning after December 15, 2018 and requires modified retrospective application. Early adoption is permitted. We are currently evaluating the impact that the adoption of ASU 2016-02 will have on our consolidated financial statements, but expect the impact to be limited to the operating lease agreement for office and laboratory space in Austin, Texas.

### Item 3. Quantitative and Qualitative Disclosures About Market Risk.

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

As of March 31, 2018, we held \$43.5 million in cash, cash equivalents, and marketable securities, all of which was denominated in U.S. dollar assets, and consisting primarily of investments in reverse repurchase agreements and U.S. government securities.

### Item 4. Controls and Procedures.

#### Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our principal executive officer and our principal financial officer, evaluated, as of the end of the period covered by this Quarterly Report on Form 10-Q, the effectiveness of our disclosure controls and procedures. Based on that evaluation of our disclosure controls and procedures as of March 31, 2018, 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 have been no changes in our internal control over financial reporting during our fiscal quarter ended March 31, 2018 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.

#### Risks Related to Our Business and Industry

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 candidate, pegzilarginase.

We have not yet demonstrated our ability to successfully complete any clinical trials, including large-scale, pivotal clinical trials, obtain marketing approvals, manufacture a commercial scale product or arrange for a third party to do so on our behalf, 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 little experience in conducting clinical trials. In part because of this lack of 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 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. We have no approved products and have only begun clinical development of pegzilarginase. 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, for any of our target indications and to obtain necessary regulatory approvals. To date, we have recognized revenue solely from a government grant and have not generated any product revenue. Even if we receive regulatory approval for any of our product candidates, we do not know when these product candidates will generate revenue for us, if at all.

In addition, since inception, we have incurred significant operating losses. For the three months ended March 31, 2018, we reported a net loss of \$8.1 million and \$6.2 million, respectively. For the years ended December 31, 2017 and 2016, we reported a net loss of \$27.2 million and \$21.7 million, respectively. As of March 31, 2018, we had an accumulated deficit of \$80.6 million. We have financed our operations primarily through private placements of our preferred stock, the initial public offering, or IPO, of our common stock, follow-on public offerings of our common stock, and collection of a research grant. We have devoted substantially all of our efforts to research and development. Currently, we are only conducting clinical development for pegzilarginase for the treatment of Arginase 1 Deficiency and advanced solid tumors, including a combination clinical trial of pegzilarginase with pembrolizumab. We have not initiated clinical development of our other product candidates and expect that it will be many years, if ever, before we have a product candidate 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 are currently only conducting clinical development for pegzilarginase for the treatment of Arginase 1 Deficiency and advanced solid tumors, including a combination clinical trial of pegzilarginase with pembrolizumab and are only 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. A decline in the value of our company would also cause you to lose part or even all of your investment.

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

In order to execute on our strategy of advancing the clinical development of our product candidates, we are currently conducting multiple clinical trials for pegzilarginase, consisting of one Phase 1/2 clinical trial for the treatment of Arginase 1 Deficiency, one Phase 1 clinical trial for the treatment of patients with advanced solid tumors with multiple cohort expansions, and one Phase 1/2 clinical trial to evaluate the combination of pegzilarginase with pembrolizumab for the

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treatment of patients with small cell lung cancer. We have recently initiated the planned expansion cohorts of our Phase 1 trial of pegzilarginase for the treatment of advanced solid tumors to study small cell lung cancer, uveal melanoma, and cutaneous melanoma, all of which have been shown in published literature and preclinical studies to demonstrate a dependence on arginine. If our product candidate fails to work as we expect, or if we need to conduct additional studies to better understand the relationship between our product candidate and clinical activity, our ability to assess the therapeutic effect, seek regulatory approval or otherwise begin or further clinical development, could be compromised. For instance, we discontinued clinical development of pegzilarginase for the treatment of the hematological malignancies acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) in December 2017 due to lack of evidence of clinical benefit. Also, while there is an established link between seizures and elevated levels of certain arginine metabolites, we may not be able to determine the relationship between clinical activity and arginine and its metabolites, if any, for the treatment of Arginase 1 Deficiency. Any such events may result in longer development times, larger trials and a greater likelihood of terminating the trial or not obtaining regulatory approval.

In addition, as we pursue oncology-related applications of our product candidates, because the natural history of different tumor types is variable, we will need to study our product candidates, including pegzilarginase, in clinical trials specific for a given tumor type and this will result in increased time and cost. Even if our product candidate demonstrates efficacy in a particular tumor type, we cannot guarantee that any product candidate, including pegzilarginase, will behave similarly in all tumor types, and we will be required to obtain separate regulatory approvals for each tumor type we intend a product candidate to treat. If any of our ongoing or planned clinical trials are unsuccessful, our business will suffer.

We or third parties may not be successful in developing companion diagnostic assays for our product candidates.

In developing a product candidate, we expect that if we use a biomarker-based test to identify and only enroll patients in clinical trials with tumors that express the biomarker, the FDA will require the development and regulatory approval of a companion diagnostic assay as a condition to approval of the product candidate. 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. Companion 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 companion 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, the delay or failure to obtain regulatory approval of the companion diagnostic would delay or prevent the approval of the therapeutic product candidate. EMA, MHRA or comparable foreign regulatory authorities may also require the development and regulatory approval of a companion diagnostic assay as a condition to approval of the product candidate.

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 discovery 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 in connection with our

continuing operations. If we are unable to raise capital when needed 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.

Based upon our planned use of our cash, cash equivalents, and marketable securities as of March 31, 2018, we estimate such funds will be sufficient for us to fund our ongoing Phase 1/2 clinical trial for the treatment of patients with Arginase 1 Deficiency, our ongoing Phase 1 clinical trial for the treatment of patients with advanced solid tumors, including our three single agent cohort expansions in small cell lung cancer, uveal melanoma, and cutaneous melanoma, as well as our ongoing Phase 1/2 combination clinical trial of pegzilarginase with pembrolizumab for the treatment of patients with small cell lung cancer. 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 costs related to 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 future commercialization activities, if any, 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.

Our product candidates, if approved, may not achieve commercial success. Our commercial revenues, if any, will be derived from sales of product candidates that we do not expect to be commercially available for many years, if at all. 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 and license and collaboration agreements. We do not have any committed external source of funds other than our grant agreement with the Cancer Prevention and Research Institute of Texas. To the extent that we raise additional capital through the sale of equity or convertible debt securities, 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. 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.

We depend heavily on the success of our most advanced product candidate, pegzilarginase. All of our product candidates, other than pegzilarginase, are still in nonclinical development or nonclinical testing, and for pegzilarginase, the early stages of clinical development. Existing and future clinical trials of our product candidates, including pegzilarginase, 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 advanced solid tumors, including a combination clinical trial of pegzilarginase with pembrolizumab. Our ability to generate product revenues, which we do not expect will occur for many years, if ever, will depend heavily on the successful development and eventual commercialization of pegzilarginase. The success of pegzilarginase and our other product candidates will depend on many factors, including the following:

- successful enrollment of patients in, and the completion of, our ongoing and planned clinical trials;
- 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.

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 of our lead product candidate pegzilarginase, and 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 and 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 pegzilarginase in patients with Arginase 1 Deficiency, and a reduction in blood arginine levels due to pegzilarginase in patients with advanced solid tumors, this data may not necessarily be predictive of the final results of all patients intended to be enrolled in these ongoing clinical trials or in future 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. In addition, while we have announced interim data from our ongoing clinical trials of pegzilarginase for the treatment of Arginase 1 Deficiency and advanced solid tumors, such reports were 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 clinically relevant treatment effects in the first two patients in the Phase 1/2 open-label study of pegzilarginase in

patients with Arginase 1 Deficiency after eight and twenty weeks of dosing may not be representative of our observations with subsequently dosed patients out to eight weeks or longer. Moreover, we have not discussed with FDA the design of a pivotal trial of pegzilarginase for the treatment of Arginase 1 Deficiency, including the endpoints for such a study and the magnitude of treatment effect we would need to demonstrate. We may design the pivotal trial before the Phase 1/2 clinical trial is complete and may not have all data available from the fully enrolled trial prior to determining the design with the FDA. Furthermore, our ongoing Phase 1/2 clinical trial for the treatment of patients with Arginase 1 Deficiency and our Phase 1 clinical trials for the treatment of advanced solid tumors will primarily evaluate the safety of our product candidates, and we will not be evaluating the efficacy of our product candidates in these early trials in a formal manner. Moreover, nonclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in nonclinical studies and clinical trials have nonetheless failed to obtain marketing approval of their products. 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;
- 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, in March 2018, a pediatric patient previously dosed in Part 1 of our Phase 1/2 clinical trial of pegzilarginase for the treatment of Arginase 1 Deficiency withdrew from the trial due to personal reasons;
- clinical sites and investigators deviating from the trial protocol, failing to conduct the trial in accordance with regulatory requirements, or dropping out of a trial;
- a clinical hold for any of our ongoing or planned clinical trials, including for pegzilarginase, 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; for example, the FDA may determine that dose findings are inadequate based on results from our Phase 1/2 trial or any future Phase 3 trial in pegzilarginase for the treatment of hyperargininemia secondary to Arginase 1 Deficiency and require additional dose finding studies to inform instructions for use that provide a safe dosing algorithm for pediatric patients.

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;

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- we may experience delays or difficulties in the enrollment of patients with Arginase 1 Deficiency or patients with tumors, including the identification of patients with Arginase 1 Deficiency or development or identification of a test, if needed, to screen for those cancer patients;
- 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 screen for patients with tumors dependent on arginine that pegzilarginase is designed to target and with 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;
- 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, we have previously delayed enrollment of pediatric patients in our Phase 1/2 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 have since reached an agreement with the FDA, 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. For example, we are currently administering neuromotor and neurocognitive evaluations in patients in this Phase 1/2 clinical trial, but the FDA may not agree with the overall burden or relevance of including these measures in a Phase 3 trial. In addition, we intend to study surrogate endpoints, such as reduction in blood arginine levels, as the primary endpoints in our Phase 3 clinical trial; however, we may need to show some evidence of stabilization or improvement of clinical signs and symptoms of Arginase 1 Deficiency, such as on neuromotor outcomes and quality-of-life measurements, to support the primary endpoint. We may face difficulties or delays in enrolling any Phase 3 trial in Arginase 1 Deficiency if we restrict enrollment to patients with baseline clinical abnormalities at a level that provides an opportunity to demonstrate neuromotor and/or neurocognitive outcomes. If we are unable to demonstrate consistent trends on such clinical endpoints, FDA may determine that there is inadequate justification to support that the surrogate endpoint is reasonably likely to predict clinical benefit, which would prohibit approval under the accelerated approval pathway. 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 advanced solid tumors, including a combination clinical trial of pegzilarginase with pembrolizumab. 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. Failure to submit or have effective INDs, CTAs or other comparable foreign equivalents and commence clinical programs will significantly limit our opportunity to generate revenue.

Our engineered human enzyme product candidates for our oncology indications represent a novel approach to cancer treatment, 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 early-stage clinical trials for pegzilarginase 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 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 are currently conducting clinical trials for pegzilarginase for the treatment of patients with Arginase 1 Deficiency and advanced solid tumors, including a combination clinical trial of pegzilarginase with pembrolizumab. Given the nature of the patient population enrolled in these trials, we have observed and expect to continue to observe serious adverse events that could be related or unrelated to pegzilarginase. In a Phase 1 trial of pegzilarginase for the treatment of patients with advanced solid tumors and a previously concluded trial of pegzilarginase for the treatment of the patients with hematological malignancies AML and MDS, we have observed serious adverse events in some patients, including death. In December 2017, we reported topline results of the dose escalation trial for the treatment of patients with advanced solid tumors and the hematological malignancies AML and MDS in which we observed serious adverse events that were considered possibly or probably related to the administration of pegzilarginase including nausea, diarrhea, vomiting, dehydration, dizziness, encephalopathy manifest as acute agitation, failure to thrive, fatigue, hypertension, asthenia, and intracranial hemorrhage. In our Phase 1/2 trial of pegzilarginase for the

treatment of patients with Arginase 1 Deficiency, we announced repeat dose data in March 2018 in which we observed three treatment-related serious adverse events in one patient, including facial flushing, facial swelling, and throat tightness. Subjects in our ongoing and planned clinical trials with pegzilarginase 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, 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 some patients who lack the target enzyme, as is the case with patients with Arginase 1 Deficiency that we are treating in our Phase 1/2 trial and our future trials for this rare genetic disease. In addition, our product candidates such as pegzilarginase break down target amino acids such as arginine, thereby releasing metabolites such as ornithine 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 are engineered from the human genome, pegzilarginase is produced in *E. coli*. This manufacturing process could lead pegzilarginase to be 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.

If we experience delays or difficulties in the enrollment of patients in our ongoing or planned clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented.

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. More specifically, many of our product candidates, including pegzilarginase, initially target indications that may be characterized as orphan markets, which can prolong the clinical trial timeline for the regulatory process 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. Newborn screening data for two reliably detected urea cycle disorders allowed disease experts to estimate the incidence of Arginase 1 Deficiency at 1:950,000 births. Assuming a less than normal life span, we believe that at least 600 individuals in global addressable markets have Arginase 1 Deficiency. Presently, only 34 U.S. states and jurisdictions screen for Arginase 1 Deficiency, and screening in Europe is not universal. Due to screening requirements and enrollment restrictions in our amended clinical trial protocol, or any additional restrictions that may be imposed by regulatory agencies, not all pediatric patients may be eligible for inclusion in our Phase 1/2 trial in the United States. To date, we have identified more than 100 patients worldwide.

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 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;

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- 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 Pharma plc has gained approval for its products 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 effect of their condition by taking RAVICTI (glycerol phenylbutyrate) or through dietary protein restriction. 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 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 are currently conducting 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. These 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. Although Merck has agreed to provide pembrolizumab in connection with our ongoing combination trial, we may be unable to secure and maintain a sufficient supply of such third-party products when needed on commercially reasonable 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 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 alone, or result in new side effects that have not previously been identified with pegzilarginase 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 landscape 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, 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 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 hyperargininemia, we may not obtain or maintain orphan drug exclusivity for pegzilarginase 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.

In March 2015, we obtained orphan drug designation in the United States for pegzilarginase for the treatment of patients with Arginase 1 Deficiency. In July 2016, we also received orphan drug designation in Europe for pegzilarginase for the treatment of patients with Arginase 1 Deficiency. A company that first obtains FDA or EMA approval for a designated orphan drug for the designated rare disease or condition receives orphan drug marketing exclusivity for that drug for the designated disease for a period of seven years in the United States or ten years in the European Union, respectively. 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, we may not be the first to obtain marketing approval for the orphan-designated indication due to the uncertainties associated with developing pharmaceutical product candidates. 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 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.

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.

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 who have advanced solid tumors dependent on arginine, as well as the potential subset of those who have the potential to benefit from treatment with our product candidates such as pegzilarginase, are based on estimates. 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.

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. For example, current cancer treatments like chemotherapy and radiation therapy are well established in the medical community, and physicians may continue to rely on these treatments instead of adopting the use of pegzilarginase for the treatment of patients with arginine dependent cancers. In addition, many new drugs have been recently approved and many more are in the pipeline to treat patients with cancer. Additionally, current treatments for Arginase 1 Deficiency include dietary protein restriction and, in some instances, nitrogen-scavenging drugs such as RAVICTI (glycerol phenylbutyrate). 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 strength of marketing and distribution support;
- the availability of third-party 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 expect to expand our development and regulatory capabilities and potentially implement sales, marketing and distribution 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 and distribution.

We currently do not have a marketing or sales team for the marketing, sales and distribution of any of our product candidates that are potentially able to obtain regulatory approval. 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 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. 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

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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 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.

We face intense competition from companies developing products to address urea cycle disorders. For example, Horizon Pharma plc has gained approval for its drug RAVICTI (glycerol phenylbutyrate), which is used to treat patients with urea cycle disorders suffering from hyperammonemia, which may include patients suffering from Arginase 1 Deficiency. Patients with Arginase 1 Deficiency may also benefit from taking RAVICTI (glycerol phenylbutyrate). Erytech Pharma announced a potential collaboration to explore preclinical development of an Arginase 1 Deficiency candidate. We also face intense competition from companies developing products and therapies to treat cancer. For example, Polaris Group is conducting numerous clinical trials of ADI-PEG 20, an enzyme derived from mycoplasma, which degrades arginine in the blood.

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 superior to 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; 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 physicians to switch from existing drug products or other therapies to our product candidates, or if physicians switch to other new drug products or choose to reserve our product candidates for use in limited circumstances.

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 safety in order to overcome price competition and to be commercially successful. 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 and marketing 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 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 such as the National Comprehensive Cancer Network and the American Society of Clinical Oncology 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, 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 future success depends on our ability to retain key executives and to attract, retain and motivate qualified personnel.

We are a clinical-stage biotechnology company with a limited operating history, and, as of March 31, 2018, had only 43 employees, including four executive officers. 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. For instance, we have appointed Dr. Anthony Quinn, a member of our board of directors, as interim Chief Executive Officer, and are currently in the process of searching for a permanent Chief Executive Officer. There is no assurance that a qualified individual will be found timely or engaged on acceptable terms. 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 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 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 original branded product is approved under a BLA. On March 6, 2015, the FDA approved the first biosimilar product under the BPCIA. 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.

We believe that if any of our product candidates are approved as a biological product under a BLA, it should qualify for the 12-year period of exclusivity. However, there is a risk that the FDA will not consider any of our product candidates to be reference products for competing products, 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. Moreover, 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.

Our information technology systems, or those used by our CROs, contractors or consultants, may fail or suffer security breaches, which could harm our business and operations.

Cyberattacks 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 cyberattacks, damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. 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 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. 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, we could incur liability or the further development of our product candidates could be delayed.

We depend on our information technology and infrastructure.

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. 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.

#### 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 rely on a contract manufacturing organization, KBI BioPharma, Inc., or KBI, to manufacture and supply nonclinical and clinical trial quantities of the biological substance of our lead product candidate, pegzilarginase and pipeline product candidates. We also expect to rely on KBI to manufacture and supply commercial quantities of pegzilarginase. In addition, we rely on Merck to provide pembrolizumab for the conduct of our combination trials.

We rely on third-party CROs to conduct our ongoing and future planned clinical trials of pegzilarginase. 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.

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.

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, and we do not have any manufacturing personnel. 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, including KBI, 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, including KBI, 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 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, KBI is supplying, and is expected to continue to supply, the drug substance requirements for our ongoing and planned clinical trials with pegzilarginase. If KBI 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 is not 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 KBI for certain studies related to potential commercial scale manufacturing of pegzilarginase at a separate KBI facility, 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, including KBI, 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, including KBI, 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:

- possible noncompliance by the third party with regulatory requirements and quality assurance;
- the possible breach of the manufacturing agreement by the third party;
- the possible misappropriation of our proprietary information, including our trade secrets and know-how; and
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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 companion diagnostics developed for use with our therapeutic product candidates for oncology indications could harm our ability to commercialize these product candidates.

We do not plan to develop companion diagnostics internally and, as a result, we are dependent on the efforts of our third-party strategic partners to successfully commercialize any needed companion diagnostics. Our strategic partners:

- may not perform their obligations as expected;
- may encounter production difficulties that could constrain the supply of the companion diagnostics;
- may have difficulties gaining acceptance of the use of the companion diagnostics in the clinical community;
- may not pursue commercialization of any companion diagnostics;
- 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 companion diagnostic product candidates; and
- may terminate their relationship with us.

If companion diagnostics needed for use with our therapeutic product candidates in oncology 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 commercialize these companion diagnostics, 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 of certain of our product candidates or successfully commercializing or competing in the market for certain indications.

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 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 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, 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.

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.

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.

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 KBI's manufacturing facilities and have a material adverse effect on our business, financial condition, results of operations and prospects. If a natural disaster,



power outage or other event occurred that prevented us from using all or a significant portion of our headquarters, that damaged critical infrastructure, such as KBI's manufacturing 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 KBI's manufacturing 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.

## Risks Related to Government Regulation

If we are not able to obtain, or if there are delays in obtaining, 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 a 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. 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 no 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 preclinical programs or clinical trials;
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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 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.

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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, the approved labeling may limit the use of our product candidates in this way, which could limit sales of the product.

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. 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.

We may also seek accelerated approval for products. 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 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. For drugs or biologics granted accelerated approval, post-marketing confirmatory trials are 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, in some cases, the FDA may require that the trial be designed and/or initiated prior to approval. 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 do not currently have Breakthrough Therapy Designation for any of our product candidates, but may seek such designation. 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. In any event, the receipt of a Breakthrough Therapy designation for a product candidate may not result in a faster development process, review or approval compared to drugs or biologics considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualify as Breakthrough Therapies, the FDA may later decide that such product candidates no longer meet the conditions for qualification.

Any product candidate for which we obtain marketing approval will be subject to extensive post-marketing regulatory requirements and could be subject to post-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 may also impose requirements for costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of any approved product. 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.

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 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. The information was made publicly available on a searchable website in September 2014 and is disclosed 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. 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.



We are subject to a variety of privacy and data security laws, and our failure to comply with them could harm our business.

We maintain a large 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 (GDPR) will take effect in the European Economic Area (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. In addition, the GDPR increases the scrutiny of transfers of personal data from clinical trial sites located in the EEA to the United States, and imposes substantial fines for breaches and violations. 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.

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.

Among the provisions of the ACA of importance to our potential product candidates are the following:

- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program;
- expansion of healthcare fraud and abuse laws, including the False Claims Act and the Anti-Kickback Statute, new government investigative powers, and enhanced penalties for noncompliance;
- a Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices;
- extension of manufacturers' Medicaid rebate liability to managed care utilization;
- expansion of eligibility criteria for Medicaid programs;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;
  - requirements to report financial arrangements with physicians and teaching hospitals;

- a requirement to annually report drug samples that manufacturers and distributors provide to physicians; and
- a Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

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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, starting in 2013. 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, and plans to repeal all or portions of the ACA have also been suggested. We cannot predict whether these challenges will continue or whether other proposals will be made or adopted, or what impact these efforts may have on us.

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. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. 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.

The U.S. government has recently enacted comprehensive tax legislation that includes significant changes to the taxation of business entities. These changes include, among others, (i) a permanent reduction to the corporate income tax rate, (ii) a partial limitation on the deductibility of business interest expense, (iii) a shift of the U.S. taxation of multinational corporations from a tax on worldwide income to a territorial system (along with certain rules designed to prevent erosion of the U.S. income tax base) and (iv) a one-time tax on accumulated offshore earnings held in cash and illiquid assets, with the latter taxed at a lower rate.

Further, the newly enacted comprehensive tax legislation, among other things, reduces 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 as it may cause us to pay federal income taxes earlier under the revised tax law than under the prior law and, despite being partially off-set by a reduction in the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, may increase our total federal tax liability attributable to such programs.

Notwithstanding the reduction in the corporate income tax rate, the overall impact of this tax reform is uncertain, and our business and financial condition could be adversely affected. In addition, it is uncertain if and to what extent various states will conform to the newly enacted federal tax law.

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.

#### 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 companion 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. For example, India does not allow patents for methods of treating the human body or

medical use claims as in other jurisdictions. 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 preclinical 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 freedom to operate 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 due to non-U.S. patent agencies. 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 many cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. However, in some cases we 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.

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.

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. For example, unlike other countries, China has a heightened requirement for patentability and specifically requires a detailed description of medical uses of a claimed therapeutic. 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 in Europe and certain developing countries, including India and China, 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 a number of 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 particular, we partner with the University of Texas at Austin, which is a U.S. academic institution, in order to accelerate our discovery and nonclinical development work under a Sponsored Research Agreement. Under the Sponsored Research

Agreement, we made payments of \$188,000 for each of the three months ended March 31, 2018 and 2017, to sponsor research in the laboratory of our director, Dr. George Georgiou, at the University of Texas at Austin on the engineering, optimization and initial animal validation of human enzymes to determine the systemic depletion of amino acids for cancer therapy and to analyze enzyme replacement for the treatment of patients having inborn metabolic defects.

The University of Texas at Austin has provided us with an option to negotiate a royalty-bearing, exclusive license to any invention or discovery that is conceived or reduced to practice during the term of the Sponsored Research Agreement. Regardless of such right of first negotiation for intellectual property, we may be unable to negotiate a license within the specified time frame or under terms that are acceptable to us. If we are unable to do so, the institution may offer the intellectual property rights to other parties, potentially blocking our ability to pursue a program based on that technology.

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 product candidates AEB3103 and AEB2109. In January and December, 2017, we and the University of Texas at Austin entered into and subsequently amended an Amended and Restated Patent License Agreement which consolidated the two license agreements, revised certain obligations, and licensed additional patent applications and invention disclosures to us, or the Restated License. The intellectual property licensed under the Restated License includes an invention that was 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;

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- 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 U.S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our products, and recent patent reform 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 and is currently implementing wide-ranging patent reform legislation. Recent U.S. Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created 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.

For our U.S. patent applications containing a claim not entitled to priority before March 16, 2013, there is a greater level of uncertainty in the patent law. On September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith Act includes a number of significant changes to U.S. patent law, which affect both the way patent applications will be prosecuted and potentially patent litigation. The U.S. PTO has promulgated regulations and developed procedures to govern administration of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act (in particular, the first to file provisions) did not come into effect until March 16, 2013. Accordingly, it is not yet clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, 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.

An important change introduced by the Leahy-Smith Act is that, as of March 16, 2013, the United States transitioned to a "first-to-file" system for deciding which party should be granted a patent when two or more patent applications are filed by different parties claiming the same invention. A third party that files a patent application in the U.S. PTO after that date but before us could therefore be awarded a patent covering an invention of ours even if we had made the invention before it was made by the third party. This will require us to be cognizant going forward of the time from invention to filing of a patent application. Furthermore, our ability to obtain and maintain valid and enforceable patents depends on whether the differences between our technology and the prior art allow our technology to be patentable over the prior art. 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.

Among some of the other changes introduced by the Leahy-Smith Act are changes that limit where a patentee may file a patent infringement suit and that allow third parties to challenge any issued patent, whether issued before or after March 16, 2013, in the U.S. PTO. Because of a lower evidentiary standard in U.S. PTO proceedings compared to the evidentiary standard in United States federal court necessary to invalidate a patent claim, a third party could potentially provide evidence in a U.S. PTO proceeding sufficient for the U.S. PTO to hold a claim invalid even though the same evidence would be insufficient to invalidate the claim if first presented in a district court action. Accordingly, a third party

may attempt to use the U.S. PTO procedures to invalidate our patent claims that would not have been invalidated if first challenged by the third party as a defendant in a district court action.

If we do not obtain patent term extensions in the United States under the Hatch-Waxman Act and in foreign countries under similar legislation, thereby potentially 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 under the Hatch-Waxman Act. The Hatch-Waxman Act 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. 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 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.

#### Risks Related to Our Common Stock

Our executive officers, directors and principal stockholders, if they choose to act together, will 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 majority of our capital stock as of March 31, 2018. As a result, if these stockholders were to choose to act together, they would 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 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.

Our internal control over financial reporting does not currently meet the standards required by Section 404 of the Sarbanes-Oxley Act, and 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 beginning with the year ended December 31, 2017. However, while we remain an emerging growth company, 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, 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. This choice of forum provision 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 Court of Chancery could face additional litigation costs in pursuing any such claim, particularly if they do not reside in or near Delaware. The Court of Chancery 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 this provision of our amended and restated certificate of incorporation 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 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; and
- the other factors described in this “Risk Factors” section.

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.





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.

Certain holders of our common stock have rights, subject to conditions, to require us to file registration statements covering their shares or to include their shares in Securities Act registration statements that we may file for ourselves or other stockholders. Once we register these shares, they can be freely sold in the public market. Moreover, we have also registered under the Securities Act shares of common stock that we may issue under our equity compensation plans.

In addition, on May 1, 2017, we filed a shelf registration statement on Form S-3 for the potential offering, issuance and sale by us of up to \$150.0 million of our common stock, preferred stock, debt securities, warrants to purchase our common stock, preferred stock and debt securities, subscription rights to purchase our common stock, preferred stock and debt securities, and units consisting of all or some of these securities. The shelf registration statement was declared effective by the SEC on May 30, 2017. In June 2017 and April 2018, we sold 3,000,000 and 5,046,510 shares of our common stock in underwritten public offerings pursuant to the shelf registration statement for aggregate gross proceeds of \$12.3 million and \$40.4 million, respectively. In addition, common stock with an aggregate offering price of up to \$20.0 million may be issued and sold pursuant to an “at-the-market” offering of our common stock pursuant to a sales agreement between us and JonesTrading Institutional Services LLC, or JonesTrading. 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 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 such shares pursuant to the sales agreement will have a dilutive effect on our existing stockholders. Further, if we sell common stock, preferred stock, convertible securities and other equity securities in other transactions pursuant to our shelf registration statement 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 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. Any such issuance could result in substantial dilution to our existing stockholders and could cause our stock price to decline.



We are an “emerging growth company,” and the reduced disclosure requirements applicable to emerging growth companies may make our common stock less attractive to investors.

We are an “emerging growth company,” as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, and may remain an emerging growth company for up to five years. For so long as we remain an emerging growth company, we are permitted and intend to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not emerging growth 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;
- not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor’s report providing additional information about the audit and the financial statements;
- reduced disclosure obligations regarding executive compensation; and
- exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved.

The JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. This allows an emerging growth company to delay the adoption of these accounting standards until they would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this exemption and, therefore, we will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

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 after 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 have been required to furnish a report by our management on our internal control over financial reporting beginning with the year ending December 31, 2017. As discussed above, if we cease to be an emerging growth company, 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.

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.

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.

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

None.

Use of Proceeds

On April 6, 2016, our Registration Statement on Form S-1 (File No. 333-200501) relating to the IPO of our common stock was declared effective by the SEC.

There has been no material change in our planned use of the net proceeds from the IPO, as described in our final prospectus filed with the SEC on April 7, 2016.

Item 3. Defaults Upon Senior Securities.  
Not applicable.

Item 4. Mine Safety Disclosures.  
Not applicable.

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Item 5. Other Information.

None.

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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
10.1*	<u>2018 Equity Inducement Plan</u>
31.1	<u>Certification of the Principal Executive Officer pursuant to Rule 13a-14(a) or 15d-14(a) of the Securities Exchange Act of 1934.</u>
31.2	<u>Certification of the Principal Financial Officer pursuant to Rule 13a-14(a) or 15d-14(a) of the Securities Exchange Act of 1934.</u>
32.1(1)	<u>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.</u>
32.2(1)	<u>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.</u>
101.INS	XBRL Instance Document
101.SCH	XBRL Taxonomy Extension Schema Document
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	XBRL Taxonomy Extension Label Linkbase Document
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document

\*Incorporated by reference to Exhibit 99.2 to the Registrant’s Registration Statement on Form S-8 (File No. 333-223614) filed with the SEC on March 13, 2018.

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



SIGNATURES

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

Date: May 8, 2018

AEGLEA BIOTHERAPEUTICS, INC.

By: /s/ Anthony G. Quinn, M.B Ch.B, Ph.D.  
Anthony G. Quinn, M.B Ch.B, Ph.D.  
Interim Chief Executive Officer and Director  
(Principal Executive Officer)

SIGNATURES

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

Date: May 8, 2018

AEGLEA BIOTHERAPEUTICS, INC.

By: /s/ Charles N. York II  
Charles N. York II  
Chief Financial Officer and Vice President  
(Principal Accounting Officer and Principal Financial Officer and duly Authorized Signatory)