AGIOS PHARMACEUTICALS INC
Form 10-Q
May 04, 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
Commission file number 001-36014

AGIOS PHARMACEUTICALS, INC.
(Exact Name of Registrant as Specified in Its Charter)

Delaware	26-0662915
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)

88 Sidney Street, Cambridge, Massachusetts	02139
(Address of Principal Executive Offices)	(Zip Code)

(617) 649-8600
(Registrant's Telephone Number, Including Area Code)
(Former Name, Former Address and Former Fiscal Year, if Changed Since Last Report)

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. (Check one):

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

Number of shares of the registrant's Common Stock, $0.001 par value, outstanding on April 30, 2018: 57,605,621

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PART I. FINANCIAL INFORMATION

Item 1. Financial Statements (Unaudited)

AGIOS PHARMACEUTICALS, INC.

Condensed Consolidated Balance Sheets

(in thousands, except share and per share data)

(Unaudited)

	March 31, 2018	December 31, 2017
Assets		
Current assets:		
Cash and cash equivalents	$364,469	$102,724
Marketable securities	417,981	321,212
Collaboration receivable – related party	3,512	2,448
Royalty receivable – related party	1,417	1,222
Prepaid expenses and other current assets	15,614	17,655
Total current assets	802,993	445,261
Marketable securities	212,297	143,814
Property and equipment, net	23,732	24,431
Other non-current assets	1,104	891
Total assets	$1,040,126	$614,397
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$17,932	$22,767
Accrued expenses	17,005	34,031
Deferred revenue – related party	39,212	37,842
Deferred rent	550	301
Total current liabilities	74,699	94,941
Deferred revenue, net of current portion – related party	81,831	125,798
Deferred rent, net of current portion	18,002	18,155
Total liabilities	174,532	238,894
Stockholders' equity:		
Preferred stock, $0.001 par value; 25,000,000 shares authorized; no shares issued or outstanding at March 31, 2018 and December 31, 2017	—	—
Common stock, $0.001 par value; 125,000,000 shares authorized; 57,541,613 and 48,826,153 shares issued and outstanding at March 31, 2018 and December 31, 2017, respectively	58	49
Additional paid-in capital	1,717,609	1,174,904
Accumulated other comprehensive loss	(2,643)	(1,389)
Accumulated deficit	(849,430)	(798,061)
Total stockholders' equity	865,594	375,503
Total liabilities and stockholders' equity	$1,040,126	$614,397

See accompanying Notes to Condensed Consolidated Financial Statements.

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AGIOS PHARMACEUTICALS, INC.
Condensed Consolidated Statements of Operations
(in thousands, except share and per share data)
(Unaudited)

	Three Months Ended March 31,	
	2018	2017
Collaboration revenue – related party	$7,345	$10,508
Royalty revenue – related party	1,417	—
Total revenue	8,762	10,508
Operating expenses:		
Research and development (net of $2,776 of cost reimbursement from related party for the three months ended March 31, 2017)	78,224	62,732
General and administrative	24,550	14,823
Total operating expenses	102,774	77,555
Loss from operations	(94,012)	(67,047)
Interest income	3,187	881
Net loss	$(90,825)	$(66,166)
Net loss per share – basic and diluted	$(1.63)	$(1.56)
Weighted-average number of common shares used in computing net loss per share – basic and diluted	55,694,603	42,280,525

See accompanying Notes to Condensed Consolidated Financial Statements.

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AGIOS PHARMACEUTICALS, INC.
Condensed Consolidated Statements of Comprehensive Loss
(in thousands)
(Unaudited)

	Three Months Ended March 31,	
	2018	2017
Net loss	$(90,825)	$(66,166)
Other comprehensive (loss) income		
Unrealized (loss) gain on available-for-sale securities	(1,254)	101
Comprehensive loss	$(92,079)	$(66,065)

See accompanying Notes to Condensed Consolidated Financial Statements.

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AGIOS PHARMACEUTICALS, INC.
Condensed Consolidated Statements of Cash Flows
(in thousands)
(Unaudited)

	Three Months Ended March 31,	
	2018	2017
Operating activities		
Net loss	$(90,825)	$(66,166)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation	1,725	1,591
Stock-based compensation expense	14,522	10,734
Net amortization of premium and discounts on investments	(406)	163
Loss on disposal of property and equipment	—	40
Changes in operating assets and liabilities:		
Collaboration receivable – related party	(1,064)	(6,379)
Royalty receivable – related party	(195)	—
Tenant improvement and other receivables	—	(24)
Prepaid expenses and other current and non-current assets	1,901	(3,425)
Accounts payable	(4,469)	(994)
Accrued expenses	(17,144)	(6,889)
Deferred revenue – related party	(3,141)	(1,924)
Deferred rent	96	(801)
Net cash used in operating activities	(99,000)	(74,074)
Investing activities		
Purchases of marketable securities	(330,971)	(26,740)
Proceeds from maturities and sales of marketable securities	164,871	136,585
Purchases of property and equipment	(1,432)	(293)
Net cash (used in) provided by investing activities	(167,532)	109,552
Financing activities		
Payment of public offering costs, net of reimbursements	(188)	(100)
Proceeds from public offering of common stock, net of commissions	516,206	—
Net proceeds from stock option exercises and employee stock purchase plan	12,259	4,146
Net cash provided by financing activities	528,277	4,046
Net change in cash and cash equivalents	261,745	39,524
Cash and cash equivalents at beginning of the period	102,724	160,754
Cash and cash equivalents at end of the period	$364,469	$200,278
Supplemental disclosure of non-cash investing and financing transactions		
Additions to property and equipment in accounts payable and accrued expenses	$605	$213
Proceeds from stock option exercises in other current assets	$73	$6
Public offering costs in other current assets	$—	$329
Public offering costs in accounts payable and accrued expenses	$158	$—

See accompanying Notes to Condensed Consolidated Financial Statements.

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AGIOS PHARMACEUTICALS, INC.
Notes to Condensed Consolidated Financial Statements
(Unaudited)

1. Overview and Basis of Presentation

References to Agios

Throughout this Quarterly Report on Form 10-Q, "we," "us," and "our," and similar expressions, except where the context requires otherwise, refer to Agios Pharmaceuticals, Inc. and its consolidated subsidiaries, and "our Board of Directors" refers to the board of directors of Agios Pharmaceuticals, Inc.

Overview

We are a biopharmaceutical company committed to the fundamental transformation of patients' lives through scientific leadership in the field of cellular metabolism, with the goal of making transformative, first- or best-in-class medicines. Our therapeutic areas of focus are cancer and rare genetic diseases, or RGDs, which are diseases that are directly caused by changes in genes or chromosomes, often passed from one generation to the next. Most RGDs are often associated with severe or life-threatening features. The incidence of a single RGD can vary widely but is generally very infrequent, usually equal to or less than one per 100,000 births. In both areas of cancer and RGDs, we are seeking to unlock the biology of cellular metabolism as a platform to create transformative therapies. We are located in Cambridge, Massachusetts.

Basis of presentation

The condensed consolidated balance sheet as of March 31, 2018, and the condensed consolidated statements of operations, comprehensive loss, and cash flows for the three months ended March 31, 2018 and 2017 are unaudited. The unaudited condensed consolidated financial statements have been prepared on the same basis as the annual financial statements and, in the opinion of our management, reflect all adjustments, which include only normal recurring adjustments, necessary to fairly state our financial position as of March 31, 2018, and our results of operations and cash flows for the three months ended March 31, 2018 and 2017. The financial data and the other financial information disclosed in these notes to the condensed consolidated financial statements related to the three-month period are also unaudited. The results of operations for the 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 year-end condensed consolidated balance sheet data was derived from our audited financial statements, but does not include all disclosures required by U.S. generally accepted accounting principles, or U.S. GAAP. Accordingly, the condensed consolidated interim financial statements should be read in conjunction with the audited consolidated financial statements and notes thereto included in our Annual Report on Form 10-K for the year ended December 31, 2017 that was filed with the Securities and Exchange Commission, or the SEC, on February 14, 2018.

Our consolidated financial statements include our accounts and the accounts of our wholly owned subsidiaries, Agios Securities Corporation, Agios International Sarl, and Agios Limited. All intercompany transactions have been eliminated in consolidation. The consolidated financial statements have been prepared in conformity with U.S. GAAP.

Liquidity

In January 2018, we completed a public offering of 7,089,553 shares of common stock at an offering price of $67.00 per share. We received net proceeds from this offering of $448.9 million, after deducting underwriting discounts and commissions paid by us. In addition, we granted the underwriters the right to purchase up to an additional 1,063,433 shares of common stock, which was exercised in January 2018, resulting in additional net proceeds to us of $67.3 million, after underwriting discounts and commissions. After giving effect to the full exercise of the over-allotment option, the number of shares sold by us in the public offering totaled 8,152,986 shares, and net proceeds to us totaled $516.2 million, after underwriting discounts and commissions.

As of March 31, 2018, we had cash, cash equivalents and marketable securities of $994.7 million. Although we have incurred recurring losses and expect to continue to incur losses for the foreseeable future, we expect our cash, cash equivalents and marketable securities will be sufficient to fund current operations for at least the next twelve months from the issuance date of these financial statements.

2. Summary of Significant Accounting Policies and Recent Accounting Pronouncements

Significant accounting policies

Revenue from Contracts with Customers

In May 2014, the Financial Accounting Standards Board, or FASB, issued ASU No. 2014-09, Revenue from Contracts with Customers (Topic 606), or ASU 2014-09. ASU 2014-09 was codified as Accounting Standards Codification, or ASC, 606,

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Revenue from Contracts with Customers, or ASC 606. Subsequently, the FASB issued ASU 2015-14, Revenue from Contracts with Customers (Topic 606), which adjusted the effective date of ASU 2014-09; ASU No. 2016-08, Revenue from Contracts with Customers (Topic 606): Principal versus Agent Considerations (Reporting Revenue Gross versus Net), which amends the principal-versus-agent implementation guidance and illustrations in ASU 2014-09; ASU No. 2016-10, Revenue from Contracts with Customers (Topic 606): Identifying Performance Obligations and Licensing, which clarifies identifying performance obligations and licensing implementation guidance and illustrations in ASU 2014-09; ASU No. 2016-12, Revenue from Contracts with Customers (Topic 606): Narrow-Scope Improvements and Practical Expedients, which addresses implementation issues and is intended to reduce the cost and complexity of applying the new revenue standard in ASU 2014-09; ASU No. 2017-13, Revenue Recognition (Topic 605), Revenue from Contracts with Customers (Topic 606), Leases (Topic 840), and Leases (Topic 842): Amendments to SEC Paragraphs Pursuant to the Staff Announcement at the July 20, 2017 EITF Meeting and Rescission of Prior SEC Staff Announcements and Observer Comments (SEC Update), which codifies recent announcements by the SEC staff; and ASU No. 2017-14, Income Statement—Reporting Comprehensive Income (Topic 220), Revenue Recognition (Topic 605), and Revenue from Contracts with Customers (Topic 606) (SEC Update), which codifies SEC Release 33-10403, or collectively with ASU 2014-09, the Revenue ASUs.

We were required to adopt the Revenue ASUs effective January 1, 2018. The guidance permits two methods of adoption: retrospectively to each prior reporting period presented (the full retrospective method), or retrospectively with the cumulative effect of initially applying the guidance recognized at the date of initial application (the modified retrospective method). We adopted the new standard under the modified retrospective method.

In adopting the Revenue ASUs, we applied the practical expedient that permits aggregating the effect of all modifications that occurred prior to January 1, 2018. No other practical expedients were used.

Upon finalization of our assessment, which resulted in changes to our estimates as of December 31, 2017, the impact of the cumulative effect of the accounting changes upon the adoption of the standard (in thousands) is as follows:

	December 31, 2017	Cumulative Effect	January 1, 2018
Deferred revenue – related party, current and net of current portions	$163,640	$(39,456)	$124,184
Accumulated deficit	(798,061)	39,456	(758,605)

The following tables summarize the effects of adopting ASC 606 on our unaudited condensed consolidated financial statements for the three months ended March 31, 2018 (in thousands, except per share data):

Condensed Consolidated Balance Sheets

	March 31, 2018		
	Under Topic 606	Under Topic 605	Effect of Change
Deferred revenue – related party	$39,212	$35,396	$3,816
Deferred revenue, net of current portion – related party	81,831	122,060	(40,229)
Accumulated deficit	(849,430)	(885,843)	36,413

Condensed Consolidated Statements of Operations

	Three Months Ended March 31, 2018		
	Under Topic 606	Under Topic 605	Effect of Change
Collaboration revenue – related party	$7,345	$9,977	$(2,632)
Research and development expense	78,224	77,813	411
Total operating expenses	102,774	102,363	411
Loss from operations	(94,012)	(90,969)	(3,043)
Net loss	(90,825)	(87,782)	(3,043)
Net loss per share – basic and diluted	(1.63)	(1.58)	(0.05)

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Condensed Consolidated Statements of Comprehensive Loss

	Three Months Ended March 31, 2018		
	Under Topic 606	Under Topic 605	Effect of Change
Net loss	$(90,825)	$(87,782)	$(3,043)
Comprehensive loss	(92,079)	(89,036)	(3,043)

Condensed Consolidated Statements of Cash Flows

	Three Months Ended March 31, 2018		
	Under Topic 606	Under Topic 605	Effect of Change
Net loss	$(90,825)	$(87,782)	$(3,043)
Adjustments to reconcile net loss to net cash used in operating activities:			
Deferred revenue – related party	(3,141)	(6,184)	3,043

Recent accounting pronouncements

In February 2016, the FASB issued ASU No. 2016-02, Leases (Topic 842), or ASU 2016-02, which establishes principles that lessees and lessors shall apply to report useful information to users of financial statements about the amount, timing and uncertainty of cash flows arising from a lease. ASU 2016-02 was codified as ASC 842, Leases. Subsequently, the FASB issued ASU 2017-13, Revenue Recognition (Topic 605), Revenue from Contracts with Customers (Topic 606), Leases (Topic 840), and Leases (Topic 842): Amendments to SEC Paragraphs Pursuant to the Staff Announcement at the July 20, 2017 EITF Meeting and Rescission of Prior SEC Staff Announcements and Observer Comments (SEC Update), which codifies recent announcements by the SEC staff; and ASU 2018-01, Leases (Topic 842): Land Easement Practical Expedient for Transition to Topic 842, which provides a transition practical expedient for existing or expired land easements, or collectively with ASU 2016-02, the Leases ASUs.

We will adopt ASC 842 effective January 1, 2019. We are currently in the process of evaluating the impact of the guidance on our consolidated financial statements.

Other accounting standards that have been issued by the FASB or other standards-setting bodies that do not require adoption until a future date are not expected to have a material impact on our financial statements upon adoption.

3. Fair Value Measurements

We record cash equivalents and marketable securities at fair value. ASC 820, Fair Value Measurements and Disclosures, establishes a fair value hierarchy for those instruments measured at fair value that distinguishes between assumptions based on market data (observable inputs) and our own assumptions (unobservable inputs). The hierarchy consists of three levels:

Level 1 – Unadjusted quoted prices in active markets for identical assets or liabilities.

Level 2 – Quoted prices for similar assets and liabilities in active markets, quoted prices in markets that are not active, or inputs which are observable, directly or indirectly, for substantially the full term of the asset or liability.

Level 3 – Unobservable inputs that reflect our own assumptions about the assumptions market participants would use in pricing the asset or liability in which there is little, if any, market activity for the asset or liability at the measurement date.

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The following table summarizes our cash equivalents and marketable securities measured at fair value on a recurring basis as of March 31, 2018 (in thousands):

	Level 1	Level 2	Level 3	Total
Cash equivalents	$262,897	$84,827	$ —	$347,724
Marketable securities:				
Certificates of deposit	—	5,226	—	5,226
U.S. Treasuries	—	179,580	—	179,580
Government securities	—	128,968	—	128,968
Corporate debt securities	—	316,504	—	316,504
Total cash equivalents and marketable securities	$262,897	$715,105	$ —	$978,002

Cash equivalents and marketable securities have been initially valued at the transaction price and subsequently valued, at the end of each reporting period, utilizing third-party pricing services or other market observable data. The pricing services utilize industry standard valuation models, including both income and market based approaches, and observable market inputs to determine value. After completing our validation procedures, we did not adjust or override any fair value measurements provided by the pricing services as of March 31, 2018.

There have been no changes to the valuation methods during the three months ended March 31, 2018. We evaluate transfers between levels at the end of each reporting period. There were no transfers between Level 1 and Level 2 during the three months ended March 31, 2018. We have no financial assets or liabilities that were classified as Level 3 at any point during the three months ended March 31, 2018.

4. Marketable Securities

Our marketable securities are classified as available-for-sale pursuant to ASC 320, Investments – Debt and Equity Securities, and are recorded at fair value, with unrealized gains and losses included as a component of accumulated other comprehensive loss in stockholders' equity and a component of total comprehensive loss in the condensed consolidated statements of comprehensive loss, until realized. Realized gains and losses are included in investment income on a specific-identification basis. There were no realized gains or losses on marketable securities for the three months ended March 31, 2018 and 2017 and, as a result, there were no reclassifications of any amounts out of accumulated other comprehensive loss for those periods.

Marketable securities at March 31, 2018 consisted of the following (in thousands):

	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value
Current:				
Certificates of deposit	$4,760	$ —	$ (8)	$4,752
U.S Treasuries	144,849	—	(209)	144,640
Government securities	71,773	—	(141)	71,632
Corporate debt securities	197,334	—	(377)	196,957
Non-current:				
Certificates of deposit	480	—	(6)	474
U.S Treasuries	35,318	—	(378)	34,940
Government securities	57,646	—	(310)	57,336
Corporate debt securities	120,752	—	(1,205)	119,547
Total marketable securities	$632,912	$ —	$ (2,634)	$630,278

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Marketable securities at December 31, 2017 consisted of the following (in thousands):

	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value
Current:				
Certificates of deposit	$ 8,081	$ —	$ (11)	$ 8,070
U.S. Treasuries	113,852	—	(119)	113,733
Government securities	44,421	—	(57)	44,364
Corporate debt securities	155,222	—	(177)	155,045
Non-current:				
Certificates of deposit	960	—	(8)	952
U.S. Treasuries	36,165	—	(311)	35,854
Government securities	23,992	—	(182)	23,810
Corporate debt securities	83,722	—	(524)	83,198
Total marketable securities	$ 466,415	$ —	$ (1,389)	$ 465,026

At March 31, 2018 and December 31, 2017, we held both current and non-current investments. Investments classified as current have maturities of less than one year. Investments classified as non-current are those that: (i) have a maturity of one to two years, and (ii) we do not intend to liquidate within the next twelve months, although these funds are available for use and therefore classified as available-for-sale.

At March 31, 2018 and December 31, 2017, we held 257 and 240 debt securities that were in an unrealized loss position for less than one year, respectively. The aggregate fair value of debt securities in an unrealized loss position at March 31, 2018 and December 31, 2017 was $572.7 million and $439.4 million, respectively. There were no individual securities that were in a significant unrealized loss position as of March 31, 2018 and December 31, 2017. Given our intent and ability to hold such securities until recovery, and the lack of material of change in the credit risk of these investments, we do not consider these marketable securities to be other-than-temporarily impaired as of March 31, 2018 and December 31, 2017.

5. Collaboration Agreements

Celgene Corporation

To date, our revenue has primarily been generated from our collaboration agreements with Celgene, or collectively, the Collaboration Agreements. Celgene is a related party through ownership of our common stock. In April 2010, we entered into a discovery and development collaboration and license agreement focused on cancer metabolism, or the 2010 Agreement. The 2010 Agreement was amended in October 2011 and July 2014. In April 2015, we entered into a joint worldwide development and profit share collaboration and license agreement with Celgene, and our wholly owned subsidiary, Agios International Sarl, entered into a collaboration and license agreement with Celgene International II Sarl, or collectively, the AG-881 Agreements, to establish a worldwide collaboration focused on the development and commercialization of AG-881 products. In May 2016, we entered into a master research and collaboration agreement with Celgene, or the 2016 Agreement.

2016 Agreement

In May 2016, we entered into the 2016 Agreement focused on metabolic immuno-oncology, or MIO, a developing field which aims to modulate the activity of relevant immune cells by targeting critical metabolic nodes, thereby, enhancing the immune mediated anti-tumor response. In addition to new programs identified under the 2016 Agreement, both parties also agreed that all future development and commercialization of two remaining cancer metabolism programs discovered under the 2010 Agreement, including AG-270, an inhibitor of methionine adenosyltransferase 2a, will now be governed by the 2016 Agreement.

During the research term of the 2016 Agreement, we plan to conduct research programs focused on discovering compounds that are active against metabolic targets in the immuno-oncology, or IO, field. The initial four-year research term will expire on May 17, 2020, and may be extended for up to two, or in specified cases, up to four additional one-year terms.

For each program under the 2016 Agreement, we may nominate compounds that meet specified criteria as development candidates and, in limited circumstances, Celgene may also nominate compounds as development

candidates for each such program. Celgene may designate the applicable program for further development following any such nomination, after which we may conduct, at our expense, additional preclinical and clinical development for such program through the completion of an initial phase 1 dose escalation study.

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At the end of the research term, Celgene may designate for continued development up to three research programs for which development candidates have yet to be nominated, which are referred to as continuation programs. We may conduct further research and preclinical and clinical development activities on any continuation program, at our expense, through the completion of an initial phase 1 dose escalation study.

We granted Celgene the right to obtain exclusive options for development and commercialization rights for each program that Celgene has designated for further development, and for each continuation program. Celgene may exercise each such option beginning on the designation of a development candidate for such program (or on the designation of such program as a continuation program) and ending on the earlier of: (i) the end of a specified period after we have furnished Celgene with specified information about the initial phase 1 dose escalation study for such program, or (ii) January 1, 2030. Research programs that have applications in the inflammation or autoimmune, or I&I, field that may result from the 2016 Agreement will also be subject to the exclusive options described above. We will retain rights to any program that Celgene does not designate for further development or as to which it does not exercise its option.

Under the terms of the 2016 Agreement, following Celgene's exercise of its option with respect to a program, the parties will enter into either a co-development and co-commercialization agreement if such program is in the IO field, or a license agreement if such program is in the I&I field. Under each co-development and co-commercialization agreement, the two parties will co-develop and co-commercialize licensed products worldwide. Either we or Celgene will lead development and commercialization of licensed products for the United States, and Celgene will lead development and commercialization of licensed products outside of the United States. Depending on the country, the parties will each have the right to provide a portion of field-based marketing activities. Under each license agreement, Celgene will have the sole right to develop and commercialize licensed products worldwide.

Co-development and co-commercialization agreements

Under each co-development and co-commercialization agreement entered into under the 2016 Agreement, the parties will split all post-option exercise worldwide development costs, subject to specified exceptions, as well as any profits from any net sales of, or commercialization losses related to, licensed products in the IO field. Celgene has the option to designate one program in the IO field as the 65/35 program, for which Celgene will be the lead party for the United States and will have a 65% profit or loss share. For programs in the IO field other than the 65/35 program, we and Celgene will alternate, on a program-by-program basis, being the lead party for the United States, with us having the right to be the lead party for the first such program, and each party will have a 50% profit or loss share. The lead party for the United States will book commercial sales of licensed products, if any, in the United States, and Celgene will book commercial sales of licensed products, if any, outside of the United States.

License agreements

Under each license agreement under the 2016 Agreement, Celgene will be responsible for all post-option exercise worldwide development and associated costs, subject to specified exceptions, as well as worldwide commercialization and associated costs, for licensed products in the I&I field.

Financial terms

Under the terms of the 2016 Agreement, we received an initial upfront payment in the amount of $200.0 million. The 2016 Agreement provides specified rights to extend the research term for up to two, or in specified cases, up to four, additional years by paying a $40.0 million per-year extension fee. Celgene will pay an $8.0 million designation fee for each program that Celgene designates for further development and for each continuation program. During the three months ended March 31, 2017, we received $8.0 million from Celgene upon the designation of AG-270 as a development candidate. For each program as to which Celgene exercises its option to develop and commercialize, subject to antitrust clearance, Celgene will pay an option exercise fee of at least $30.0 million for any designated development program and at least $35.0 million for any continuation programs. In certain cases, Celgene may exercise its option to develop and commercialize two early-stage I&I programs, prior to Celgene designating the program for further development, by paying an option exercise fee of $10.0 million.

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We are eligible to receive the following milestone-based payments associated with the 2016 Agreement:

Program	Milestone	Amount
65/35 program in IO field	Specified clinical development event	$25.0 million
65/35 program in IO field	Specified regulatory milestone events	Up to $183.8 million
50/50 program in IO field	Specified clinical development event	$20.0 million
50/50 program in IO field	Specified regulatory milestone events	Up to $148.8 million
I&I field	Specified clinical development event	$25.0 million
I&I field	Specified regulatory milestone events	Up to $236.3 million
I&I field	Specified commercial milestone events	Up to $125.0 million

Additionally, for each licensed program in the I&I field, we are eligible to receive royalties at tiered, low double-digit percentage rates on Celgene's net sales, if any.

Opt-out right

Under the 2016 Agreement, we may elect to opt out of the cost and profit share under any co-development and co-commercialization agreement, subject to specified exceptions. Upon opting out, Celgene will have the sole right to develop, manufacture and commercialize the applicable licensed products throughout the world, at its cost, and we will undertake transitional activities reasonably necessary to transfer the development, manufacture and commercialization of such licensed products to Celgene, at our expense. Further, in lieu of the profit or loss sharing described above, we would be eligible to receive royalties at tiered, low double-digit percentage rates on Celgene's net sales, if any, of the applicable licensed products. However, we would continue to be eligible to receive the developmental and regulatory milestone-based payments described above.

Term

The term of the 2016 Agreement commenced on May 17, 2016 and, if not terminated earlier, will expire upon the later of the last-to-expire of the research term and all option exercise periods, or, if an option is exercised by Celgene for one or more programs in the collaboration, upon the termination or expiration of the last-to-exist co-development and co-commercialization agreement or license agreement, as applicable, for any such program.

Termination

Subject to specified exceptions, Celgene may terminate the 2016 Agreement in its entirety for any reason by providing us with prior written notice if there are no active co-development and co-commercialization agreements or license agreements in place or on a program-by-program basis if there are no active co-development and co-commercialization agreements or license agreements in place for the terminated program(s). Either party may terminate the 2016 Agreement for the insolvency of the other party. On a program-by-program basis, prior to the exercise of an option, either party may terminate the 2016 Agreement either in its entirety or with respect to one or more programs on prior written notice to the other party in the case of an uncured material breach by the other party that frustrates the fundamental purpose of the 2016 Agreement. Following the exercise of an option for a program, either party may terminate the 2016 Agreement with respect to such program if such party terminates the co-development and co-commercialization agreement or license agreement for such program for an uncured material breach by the other party that frustrates the fundamental purpose of such agreement. Either party may terminate a co-development and co-commercialization agreement or a license agreement upon the bankruptcy or insolvency of the other party. Either party also has the right to terminate the co-development and co-commercialization agreement or license agreement if the other party or any of its affiliates challenges the validity, scope or enforceability of or otherwise opposes, any patent included within the intellectual property rights licensed to the other party under such agreement.

Exclusivity

While any of Celgene's options remain available under the 2016 Agreement, subject to specified exceptions, we may not directly or indirectly develop, manufacture or commercialize, outside of the 2016 Agreement, any therapeutic modality in the IO or I&I field with specified activity against a metabolic target.

During the term of each co-development and co-commercialization agreement and license agreement, subject to specified exceptions, neither we nor Celgene may directly or indirectly develop, manufacture or commercialize outside of such agreement any therapeutic modality in any field with specified activity against the metabolic target

that is the focus of the program licensed under such agreement.

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TIBSOVO® (ivosidenib) Letter Agreement

In May 2016, we entered into a letter agreement with Celgene regarding TIBSOVO® (ivosidenib), or the TIBSOVO® (ivosidenib) Letter Agreement. Under the TIBSOVO® (ivosidenib) Letter Agreement, the parties agreed to terminate the 2010 Agreement, effective as of August 15, 2016, as to the program directed to the isocitrate dehydrogenase 1, or IDH1, target, for which TIBSOVO® (ivosidenib) is the lead development candidate. Under the 2010 Agreement, Celgene had held development and commercialization rights to the IDH1 program outside of the United States, and we held such rights inside the United States. As a result of the termination, we obtained global rights to TIBSOVO® (ivosidenib) and the IDH1 program. Neither party will have any further financial obligation, including royalties or milestone payments, to the other concerning TIBSOVO® (ivosidenib) or the IDH1 program. Under the terms of the termination, the parties also agreed to conduct specified transitional activities in connection with the termination. In addition, pursuant to the TIBSOVO® (ivosidenib) Letter Agreement, the parties are released from their exclusivity obligations under the 2010 Agreement with respect to the IDH1 program. The termination does not affect the AG-881 Agreements, which are directed to both the IDH1 target and the isocitrate dehydrogenase 2, or IDH2, target.

AG-881 Agreements

In April 2015, we entered into the AG-881 Agreements. The AG-881 Agreements establish a joint worldwide collaboration focused on the development and commercialization of AG-881 products. Under the terms of the AG-881 Agreements, we received an initial upfront payment of $10.0 million in May 2015 and are eligible to receive milestone-based payments described below. The parties will split all worldwide development costs equally, subject to specified exceptions, as well as any profits from any net sales of, or commercialization losses related to, licensed AG-881 products. Either party may, at its own expense and with the other party's permission, undertake additional development activities outside of the scope of the development plan agreed upon with the other party.

We are eligible to receive up to $70.0 million in potential milestone payments under the AG-881 Agreements. The potential milestone payments are comprised of: (i) a $15.0 million milestone payment for filing of a first new drug application, or NDA, in a major market, and (ii) up to $55.0 million in milestone payments upon achievement of specified regulatory milestone events. We may also receive royalties at tiered, low-double digit to mid-teen percentage rates on net sales if we elect not to participate in the development and commercialization of AG-881.

Termination

Celgene may terminate the AG-881 Agreements in their entirety for any reason upon ninety days written notice to us. Either party may terminate the AG-881 Agreements for the insolvency of the other party. Either party may terminate the AG-881 Agreements in their entirety or with respect to one of the agreements upon prior written notice to the other party in the case of an uncured material breach by the other party that frustrates the fundamental purpose of the AG-881 Agreements. If one of the AG-881 Agreements terminates, the other will terminate automatically.

2010 Agreement

In April 2010, we entered into the 2010 Agreement, which was amended in October 2011 and July 2014. The goal of the collaboration was to discover, develop and commercialize disease-altering therapies in oncology based on our cancer metabolism research platform. We initially led discovery, preclinical and early clinical development for all cancer metabolism programs under the collaboration. The discovery phase of the 2010 Agreement expired in April 2016.

Upon agreement to terminate the 2010 Agreement, effective as of August 15, 2016, as to the program directed to the IDH1 target, for which TIBSOVO® (ivosidenib) is the lead development candidate, the sole program remaining under the 2010 Agreement is IDHIFA®, a co-commercialized licensed program for which Celgene leads and funds global development and commercialization activities. We have exercised our right to participate in a portion of commercialization activities in the United States for IDHIFA® in accordance with the applicable commercialization plan. On August 1, 2017, the U.S. Food and Drug Administration, or FDA, granted Celgene approval of IDHIFA® for the treatment of adult patients with relapsed or refractory acute myeloid leukemia, or R/R AML, with an IDH2 mutation as detected by an FDA-approved test.

Under the remaining terms of the 2010 Agreement, we are eligible to receive up to $95.0 million in potential milestone payments for the IDHIFA® program. The potential milestone payments are comprised of: (i) up to $70.0 million in milestone payments upon achievement of specified ex-U.S. regulatory milestone events, and (ii) a $25.0

million milestone payment upon achievement of a specified ex-U.S. commercial milestone event.

Under the 2010 Agreement, we may also receive royalties at tiered, low-double digit to mid-teen percentage rates on net sales of IDHIFA®. Assuming all other revenue recognition criteria are met, royalty payments will be recognized as revenue in the period in which they are earned. During the three months ended March 31, 2018, we earned $1.4 million in royalty revenue under the 2010 Agreement.

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Unless terminated earlier by either party, the term of the 2010 Agreement will continue until the expiration of all royalty terms with respect to IDHIFA®. Celgene may terminate this agreement for convenience in its entirety upon ninety days written notice to us. If either party is in material breach and fails to cure such breach within the specified cure period, the other party may terminate the 2010 Agreement in its entirety. Either party may terminate the agreement in the event of specified insolvency events involving the other party.

Accounting analysis and revenue recognition – collaboration revenue

On January 1, 2018 we adopted ASC 606 under the modified retrospective method. Prior to January 1, 2018 we accounted for the Collaboration Agreements under ASC 605-25, Multiple Element Arrangements.

Accounting under ASC 606

In adopting ASC 606, we applied the practical expedient that permits aggregating the effect of all modifications that occurred prior to January 1, 2018. No other practical expedients were used. Similar to the accounting under ASC 605-25, the 2016 Agreement was determined to be a modification of the 2010 Agreement and the AG-881 Agreements. In determining the appropriate amount of revenue to be recognized under ASC 606, we performed the following steps: (i) identified the promised goods or services in the contract; (ii) determined whether the promised goods or services are performance obligations including whether they are distinct in the context of the contract; (iii) measured the transaction price, including the constraint on variable consideration; (iv) allocated the transaction price to the performance obligations; and (v) recognized revenue when (or as) we satisfy each performance obligation.

As part of the accounting for these arrangements, we must develop assumptions that require judgment to determine the stand-alone selling price, or SSP, for each performance obligation identified in the contract. We use key assumptions to determine the SSP, which include forecast of revenues, development timelines, reimbursement rates for personnel costs, discount rates and probabilities of technical and regulatory success.

The satisfied and unsatisfied performance obligations at the time of the ASC 606 adoption, each of which are considered by us to be distinct within the context of the contract, their SSP, the method of recognizing the allocated consideration, and the period through which they are expected to be recognized are as follows:

Performance Obligations	SSP	No. of Performance Obligation(s)	Recognition Method
Fully satisfied at time of adoption			
Licenses (1)	$86.7 million	4	Fully satisfied; recognized upon adoption of ASC 606
Research and development services (2) (3)	$350.7 million	10	Fully satisfied; recognized upon adoption of ASC 606
Partially satisfied at time of adoption			
Research and development services (2) (3)	$266.6 million	6	Proportionally as services are delivered over the performance period, expected to be through September 2022 (4)

(1) The SSP was developed by probability weighting multiple cash flow scenarios using the income approach. Our management estimates within the models include the expected, probability-weighted net profits from estimated future sales, an estimate of the direct cost incurred to generate future cash flows, a discount rate and other business forecast factors. There are significant judgments and estimates inherent in the determination of the SSP of these units of accounting. These judgments and estimates include assumptions regarding future operating performance, the timelines of the clinical trials and regulatory approvals, and other factors. If different reasonable assumptions are utilized, the SSP and revenue recognized would vary.

(2) The SSP was developed using our management's best estimate of the cost of obtaining these services at arm's length from a third-party provider.

(3) The SSP was developed using internal full time equivalent costs to support the development services.

(4) We determined that recognizing revenue on a proportional basis using the ratio of effort incurred to date compared to the total estimated effort required to complete the performance obligation best depicts the satisfaction of our obligations under the Collaboration Agreements.

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During the three months ended March 31, 2018, we recognized the following as collaboration revenue (in thousands):

	Three Months Ended March 31, 2018		
Performance Obligation	Under Topic 606	Under Topic 605	Effect of Change
Collaboration revenue - related party			
Research and development services	$6,364	$8,953	$(2,589)
Committee participations	—	43	(43)
Reduction of research and development expenses			
Development services	—	411	(411)

During the three months ended March 31, 2017, we recognized as collaboration revenue the following non-contingent consideration allocated to each undelivered element (in thousands):

Undelivered Element	Revenue Recognized
On-going research and development services	$ 10,387
Committee participations	42
Total collaboration revenue - related party	$ 10,429

During the three months ended March 31, 2017, we recognized $2.8 million as a reduction of research and development expenses. During the three months ended March 31, 2018, we did not recognize any reductions to research and development expenses.

Development and commercialization expenses that were not contemplated as of the modification dates due to the high level of uncertainty are recognized as collaboration revenue or a reduction of research and development expenses in the period in which they are earned. There was no impact from the adoption of ASC 606 on these obligations. For the three months ended March 31, 2018 and 2017, we recognized the following collaboration revenue and reduction of research and development expenses related to such expenses (in thousands):

	Three Months Ended March 31,	
	2018	2017
Collaboration revenue - related party		
Commercialization activities	$981	$ 79
Reduction of research and development expenses		
Research and development activities	—	14

For the three months ended March 31, 2018 and 2017, we recognized the following totals of collaboration revenue and reduction of research and development expenses (in thousands):

	Three Months Ended March 31,	
	2018	2017
Collaboration revenue - related party	$7,345	$10,508
Reduction of research and development expenses	—	2,776

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The following table presents changes in our contract assets and liabilities during the three months ended March 31, 2018 (in thousands):

	December 31, 2017	Additions	Deductions	March 31, 2018
Contract assets (1)				
Collaboration receivable – related party	$ 2,448	$ 3,512	$ (2,448)	$ 3,512
Royalty receivable – related party	1,222	1,417	(1,222)	1,417
Contract liabilities (2)				
Deferred revenue – related party, current and net of current portions	163,640	4,204	(46,801)	121,043

(1) Additions to contract assets relate to amounts billed to Celgene for reimbursable costs incurred by us during the reporting period. Deductions to contract assets relate to collection of receivables during the reporting period.

(2) Additions to contract liabilities relate to consideration from Celgene during the reporting period. Deductions to contract liabilities relate to deferred revenue recognized as revenue during the reporting period and cumulative catch-up adjustment recognized upon adoption of ASC 606 on January 1, 2018.

During the three months ended March 31, 2018, we recognized the following as revenue due to changes in the contract asset and the contract liability balances (in thousands):

Amounts included in the contract liability at the beginning of the period	$5,984
Performance obligations satisfied in previous periods	323

As of March 31, 2018, the aggregate amount of the transaction price allocated to performance obligations that are partially unsatisfied was $132.6 million.

We consider the total consideration expected to be earned in the next twelve months for services to be performed as current deferred revenue, and consideration that is expected to be earned subsequent to twelve months from the balance sheet date as noncurrent deferred revenue.

Accounting analysis and revenue recognition – milestone revenue

At each reporting period we evaluate whether milestones are considered probable of being reached and, to the extent that a significant reversal would not occur in future periods, estimate the amount to be included in the transaction price using the most likely amount method. Milestone payments that are not within our control, such as regulatory approvals, are not considered probable of being achieved and are excluded from the transaction price until those approvals are received.

No milestones were earned during the three months ended March 31, 2018 and 2017. The next potential milestone expected to be achieved under our collaboration agreements with Celgene is the filing of a first new drug application equivalent in an ex-U.S. country. Achievement of this event will result in milestone payments of $15.0 million under the 2010 Agreement.

Aurigene Discovery Technologies Limited

In April 2017, we entered into a new global license agreement with Aurigene Discovery Technologies Limited, or Aurigene, to research, develop and commercialize small molecule inhibitors for dihydroorotate dehydrogenase, or DHODH, or the Aurigene Agreement.

Under the terms of the Aurigene Agreement, Aurigene will provide to us exclusive rights to its portfolio of novel small molecules for DHODH. Financial terms of the Aurigene Agreement include a $3.0 million upfront payment and potential future milestone payments of up to $17.0 million if we achieve certain development and regulatory milestones. The next potential milestone expected to be achieved under our collaboration agreements with Aurigene is the initiation of the first phase 1 clinical trial for AG-636, our DHODH inhibitor. Achievement of this event will result in milestone payments owed to Aurigene of $2.0 million.

Aurigene is also eligible to receive low single-digit royalties on net product sales, if any. We will conduct preclinical studies and, if successful, fund further global research and development, as well as regulatory and commercial activities.

The term of the Aurigene Agreement will continue until the earlier of: (a) termination for convenience at our sole discretion upon 90 days prior written notice, (b) termination by either party for material breach, or (c) the expiration of the last-to-expire of all payment obligations hereunder with respect to all licensed products under the Aurigene

Agreement.

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Accounting analysis

The $3.0 million upfront payment was incurred in May 2017 and recorded as research and development expense. Costs incurred and milestone payments due to Aurigene prior to regulatory approval are recognized as expenses in the period incurred. Payments due to Aurigene upon or subsequent to regulatory approval will be capitalized and amortized over the shorter of the remaining license or product patent life.

6. Accrued Expenses

Accrued expenses consist of the following (in thousands):

	March 31, 2018	December 31, 2017
Accrued compensation	$4,966	$ 15,693
Accrued research and development costs	9,951	14,849
Accrued professional fees	1,853	3,140
Accrued other	235	349
Total accrued expenses	$17,005	$ 34,031

7. Share-Based Payments

2013 Stock Incentive Plan

In June 2013, our Board of Directors adopted and, in July 2013 our stockholders approved, the 2013 Stock Incentive Plan, or the 2013 Plan. The 2013 Plan became effective upon the closing of our initial public offering and provides for the grant of incentive stock options, non-qualified stock options, stock appreciation rights, restricted stock awards, restricted stock units, or RSUs, performance-based stock units, or PSUs, and other stock-based awards. Following the adoption of the 2013 Plan, we granted no further stock options or other awards under the 2007 Stock Incentive Plan, or the 2007 Plan. Any options or awards outstanding under the 2007 Plan at the time of adoption of the 2013 Plan remained outstanding and effective. As of March 31, 2018, the total number of shares reserved under the 2007 Plan and the 2013 Plan are 8,624,887, and we had 1,938,247 shares available for future issuance under the 2013 Plan.

Stock options

The following table presents stock option activity for the three months ended March 31, 2018:

	Number of Stock Options	Weighted-Average Exercise Price
Outstanding at December 31, 2017	5,577,562	$ 49.58
Granted	1,107,220	77.22
Exercised	(477,847)	22.81
Forfeited/Expired	(102,127)	88.78
Outstanding at March 31, 2018	6,104,808	$ 56.03
Exercisable at March 31, 2018	2,863,417	$ 48.14
Vested and expected to vest at March 31, 2018	6,104,808	$ 56.03

At March 31, 2018, the total unrecognized compensation expense related to unvested stock option awards was $130.0 million, which we expect to recognize over a weighted-average period of approximately 3.0 years.

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Restricted stock units

The following table presents RSU activity for the three months ended March 31, 2018:

	Number of Stock Units	Weighted-Average Grant Date Fair Value
Unvested shares at December 31, 2017	125,584	$ 47.46
Granted	338,093	77.54
Vested	(57,250)	41.76
Forfeited	(781)	77.70
Unvested shares at March 31, 2018	405,646	$ 73.28

As of March 31, 2018, there was approximately $26.7 million of total unrecognized compensation expense related to RSUs, which we expect to be recognized over a weighted-average period of approximately 2.6 years.

Performance-based stock units

The following table presents PSU activity for the three months ended March 31, 2018:

	Number of Stock Units	Weighted-Average Grant Date Fair Value
Unvested shares at December 31, 2017	176,186	$ 52.98
Granted	—	—
Vested	—	—
Forfeited	—	—
Unvested shares at March 31, 2018	176,186	$ 52.98

Stock-based compensation expense associated with these PSUs is recognized if the underlying performance condition is considered probable of achievement using our management's best estimates. Performance-based vesting criteria primarily relate to milestone events specific to our corporate goals, specifically regulatory milestones related to our product candidates.

As of March 31, 2018, there was approximately $9.3 million of total unrecognized compensation expense related to PSUs with performance-based vesting criteria that are not considered probable of achievement.

2013 Employee Stock Purchase Plan

In June 2013, our Board of Directors adopted, and in July 2013 our stockholders approved, the 2013 Employee Stock Purchase Plan, or the 2013 ESPP. We issued 27,377 shares and 33,521 shares during the three months ended March 31, 2018 and 2017, respectively, under the 2013 ESPP. The 2013 ESPP provides participating employees with the opportunity to purchase up to an aggregate of 327,272 shares of our common stock. As of March 31, 2018, we had 186,414 shares available for future issuance under the 2013 ESPP.

Stock-based compensation expense

Stock-based compensation expense by award type included within the condensed consolidated statements of operations is as follows (in thousands):

	Three Months Ended March 31,	
	2018	2017
Stock options	$12,472	$9,902
Restricted stock units	1,797	595
Employee Stock Purchase Plan	253	237
Total stock-based compensation expense	$14,522	$10,734

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Expenses related to equity-based awards were allocated as follows in the condensed consolidated statements of operations (in thousands):

	Three Months Ended March 31,	
	2018	2017
Research and development expense	$8,640	$7,025
General and administrative expense	5,882	3,709
Total stock-based compensation expense	$14,522	$10,734

8. Loss per Share

Basic net loss per share is calculated by dividing net loss by the weighted average shares outstanding during the period, without consideration for common stock equivalents. Diluted net loss per share is calculated by adjusting the weighted average shares outstanding for the dilutive effect of common stock equivalents outstanding for the period, determined using the treasury stock method. For purposes of the dilutive net loss per share calculation, stock options, RSUs and ESPP options are considered to be common stock equivalents, while PSUs with vesting conditions that were not met as of March 31, 2018 are not considered to be common stock equivalents.

Since we had a net loss for all periods presented, the effect of all potentially dilutive securities is anti-dilutive. Accordingly, basic and diluted net loss per share was the same for all periods presented.

The following common stock equivalents were excluded from the calculation of diluted net loss per share applicable to common stockholders for the periods indicated because including them would have had an anti-dilutive effect:

	Three Months Ended March 31,	
	2018	2017
Stock options	6,104,808	6,129,794
Restricted stock units	405,646	126,850
Employee Stock Purchase Plan options	5,289	5,533
Total common stock equivalents	6,515,743	6,262,177

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Item 2. Management's Discussion and Analysis of Financial Condition and Results of Operations

Forward-looking Information

The following discussion of our financial condition and results of operations should be read with our unaudited condensed consolidated financial statements as of March 31, 2018 and December 31, 2017 and for the three months ended March 31, 2018 and 2017, and related notes included in Part I. Item 1. of this Quarterly Report on Form 10-Q, 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 Securities and Exchange Commission, or SEC, on February 14, 2018. This Management's Discussion and Analysis of Financial Condition and Results of Operations contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements are based on current expectations, estimates, forecasts and projections, and the beliefs and assumptions of our management, and include, without limitation, statements with respect to our expectations regarding our research, development and commercialization plans and prospects, results of operations, general and administrative expenses, research and development expenses, and the sufficiency of our cash for future operations. Words such as "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "target," "potential," "will," "would," "could," "
similar statements or variation of these terms or the negative of those terms and similar expressions are intended to identify these forward-looking statements. Readers are cautioned that these forward-looking statements are predictions and are subject to risks, uncertainties and assumptions that are difficult to predict. Therefore, actual results may differ materially and adversely from those expressed in any forward-looking statements. Among the important factors that could cause actual results to differ materially from those indicated by our forward-looking statements are those discussed under the heading "Risk Factors" in Part II, Item 1A. and elsewhere in this report, and in our Annual Report on Form 10-K. We undertake no obligation to revise the forward-looking statements contained herein to reflect events or circumstances after the date hereof or to reflect the occurrence of unanticipated events, except as required by law.

Overview

We are a biopharmaceutical company committed to the fundamental transformation of patients' lives through scientific leadership in the field of cellular metabolism, with the goal of making transformative, first- or best-in-class medicines. Our therapeutic areas of focus are cancer and rare genetic diseases, or RGDs, which are diseases that are directly caused by changes in genes or chromosomes, often passed from one generation to the next. Most RGDs are often associated with severe or life-threatening features. The incidence of a single RGD can vary widely but is generally very infrequent, usually equal to or less than one per 100,000 births. In both areas of cancer and RGDs, we are seeking to unlock the biology of cellular metabolism as a platform to create transformative therapies.

Our first commercial cancer product is IDHIFA®. In August 2017, the U.S. Food and Drug Administration, or FDA, granted our collaboration partner Celgene Corporation, or Celgene, approval of IDHIFA® for the treatment of adult patients with relapsed or refractory acute myeloid leukemia, or R/R AML, and an isocitrate dehydrogenase 2, or IDH2, mutation as detected by an FDA-approved test. IDHIFA®, an oral targeted inhibitor of the mutated IDH2 enzyme, is the first and only FDA-approved therapy for patients with R/R AML and an IDH2 mutation. We are eligible to receive royalties at tiered low-double digit to mid-teen percentage rates on any net sales of IDHIFA® and have exercised our rights to provide up to one-third of the field-based commercialization efforts in the United States.

Our most advanced clinical cancer product candidates are TIBSOVO® (ivosidenib), which is wholly-owned by us and targets mutated isocitrate dehydrogenase 1, or IDH1, and AG-881, which is a brain-penetrant pan-IDH mutant inhibitor and is subject to our joint worldwide development and profit share collaboration and license agreement with Celgene. These mutations are found in a wide range of hematological malignancies and solid tumors. In December 2017, we submitted a new drug application, or NDA, to the FDA for TIBSOVO® (ivosidenib) for the treatment of patients with R/R AML and an IDH1 mutation, which was accepted with priority review and granted a Prescription Drug User Fee Act, or PDUFA, action date of August 21, 2018. We plan to submit a Marketing Authorization Application, or MAA, to the European Medicines Agency, or EMA, for TIBSOVO® (ivosidenib) for IDH1 mutant-positive R/R AML in the fourth quarter of 2018.

Our next most advanced cancer product candidate is AG-270, an inhibitor of methionine adenosyltransferase 2a, or MAT2A. We submitted an investigational new drug application, or IND, for AG-270 in November 2017, and in

December 2017 the FDA concluded that we may proceed with our planned phase 1 dose-escalation trial of AG-270 in multiple tumor types carrying a methylthioadenosine phosphorylase, or MTAP, deletion, which we initiated in March 2018.

Our most advanced preclinical cancer product candidate is an inhibitor of the metabolic enzyme dihydroorotate dehydrogenase, or DHODH. We plan to submit an IND for our DHODH inhibitor for the treatment of hematologic malignancies in the fourth quarter of 2018.

The lead product candidate in our RGD program, AG-348, targets pyruvate kinase-R for the treatment of pyruvate kinase, or PK, deficiency. PK deficiency is a rare genetic disorder that often results in severe hemolytic anemia, jaundice and lifelong

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conditions associated with chronic anemia and secondary complications due to inherited mutations in the pyruvate kinase enzyme within red blood cells, or RBCs. In April 2018, we initiated ACTIVATE-T, a single arm, global, pivotal trial of AG-348 in approximately 20 regularly transfused patients with PK deficiency. We expect to initiate ACTIVATE, a 1:1 randomized, placebo-controlled, global, pivotal trial of AG-348 in approximately 80 patients with PK deficiency who do not receive regular transfusions, in the second quarter of 2018. We also expect to initiate a phase 2 proof of concept trial of AG-348 in thalassemia in the fourth quarter of 2018.

In addition to the aforementioned development programs, we are seeking to advance a number of early-stage discovery programs in the areas of cancer metabolism, RGDs and metabolic immuno-oncology, or MIO, a developing field which aims to modulate the activity of relevant immune cells by targeting critical metabolic nodes, thereby, enhancing the immune mediated anti-tumor response.

2016 Agreement

In May 2016, we entered into a master research and collaboration agreement, or the 2016 Agreement, with Celgene, and Celgene RIVOT Ltd., a wholly owned subsidiary of Celgene. The 2016 Agreement focuses on the discovery and development of cancer programs in the field of MIO. In addition to new programs identified under the 2016 Agreement, both parties also agreed that all future development and commercialization of two remaining cancer metabolism programs discovered under the 2010 discovery and development collaboration and license agreement with Celgene, or the 2010 Agreement, including AG-270, will now be governed by the 2016 Agreement.

During the research term of the 2016 Agreement, we plan to conduct research programs focused on discovering compounds that are active against metabolic targets in the immuno-oncology, or IO, field. The initial four-year research term will expire on May 17, 2020, and may be extended for up to two, or in specified cases, up to four additional one-year terms.

For each program under the 2016 Agreement, we may nominate compounds that meet specified criteria as development candidates and, in limited circumstances, Celgene may also nominate compounds as development candidates for each such program. Celgene may designate the applicable program for further development following any such nomination, after which we may conduct, at our expense, additional preclinical and clinical development for such program through the completion of an initial phase 1 dose escalation study.

At the end of the research term, Celgene may designate for continued development up to three research programs for which development candidates have yet to be nominated, which are referred to as continuation programs. We may conduct further research and preclinical and clinical development activities on any continuation program, at our expense, through the completion of an initial phase 1 dose escalation study.

We granted Celgene the right to obtain exclusive options for development and commercialization rights for each program that Celgene has designated for further development, and for each continuation program. Celgene may exercise each such option beginning on the designation of a development candidate for such program (or on the designation of such program as a continuation program) and ending on the earlier of: (i) the end of a specified period after we have furnished Celgene with specified information about the initial phase 1 dose escalation study for such program, or (ii) January 1, 2030. Research programs that have applications in the inflammation or autoimmune, or I&I, field that may result from the 2016 Agreement will also be subject to the exclusive options described above. We will retain rights to any program that Celgene does not designate for further development or as to which it does not exercise its option.

Under the terms of the 2016 Agreement, following Celgene’s exercise of its option with respect to a program, the parties will enter into either a co-development and co-commercialization agreement if such program is in the IO field, or a license agreement if such program is in the I&I field. Under each co-development and co-commercialization agreement, the two parties will co-develop and co-commercialize licensed products worldwide. Either we or Celgene will lead development and commercialization of licensed products for the United States, and Celgene will lead development and commercialization of licensed products outside of the United States. Depending on the country, the parties will each have the right to provide a portion of field-based marketing activities. Under each license agreement, Celgene will have the sole right to develop and commercialize licensed products worldwide.

TIBSOVO® (ivosidenib) Letter Agreement

In May 2016, we entered into a letter agreement with Celgene regarding TIBSOVO® (ivosidenib), or the TIBSOVO® (ivosidenib) Letter Agreement. Under the TIBSOVO® (ivosidenib) Letter Agreement, the parties agreed to terminate the 2010 Agreement, effective as of August 15, 2016, as to the program directed to the IDH1 target, for which TIBSOVO® (ivosidenib) is the lead development candidate. Under the 2010 Agreement, Celgene had held development and commercialization rights to the IDH1 program outside of the United States, and we held such rights inside the United States. As a result of the termination, we obtained global rights to TIBSOVO® (ivosidenib) and the IDH1 program. Neither party will have any further financial

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obligation, including royalties or milestone payments, to the other concerning TIBSOVO® (ivosidenib) or the IDH1 program. Under the terms of the termination, the parties also agreed to conduct specified transitional activities in connection with the termination. In addition, pursuant to the TIBSOVO® (ivosidenib) Letter Agreement, the parties are released from their exclusivity obligations under the 2010 Agreement with respect to the IDH1 program. The termination does not affect the AG-881 Agreements described below, which are directed to both the IDH1 target and the IDH2 target.

AG-881 Agreements

In April 2015, we entered into a joint worldwide development and profit share collaboration and license agreement with Celgene, and our wholly owned subsidiary, Agios International Sarl, entered into a collaboration and license agreement with Celgene International II Sarl. Both of these agreements are collectively referred to as the AG-881 Agreements. The AG-881 Agreements establish a joint worldwide collaboration focused on the development and commercialization of AG-881 products. Under the terms of the AG-881 Agreements, we received an initial upfront payment of $10.0 million in May 2015 and are eligible to receive up to $70.0 million in milestone-based payments. The parties will split all worldwide development costs equally, subject to specified exceptions, as well as any profits from any net sales of, or commercialization losses related to, licensed AG-881 products. Either party may, at its own expense and with the other party's permission, undertake additional development activities outside of the scope of the development plan agreed upon with the other party.

2010 Agreement

In April 2010, we entered into the 2010 Agreement, which was amended in October 2011 and July 2014. The goal of the collaboration was to discover, develop and commercialize disease-altering therapies in oncology based on our cancer metabolism research platform. We initially led discovery, preclinical and early clinical development for all cancer metabolism programs under the collaboration. The discovery phase of the 2010 Agreement expired in April 2016.

Upon agreement to terminate the 2010 Agreement, effective as of August 15, 2016, as to the program directed to the IDH1 target, for which TIBSOVO® (ivosidenib) is the lead development candidate, the sole program remaining under the 2010 Agreement is IDHIFA®, a co-commercialized licensed program for which Celgene leads and funds global development and commercialization activities. We have exercised our right to participate in a portion of commercialization activities in the United States for IDHIFA® in accordance with the applicable commercialization plan. We are eligible to receive up to $95.0 million in potential milestone payments for the IDHIFA® program. The potential milestone payments are comprised of: (i) up to $70.0 million in milestone payments upon achievement of specified ex-U.S. regulatory milestone events, and (ii) a $25.0 million milestone payment upon achievement of a specified ex-U.S. commercial milestone event. Additionally, we are eligible to royalties tiered, low-double digits to mid-teen percentage rates on any net sales of IDHIFA®.

Critical Accounting Policies and Estimates

Our critical accounting policies are those policies which require the most significant judgments and estimates in the preparation of our consolidated financial statements. We have determined that our most critical accounting policies are those relating to revenue recognition, accrued research and development expenses, and stock-based compensation. There have been no significant changes to our critical accounting policies discussed in the Annual Report on Form 10-K for the year ended December 31, 2017.

Financial Operations Overview

General

Since inception, our operations have focused on organizing and staffing our company, business planning, raising capital, assembling our core capabilities in cellular metabolism, identifying potential product candidates, undertaking preclinical studies and conducting clinical trials. To date, we have financed our operations primarily through funding received from the 2010 Agreement, the AG-881 Agreements, the 2016 Agreement, private placements of our preferred stock, our initial public offering of our common stock and concurrent private placement of common stock to an affiliate of Celgene, and our follow-on public offerings.

Additionally, since inception, we have incurred significant operating losses. Our net losses were $90.8 million and $66.2 million for the three months ended March 31, 2018 and 2017, respectively. As of March 31, 2018, we had an

accumulated deficit of $849.4 million. We expect to continue to incur significant expenses and operating losses over the next several years. Our net losses may fluctuate significantly from year to year. We anticipate that our expenses will increase significantly as we continue to advance and expand clinical development activities for our lead programs: IDHIFA®, TIBSOVO® (ivosidenib), AG-881, AG-348, and AG-270; continue to discover and validate novel targets and drug product candidates; expand and protect our intellectual property portfolio; and hire additional commercial, development and scientific personnel.

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Revenue

Through March 31, 2018, we have not generated any revenue from product sales. All of our revenue to date has been derived from our collaborations or royalty revenue on sales of IDHIFA®. In the future, we expect to generate revenue from a combination of product sales, royalties on product sales, cost reimbursements, milestone payments, and upfront payments to the extent we enter into future collaborations or licensing agreements.

Research and development expenses

Research and development activities are central to our business model. Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. We expect research and development costs to increase significantly for the foreseeable future as our product candidate development programs progress. However, the successful development of our product candidates is highly uncertain. As such, at this time, we cannot reasonably estimate or know the nature, timing and estimated costs of the efforts that will be necessary to complete the remainder of the development and commercialize these product candidates. We are also unable to predict when, if ever, material net cash inflows will commence from IDHIFA®, ivosidenib, AG-881, AG-348, AG-270, or any of our other product candidates. This is due to the numerous risks and uncertainties associated with developing medicines, including the uncertainty of:

- establishing an appropriate safety profile with IND, and/or NDA enabling toxicology and clinical studies;
- the successful enrollment in, and completion of, clinical trials;
- the receipt of marketing approvals from applicable regulatory authorities;
- establishing compliant commercial manufacturing capabilities or making arrangements with third-party manufacturers;
- obtaining and maintaining patent and trade secret protection, and regulatory exclusivity for our product candidates;
- launching commercial sales of the products, if and when approved, whether alone or in collaboration with others; and
- maintaining an acceptable safety profile of the products following approval.

A change in the outcome of any of these variables with respect to the development of any of our product candidates would significantly change the costs and timing associated with the development of that product candidate.

Research and development expenses consist primarily of costs incurred for our research activities, including our drug discovery efforts, and the development of our product candidates, which include:

- employee-related expenses, including salaries, benefits and stock-based compensation expense;
- expenses incurred under agreements with third parties, including contract research organizations, or CROs, that conduct research and development and both preclinical and clinical activities on our behalf, and the cost of consultants;
- the cost of lab supplies and acquiring, developing and manufacturing preclinical and clinical study materials; and
- facilities, depreciation, and other expenses, which include direct and allocated expenses for rent and the maintenance of facilities, insurance and other operating costs.

The following summarizes our most advanced programs:

IDHIFA®

IDHIFA® is an orally available, selective, potent inhibitor of the mutated IDH2 protein, making it a highly targeted therapeutic candidate for the treatment of patients with cancers that harbor IDH2 mutations, including those with AML, who have a historically poor prognosis. In August 2017, the FDA granted Celgene approval of IDHIFA® for the treatment of adult patients with R/R AML and an IDH2 mutation as detected by an FDA-approved test.

Celgene maintains worldwide development and commercial rights to IDHIFA® and will fund the future development and commercialization costs related to this program. Under the 2010 Agreement, Celgene is responsible for all development costs for IDHIFA®, and we are eligible to receive up to $95.0 million in milestone payments, which are comprised of: (i) up to $70.0 million in milestone payments upon achievement of specified ex-U.S. regulatory milestone events and (ii) a $25.0 million milestone payment upon achievement of a specified ex-U.S. commercial milestone event. Additionally, we are eligible to receive tiered royalties on any net sales of IDHIFA®.

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We continue to evaluate IDHIFA® in the following clinical trials, which are led and funded by Celgene:

Phase 1/2 clinical trial

The FDA's approval of IDHIFA® in R/R AML was based on clinical data from an open-label, single-arm, multicenter, two-cohort phase 1/2 clinical trial of adult patients with R/R AML and an IDH2 mutation.

In June 2017, we and Celgene presented clinical data from the phase 1 dose-escalation and expansion portions of this trial in R/R AML at the American Society of Clinical Oncology, or ASCO 2017, in Chicago, Illinois. Also in June 2017, we and Celgene presented updated clinical data from this trial, including data from the phase 2 portion of the trial, at the 22nd Congress of the European Hematology Association, or EHA 2017, in Madrid, Spain.

Phase 1b frontline combination trial (TIBSOVO® (ivosidenib) also being evaluated)

IDHIFA® is being evaluated in a phase 1b, multicenter, international, open-label clinical trial, conducted by us, to evaluate the safety and clinical activity of IDHIFA® or TIBSOVO® (ivosidenib) in combination with induction and consolidation therapy in patients with newly diagnosed AML with an IDH2 or IDH1 mutation who are eligible for intensive chemotherapy using a primary endpoint of safety and tolerability of IDHIFA® or TIBSOVO® (ivosidenib) when administered with induction and consolidation therapy. The trial is currently enrolling patients.

In December 2017, we presented interim data from this trial at American Society of Hematology meeting in Atlanta, Georgia, or ASH 2017.

Phase 1/2 frontline combination trial (TIBSOVO® (ivosidenib) also being evaluated)

IDHIFA® is being evaluated in a phase 1/2 frontline combination clinical trial, conducted by Celgene, of either IDHIFA® or TIBSOVO® (ivosidenib) in combination with VIDAZA® (azacitidine) in newly diagnosed AML patients not eligible for intensive chemotherapy, with a phase 1 component to determine the safety of the combinations, followed by a phase 2 randomized component evaluating the safety and clinical activity of each investigational combination versus single-agent VIDAZA® using a primary endpoint of overall response rate. The trial has completed the phase 1 component and is currently enrolling in the phase 2 component.

In December 2017, we presented interim data from this trial at ASH 2017.

IDHENTIFY

IDHIFA® is being evaluated in IDHENTIFY, an international phase 3, multi-center, open-label, randomized clinical trial, conducted by Celgene, designed to compare the efficacy and safety of IDHIFA® versus conventional care regimens in patients 60 years or older with IDH2 mutant-positive AML that is refractory to or relapsed after second- or third-line therapy. In January 2016, in conjunction with the initiation of the IDHENTIFY clinical trial, we received a milestone payment of $25.0 million from Celgene pursuant to the 2010 Agreement. This trial is currently enrolling patients and we have not yet presented any clinical data from this trial.

Phase 3 frontline combination trial

We plan to support, with Celgene, the initiation of an intergroup sponsored, global, registration-enabling phase 3 trial combining TIBSOVO® (ivosidenib) or IDHIFA® and standard induction (7+3) and consolidation chemotherapy with a primary endpoint of event-free survival in frontline AML patients with an IDH1 or IDH2 mutation in the fourth quarter of 2018.The trial is expected to enroll approximately 500 patients with an IDH1 mutation and approximately 500 patients with an IDH2 mutation.

TIBSOVO® (ivosidenib)

TIBSOVO® (ivosidenib) is an orally available, selective, potent inhibitor of the mutated IDH1 protein, making it a highly targeted therapeutic candidate for the treatment of patients with cancers that harbor IDH1 mutations. We hold worldwide development and commercial rights to TIBSOVO® (ivosidenib) and will fund the future development and commercialization costs related to this program. Mutations in IDH1 have been identified in difficult to treat hematologic and solid tumor cancers, including AML, chondrosarcoma, cholangiocarcinoma, and glioma, where both the treatment options and prognosis for patients are poor. The FDA granted fast track designation for TIBSOVO® (ivosidenib) for treatment of patients with AML that harbor an IDH1 mutation, and granted orphan drug designation for TIBSOVO® (ivosidenib) for treatment of patients with AML. Additionally, the FDA granted fast track designation for TIBSOVO® (ivosidenib) for treatment of patients with previously treated, unresectable or metastatic cholangiocarcinoma with an IDH1 mutation, and granted orphan drug designation for TIBSOVO® (ivosidenib) for the treatment of cholangiocarcinoma.

In December 2017, we submitted an NDA to the FDA for TIBSOVO® (ivosidenib) for the treatment of patients with R/R AML and an IDH1 mutation, which was accepted with priority review and granted a PDUFA action date of August 21, 2018. We plan to submit an MAA to the EMA for TIBSOVO® (ivosidenib) for IDH1 mutant-positive R/R AML in the fourth quarter of 2018.

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We are evaluating TIBSOVO® (ivosidenib) in the following clinical trials:

Phase 1 clinical trial (advanced hematologic malignancies)

TIBSOVO® (ivosidenib) is being evaluated in a phase 1 multicenter, open-label, dose-escalation and expansion clinical trial, designed to assess its safety, clinical activity and tolerability as a single agent in patients with advanced hematologic malignancies with an IDH1 mutation. Four expansion cohorts have been added to the trial.

In December 2017, we presented interim clinical data from 258 patients treated with ivosidenib in the dose escalation and expansion arms of the trial at ASH 2017.

Phase 1b frontline combination trial

As discussed above, TIBSOVO® (ivosidenib) and IDHIFA® are also being evaluated in a phase 1b, multicenter, international, open-label clinical trial, in combination with induction and consolidation therapy. The trial is currently enrolling patients.

In December 2017, we presented interim data from this trial at ASH 2017.

Phase 1/2 frontline combination trial

As discussed above, TIBSOVO® (ivosidenib) and IDHIFA® are also being evaluated in a phase 1/2 frontline clinical trial in combination with VIDAZA®, conducted by Celgene. The trial has completed the phase 1 component and is currently enrolling in the phase 2 component.

In December 2017, we presented interim data from this trial at ASH 2017.

AGILE

TIBSOVO® (ivosidenib) is being evaluated in AGILE, a global, registration-enabling phase 3 clinical trial, combining TIBSOVO® (ivosidenib) and VIDAZA® in newly diagnosed AML patients with an IDH1 mutation who are ineligible for intensive chemotherapy. The trial is enrolling patients and we expect to complete enrollment in 2021.

Phase 3 frontline combination trial

As discussed above, we plan to support, with Celgene, the initiation of an intergroup sponsored, global, registration-enabling phase 3 trial combining TIBSOVO® (ivosidenib) or IDHIFA® and standard induction (7+3) and consolidation chemotherapy with a primary endpoint of event-free survival in frontline AML patients with an IDH1 or IDH2 mutation in the fourth quarter of 2018.

Phase 1 clinical trial (advanced solid tumors)

TIBSOVO® (ivosidenib) is being evaluated in a phase 1 multicenter, open-label, dose-escalation and expansion clinical trial, designed to assess its safety, clinical activity and tolerability as a single agent in patients with advanced solid tumors with an IDH1 mutation, including glioma, cholangiocarcinoma, and chondrosarcoma. Enrollment is now complete for four expansion cohorts of 25 patients each in (i) low grade glioma with at least six months of prior scans to assess volumetric changes, (ii) second-line cholangiocarcinoma, (iii) high grade, or metastatic, chondrosarcoma, and (iv) other solid tumors with an IDH1 mutation, who will receive the recommended dose of 500 mg of TIBSOVO® (ivosidenib) once daily.

In June 2017, we reported updated interim data from the dose escalation and dose expansion cohorts of our ongoing phase 1 clinical trial evaluating TIBSOVO® (ivosidenib) in patients with IDH1 mutant-positive cholangiocarcinoma at the ASCO 2017. In November 2017, we reported updated interim data from the dose expansion cohort of our ongoing phase 1 clinical trial evaluating TIBSOVO® (ivosidenib) in patients with progressive low-grade IDH1 mutant-positive glioma at the Society for Neuro-Oncology Annual Meeting in San Francisco, California.

ClarIDHy

TIBSOVO® (ivosidenib) is being evaluated in ClarIDHy, a registration-enabling phase 3, multicenter, randomized, double-blind, placebo-controlled clinical trial of TIBSOVO® (ivosidenib) in previously-treated patients with nonresectable or metastatic cholangiocarcinoma with an IDH1 mutation. The trial was initiated in December 2016 and is currently enrolling patients, and we expect to complete enrollment in the first half of 2019.

AG-881: brain penetrant pan-IDH program

AG-881 is an orally available, selective, brain-penetrant, pan-IDH mutant inhibitor, which provides added flexibility to our current portfolio of IDH mutant inhibitors. We are currently focusing our development efforts for AG-881 in glioma.

We and Celgene are jointly collaborating on a worldwide development program for AG-881, wherein we share worldwide development costs, subject to specified exceptions, and profits and Celgene would book any worldwide commercial sales. Either party may, at its own expense and with the other party's permission, undertake additional development activities outside

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of the scope of the development plan agreed upon with the other party. We will lead commercialization in the United States with both companies sharing equally in field-based commercial activities, and Celgene will lead commercialization outside of the United States with us providing one third of field-based commercial activities in the major European Union markets. Under the AG-881 Agreements, we are eligible to receive up to $70.0 million in potential milestone payments related to AG-881. We may also receive royalties at tiered, low-double digit to mid-teen percentage rates on net sales if we elect not to participate in the development and commercialization of AG-881.

We are conducting two phase 1 multi-center, open-label clinical trials of AG-881, one in patients with advanced IDH1 or IDH2 mutant-positive solid tumors, including glioma, and the other in patients with advanced IDH1 or IDH2 mutant-positive hematologic malignancies whose cancer has progressed on a prior IDH inhibitor therapy. The goal of these trials is to evaluate the safety, pharmacokinetics, pharmacodynamics and clinical activity of AG-881 in advanced solid tumors and hematologic malignancies, respectively.

The phase 1 trial in patients with advanced IDH1 or IDH2 mutant-positive hematologic malignancies has completed its dose escalation portion, establishing proof of mechanism as measured by reductions in 2-hydroxygluturate levels, and is now closed for enrollment. No maximum tolerable dose, or MTD, was reached. In the phase 1 trial in IDH1 or IDH2 mutant-positive advanced solid tumors, an MTD was established and enrollment is complete.

We have not yet presented any clinical data from these trials. In October 2017, we presented the first preclinical data of AG-881 in IDH mutant-positive solid and hematologic malignancies at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics in Philadelphia, Pennsylvania.

In the first quarter of 2018, we initiated a perioperative study with TIBSOVO® (ivosidenib) and AG-881 in low grade glioma to further investigate their effects on brain tumor tissue. Pursuant to the AG-881 Agreements, Celgene has elected not to participate in this clinical trial and, as a result, we will fund the trial ourselves. Celgene will continue to co-fund the ongoing phase 1 trials of AG-881 described above.

AG-348: PK deficiency program

AG-348 is an orally available small molecule and a potent activator of the wild-type (normal) and mutated PKR enzyme, which has resulted in restoration of adenosine triphosphate, or ATP, levels and a decrease in 2,3-diphosphoglycerate, or 2,3-DPG, levels in blood sampled from patients with PK deficiency and treated ex-vivo with AG-348. The wild-type PKR activity of AG-348 allowed the study of enzyme activation in healthy volunteers, providing an opportunity to understand the safety, dosing and pharmacodynamic activity of AG-348 prior to entering a proof-of-concept study in patients. We have worldwide development and commercial rights to AG-348 and expect to fund the future development and commercialization costs related to this program. The FDA granted orphan drug designation for AG-348 for treatment of patients with PK deficiency and granted us fast track designation to AG-348 for the treatment of patients with PK deficiency. In December 2016, we announced our decision to advance AG-348 into pivotal development as the first potential disease-modifying treatment for PK deficiency.

We have worldwide development and commercial rights to AG-348 and expect to fund the future development and commercialization costs related to this program.

DRIVE PK

In June 2015, we initiated DRIVE PK, a global phase 2, first-in-patient, open-label safety and efficacy clinical trial of AG-348 in adult, transfusion-independent patients with PK deficiency. In June 2016, we reported the first clinical data from DRIVE PK at EHA 2017, establishing proof of concept for AG-348. The trial reached target enrollment of 52 patients in November 2016, and in December 2017, we reported updated data from the trial at ASH 2017.

ACTIVATE-T/ACTIVATE

In April 2018, we initiated ACTIVATE-T, a single arm, global, pivotal trial of AG-348 in approximately 20 regularly transfused patients with PK deficiency. We expect to initiate ACTIVATE, a 1:1 randomized, placebo-controlled, global, pivotal trial of AG-348 in approximately 80 patients with PK deficiency who do not receive regular transfusions, in the second quarter of 2018. The primary endpoint of the ACTIVATE-T trial is a reduction in transfusion burden over a six-month period compared to the patient’s transfusion history, and the primary endpoint of the ACTIVATE trial is the proportion of patients who achieve at least a 1.5 g/dL increase in hemoglobin sustained over multiple visits.

In addition to the above planned and ongoing clinical trials of AG-348, we plan to initiate a phase 2 proof of concept trial of AG-348 in thalassemia in the fourth quarter of 2018.

AG-270: Targeting MAT2A for the treatment of MTAP-deleted cancers

AG-270, a MAT2A inhibitor, is our development candidate focused on MTAP-deleted cancer. MTAP is a metabolic gene that is deleted in approximately 15 percent of all cancers. We have shown in preclinical studies that MTAP deletion predicts sensitivity to inhibition of a subset of enzymes involved in the synthesis or utilization of the methyl donor S-adenosylmethionine, or

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SAM. Among this subset of enzymes, we have targeted MAT2A, the enzyme responsible for the synthesis of SAM in tumor cells.

We submitted an IND for AG-270 in November 2017 and, in December 2017, the FDA concluded that we may proceed with a proposed phase 1 dose-escalation trial in multiple tumor types carrying an MTAP deletion, which we initiated in March 2018. The purpose of this phase 1 multi-center, open-label study is to evaluate the safety, pharmacokinetics, pharmacodynamics and clinical activity of AG-270 in approximately 50 patients with advanced solid tumors or lymphoma with MTAP deletion. AG-270 will be administered as a single agent dosed orally once daily in 28-day cycles. The first part of the study is a dose-escalation phase in which cohorts of patients will receive ascending doses of AG-270 to determine the MTD or optimal dose. The second part of the study is a dose expansion phase where additional patients will receive AG-270 at the MTD or optimal dose to further evaluate its safety, tolerability and clinical activity as a potential dose for future studies. Patients must have evidence of loss of the MTAP protein from their tumor tissue, or evidence of loss of the CDKN2A tumor suppressor gene (commonly co-deleted with the MTAP gene), in order to be eligible for the study.

AG-636: Targeting DHODH for the treatment of hematologic malignancies

In January 2018, we announced that we plan to submit an IND in the fourth quarter of 2018 for AG-636, an inhibitor of DHODH, licensed by us from Aurigene Discovery Technologies Limited, for the treatment of hematologic malignancies. We have discovered a lineage-specific dependence on DHODH in hematologic malignancies, particularly AML and diffuse large B-cell lymphoma. DHODH catalyzes a critical step in the biosynthesis of pyridimidines, which are critical for the production of RNA and DNA. We believe that DHODH inhibition will be differentiated from standard-of-care therapies, both by exhibiting activity in cancers that are resistant to standard-of-care chemotherapeutics and through a mechanism of anti-tumor effect that combines cell growth arrest and cellular differentiation.

Other research and platform programs

Other research and platform programs include activities related to exploratory efforts, target validation and lead optimization for our discovery and follow-on programs, and our proprietary metabolomics platform.

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, business development, commercial, legal and human resources functions. Other significant costs include facility related costs not otherwise included in research and development expenses, legal fees relating to patent and corporate matters, and fees for accounting and consulting services.

We anticipate that our general and administrative expenses will increase in the future to support continued research and development activities and potential commercialization of our product candidates. These increases will likely include increased costs related to the hiring of additional personnel and fees to outside consultants, lawyers and accountants, among other expenses.

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 ($ in thousands):

	Three Months Ended March 31,			
	2018	2017	$ Change	% Change
Collaboration revenue – related party	$7,345	$10,508	$(3,163)	(30)%
Royalty revenue – related party	1,417	—	1,417	N/A
Total revenue	8,762	10,508	(1,746)	(17)%
Operating expenses:				
Research and development (net of $2,776 of cost reimbursement from related party for the three months ended March 31, 2017)	78,224	62,732	15,492	25 %
General and administrative	24,550	14,823	9,727	66 %
Loss from operations	(94,012)	(67,047)	(26,965)	40 %

Interest income	3,187	881	2,306	262	%
Net loss	$(90,825)	$(66,166)	$(24,659)	37	%

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Revenue. For the three months ended March 31, 2018, we recognized $7.3 million in collaboration revenue. The revenue recognized during the three months ended March 31, 2018 were under Accounting Standards Codification, or ASC, 606, Revenue from Contracts with Customers, or ASC 606, which we adopted as of January 1, 2018. The adoption of ASC 606 resulted in $2.6 million decrease in revenue recognized during the three months ended March 31, 2018. For further discussion regarding adoption of ASC 606, refer to Note 2, Summary of Significant Accounting Policies, and Note 5, Collaboration Agreements, in the Notes to Condensed Consolidated Financial Statements included in Part I, Item 1 of this Quarterly Report on Form 10-Q. In addition to collaboration revenue, we also recognized $1.4 million in royalty revenue on Celgene net sales of IDHIFA® under the 2010 Agreement.

For the three months ended March 31, 2017, we recognized $10.5 million in revenue, which includes partial recognition of the development candidate designation payment for AG-270, our program focused on MTAP-deleted cancers, of $1.5 million.

Research and Development Expense. The increase in research and development expenses was primarily attributable to net increases of $1.4 million in external services and $14.1 million in internal expenses; both of these increases are inclusive of cost reimbursements recorded as a reduction of research and development expenses.

We use our employee and infrastructure resources across multiple research and development programs, and we allocate internal employee-related and infrastructure costs, including stock-based compensation and facilities costs, as well as certain third-party costs, net of reimbursements from Celgene, to our research and development programs based on the personnel resources allocated to such program.

Our allocated research and development expenses, by major program, are outlined in the table below ($ in thousands):

	Three Months Ended March 31,			
	2018	2017	$ Change	% Change
IDH2 inhibitor (IDHIFA®)	$2,539	$1,580	$959	61 %
IDHIFA® reduction of R&D expenses	—	(14)	14	(100)%
IDH1 inhibitor (TIBSOVO® (ivosidenib))	30,507	30,778	(271)	(1)%
Pan-IDH inhibitor (AG-881)	3,681	5,586	(1,905)	(34)%
AG-881 reduction of R&D expenses	—	(2,762)	2,762	(100)%
PKR activator (AG-348)	13,115	7,469	5,646	76 %
MTAP-deleted cancers program (AG-270)	6,028	4,549	1,479	33 %
Other research and platform programs	22,354	15,546	6,808	44 %
Total research and development expenses, net	$78,224	$62,732	$15,492	25 %

The changes in research and development expense depicted in the table above were primarily attributable to the following:

- IDHIFA® costs increased as a result of increased internal and external expenses related to our ongoing phase 1b frontline combination trial development work.
- TIBSOVO® (ivosidenib) costs decreased compared to prior period as prior period costs included manufacturing expenses associated with our initial commercial inventory of TIBSOVO® (ivosidenib) as part of our NDA submission in December 2017.
- AG-881 costs decreased as our phase 1 trial in patients with advanced IDH1 or IDH2 mutant-positive hematologic malignancies and our phase 1 trial in IDH1 or IDH2 mutant-positive advanced solid tumors, including glioma, both completed their dose escalation portions. However, we continue to incur costs related to patients still on both studies and planning for future development.

Cost reimbursements for AG-881 were recognized as revenue in the current period.

- AG-348 costs increased as a result of the start-up costs for the ACTIVATE-T trial and the planned initiation of ACTIVATE in the second quarter of 2018.
- AG-270 costs increased as we initiated a phase 1 trial in March 2018.
- The increase in the costs of other research and platform programs include activities related to exploratory efforts, target validation and lead optimization for our discovery and follow-on programs, and our proprietary metabolomics

platform.

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General and Administrative Expense. The increase in general and administrative expenses was primarily attributable to an increase of $7.3 million related to supporting our growing commercial organization for the potential launch of TIBSOVO® (ivosidenib) in 2018.

Liquidity and Capital Resources

Sources of liquidity

Since our inception, and through March 31, 2018, we have funded our operations through upfront, milestone, extension, cost reimbursement and royalty payments related to our collaboration agreements, proceeds received from our issuance of preferred stock, our initial public offering and concurrent private placement of common stock to an affiliate of Celgene, and our follow-on public offerings.

In January 2018, we completed a public offering of 7,089,553 shares of common stock at an offering price of $67.00 per share. We received net proceeds from this offering of $448.9 million, after deducting underwriting discounts and commissions paid by us. In addition, we granted the underwriters the right to purchase up to an additional 1,063,433 shares of common stock, which was exercised in January 2018, resulting in additional net proceeds to us of $67.3 million, after underwriting discounts and commissions. After giving effect to the full exercise of the over-allotment option, the number of shares sold by us in the public offering totaled 8,152,986 shares, and net proceeds to us totaled $516.2 million, after underwriting discounts and commissions.

In addition to our existing cash, cash equivalents and marketable securities, we are eligible to earn a significant amount of milestone payments, designation fees, license option fees and extension fees, and we are entitled to cost reimbursements and royalty payments under our collaboration agreements with Celgene. Our ability to earn the milestone payments, cost reimbursements and royalty payments, and the timing of earning these amounts are dependent upon the timing and outcome of our development, regulatory and commercial activities, and is uncertain at this time. Our right to payments under our collaboration agreements with Celgene is our only committed potential external source of funds.

Cash flows

The following table provides information regarding our cash flows for the three months ended March 31, 2018 and 2017 (in thousands):

	Three Months Ended March 31,	
	2018	2017
Net cash used in operating activities	$(99,000)	$(74,074)
Net cash (used in) provided by investing activities	(167,532)	109,552
Net cash provided by financing activities	528,277	4,046
Net change in cash and cash equivalents	$261,745	$39,524

Net cash used in operating activities. During the three months ended March 31, 2018, we received $4.4 million in cost reimbursements related to our collaboration agreements with Celgene. These amounts were offset by increased operating expenses that relate to increases in clinical study costs due to advancements in our most advanced product candidates, expanded facilities and increased staffing needs due to our expanding operations.

During the three months ended March 31, 2017, we received $5.0 million in cost reimbursements related to our collaboration agreements with Celgene. These amounts were offset by increased operating expenses which relate to increases in clinical study costs due to advancements in our most advanced product candidates, expanded facilities and increased staffing needs due to our expanding operations.

Net cash (used in) provided by investing activities. The cash used in investing activities for the three months ended March 31, 2018 and 2017 was primarily the result of higher purchases of marketable securities than proceeds from maturities and sales of marketable securities, and $1.4 million and $0.3 million in purchases of property and equipment, respectively.

Net cash provided by financing activities. The cash provided by financing activities for the three months ended March 31, 2018 was primarily the result of the $516.2 million net proceeds received from our January 2018 follow-on public offering, after underwriting discounts and commissions, as well as proceeds received from stock option exercises and purchases made pursuant to our employee stock purchase plan. The cash provided by financing activities for the three

months ended March 31, 2017 was the result of proceeds received from stock option exercises and purchases made pursuant to our employee stock purchase plan.

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Funding requirements

We expect our expenses to increase in connection with our ongoing activities, particularly as we continue the research, development and clinical trials of, and seek additional marketing approvals for, our product candidates. If we obtain additional marketing approval for any of our other product candidates, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution to the extent that such sales, marketing, manufacturing and distribution are not the responsibility of Celgene or other collaborators. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations.

We expect that our existing cash, cash equivalents and marketable securities as of March 31, 2018, together with anticipated product and royalty revenue, anticipated interest income and anticipated expense reimbursements under our collaboration agreements, but excluding any additional program-specific milestone payments, will enable us to fund our operating expenses and capital expenditure requirements through at least the end of 2020. Our future capital requirements will depend on many factors, including:

- the scope, progress, results and costs of drug discovery, preclinical development, laboratory testing and clinical trials for our product candidates;
- the success of our collaborations;
- the extent to which we acquire or in-license other medicines and technologies;
- the costs, timing and outcome of regulatory review of our product candidates;
- the costs associated with preparation for the potential commercial launch of one or more of our product candidates;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims; and
- our ability to establish and maintain additional collaborations on favorable terms, if at all.

Until such time, if ever, as we can generate substantial product revenue, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances and licensing arrangements. We do not have any committed external source of funds other than our collaborations. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interest of our stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our common stockholders. Debt 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 funds through additional collaborations, strategic alliances 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. If we are unable to raise additional funds through equity or debt financings when needed or on attractive terms, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts, or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Off-balance Sheet Arrangements

We did not have, during the periods presented, and we do not currently have, any off-balance sheet arrangements, as defined under applicable SEC rules.

Contractual obligations

We have entered into agreements in the normal course of business with CROs for clinical trials and clinical supply manufacturing 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 prior written notice to the vendor.

During the three months ended March 31, 2018, there were no material changes to our contractual obligations and commitments described under Management’s Discussion and Analysis of Financial Condition and Results of Operations in the Annual Report on Form 10-K for the year ended December 31, 2017.

Item 3. Quantitative and Qualitative Disclosures about Market Risk

We are exposed to market risk related to changes in interest rates. As of March 31, 2018 and December 31, 2017, we had cash, cash equivalents and marketable securities of $994.7 million and $567.8 million, respectively, consisting

primarily of

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investments in certificates of deposit, U.S. Treasuries, government securities and corporate debt securities. 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 short-term marketable securities. Our marketable securities are subject to interest rate risk and could fall in value if market interest rates increase. Due to the short-term duration of our investment portfolio and the low risk profile of our investments, we do not believe an immediate and uniform 100 basis point increase in interest rates would have a material effect on the fair market value of our investment portfolio.

We are also exposed to market risk related to changes in foreign currency exchange rates. We have contracts with CROs located in Asia and Europe that are denominated in foreign currencies. We are subject to fluctuations in foreign currency rates in connection with these agreements. We do not currently hedge our foreign currency exchange rate risk. As of March 31, 2018 and December 31, 2017, we had minimal or no liabilities denominated in foreign currencies.

Item 4. Controls and Procedures

Our management, with the participation of our principal executive officer and principal financial officer, evaluated, as of the end of the period covered by this Quarterly Report on Form 10-Q, the effectiveness of our disclosure controls and procedures. Based on that evaluation of our disclosure controls and procedures as of March 31, 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 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. Our 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.

No change in our internal control over financial reporting, as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act, occurred during the fiscal quarter ended March 31, 2018 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

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PART II. OTHER INFORMATION

Item 1A. Risk Factors

This Quarterly Report on Form 10-Q contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained herein, including statements regarding our strategy, future operations, future financial position, future revenue, projected costs, prospects, plans and objectives of our management are forward-looking statements. These statements involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. The words “anticipate,” “believe,” “estimate,” “expect,” “intend,” “may,” “plan,” “predict,” “proje “potential,” “will,” “would,” “could,” “should,” “continue” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. You should read this Quarterly Report on Form 10-Q completely and with the understanding that our actual future results may be materially different from what we expect. The risks described are not the only risks facing our company. Additional risks and uncertainties not currently known to us or that we currently deem to be immaterial also may materially adversely affect our business, financial condition and/or operating results. We do not assume any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law. These risk factors restate and supersede the risk factors set forth under the heading “Risk Factors” in our Annual Report on Form 10-K for the year ended December 31, 2017.

Risks Related to Our Financial Position and Need for Additional Capital

We have incurred significant losses since inception. We expect to incur losses for the foreseeable future and may never achieve or maintain profitability.

Since inception, we have incurred significant operating losses. Our net losses were $314.7 million, $198.5 million, and $117.7 million for the years ended December 31, 2017, 2016 and 2015, respectively, and $90.8 million for the three months ended March 31, 2018. As of March 31, 2018, we had an accumulated deficit of $849.4 million. Other than revenue from royalties on sales of IDHIFA®, we have not generated any revenue from product sales. Our most advanced product candidates are in clinical development stages and we have not yet obtained marketing approval for a product candidate, other than U.S. Food and Drug Administration's, or FDA, approval of IDHIFA® in August 2017 for the treatment of adult patients with relapsed or refractory acute myeloid leukemia, or R/R AML, and an IDH2 mutation as detected by an FDA-approved test. We have financed our operations primarily through private placements of our preferred stock, our initial public offering and the concurrent private placement, our follow-on public offerings and our collaboration agreements with Celgene Corporation and its subsidiaries, or Celgene, focused on cancer metabolism and metabolic immuno-oncology. We have devoted substantially all of our efforts to research and development. Although we may from time to time report profitable results, we expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. The net losses we incur may fluctuate significantly from quarter to quarter. We anticipate that our expenses will increase substantially if and as we:

- initiate and continue clinical trials for our product candidates, including: TIBSOVO® (ivosidenib), AG-881, AG-348, and AG-270;
- continue our research and preclinical development of our product candidates;
- seek to identify additional product candidates;
- seek marketing approvals for our product candidates that successfully complete clinical trials;
- establish a sales, marketing and distribution infrastructure to commercialize any medicines for which we may obtain marketing approval;
- require the manufacture of larger quantities of product candidates for clinical development and, potentially, commercialization;
- maintain, expand and protect our intellectual property portfolio;

- hire additional clinical, quality control and scientific personnel;
- add additional personnel to support our product development and planned future commercialization efforts and our operations;

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- add equipment and physical infrastructure to support our research and development; and
- acquire or in-license other medicines and technologies.

To become and remain profitable, we must develop and eventually commercialize a medicine or medicines with significant market potential. This will require us to be successful in a range of challenging activities, including completing preclinical testing and clinical trials of our product candidates, obtaining marketing approval for these product candidates, manufacturing, marketing and selling those medicines for which we may obtain marketing approval and satisfying any post-marketing requirements. We may never succeed in these activities and, even if we do, may never generate revenue that are significant or large enough to achieve profitability. 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 our company and could impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations. A decline in the value of our company could also cause our stockholders to lose all or part of their investment.

We will need substantial additional funding. If we are unable to raise capital when needed, we would be forced to delay, reduce or eliminate our product development programs or commercialization efforts.

We expect our expenses to increase in connection with our ongoing activities, particularly as we continue the research and development of, initiate and continue clinical trials of, and seek marketing approvals for, our product candidates. For example, we submitted a new drug application, or NDA, for TIBSOVO® (ivosidenib) in IDH1 mutant-positive R/R AML in December 2017, which was accepted with priority review and granted a Prescription Drug User Fee Act, or PDUFA, action date of August 21, 2018. Although Celgene will reimburse us for our co-promotion efforts in the U.S. for IDHIFA® under the 2010 Agreement, if we obtain additional marketing approvals for any of our other product candidates, such as TIBSOVO® (ivosidenib), we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution to the extent that such sales, marketing, manufacturing and distribution are not the responsibility of Celgene or other collaborators. 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 attractive terms, we would be forced to delay, reduce or eliminate our research and development programs or future commercialization efforts.

We expect that our existing cash, cash equivalents and marketable securities as of March 31, 2018, together with anticipated product and royalty revenue, anticipated interest income and anticipated expense reimbursements under our collaboration agreements, but excluding any additional program-specific milestone payments, will enable us to fund our operating expenses and capital expenditure requirements through at least the end of 2020. Our estimate as to how long we expect our existing cash and cash equivalents to be available to fund our operations is based on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect. Further, changing circumstances, some of which may be beyond our control, could cause us to consume capital significantly faster than we currently anticipate, and we may need to seek additional funds sooner than planned. Our future capital requirements will depend on many factors, including:

- the scope, progress, results and costs of drug discovery, preclinical development, laboratory testing and clinical trials for our product candidates;
- the success of, and developments regarding, our collaborations;
- the costs, timing and outcome of regulatory review of our product candidates;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;
- our ability to establish and maintain additional collaborations on favorable terms, if at all; and
- the extent to which we acquire or in-license other medicines and technologies.

Identifying potential product candidates and conducting preclinical testing and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain additional marketing approvals and achieve product sales. In addition, our product candidates, if approved, may not achieve commercial success. Even if we succeed in developing and commercializing one or more of our product candidates, we may never achieve sufficient sales revenue to achieve or maintain profitability. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. Adequate

additional financing 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 revenue, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances and licensing arrangements. We do not have any committed external source of funds, other than our collaborations, which are limited in scope and duration. To the extent

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that we raise additional capital through the sale of equity or convertible debt securities, ownership interests will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our common stockholders. Debt financing, if available, may require us to enter into agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. In addition, securing financing could require a substantial amount of time and attention from our management and may divert a disproportionate amount of their attention away from day-to-day activities, which may adversely affect our management's ability to oversee the development of our product candidates. If we raise funds through additional collaborations, strategic alliances 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 to grant licenses on terms that may not be favorable to us.

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

We were founded in the second half of 2007 and commenced operations in late 2008. 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 preclinical and clinical studies of our product candidates, and establishing a commercial infrastructure. All of our product candidates are still in preclinical and clinical development, with the exception of IDHIFA®. We have not yet demonstrated our ability to successfully complete any large-scale or pivotal clinical trials, obtain other marketing approvals for our product candidates, manufacture a commercial scale medicine, or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful commercialization. Typically, it takes about 10 to 15 years to develop one new medicine from the time it is discovered to when it is available for treating patients, assuming that it successfully completes all stages of research and development and achieves marketing approval, all of which is highly uncertain. Consequently, any predictions you make about our future success or viability may not be as accurate as they could be if we had a longer operating history.

We may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors that may adversely affect our ability to successfully commercialize our product candidates. 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 expect our financial condition and operating results to continue to fluctuate significantly from quarter to quarter and year to year due to a variety of factors, many of which are beyond our control. Accordingly, you should not rely upon the results of any quarterly or annual periods as indications of future operating performance.

Risks Related to the Discovery, Development, and Commercialization of our Product Candidates

We do not know whether we will be able to develop any medicines of commercial value, based on our approach to the discovery and development of product candidates that target cellular metabolism.

Our scientific approach focuses on using our proprietary technology to identify key metabolic enzymes in cancer, rare genetic diseases, or RGDs, or other diseased cells in the laboratory and then using these key enzymes to screen for and identify product candidates targeting cellular metabolism. We are also focused on metabolic immuno-oncology, an emerging field of cancer research focused on altering the metabolic state of immune cells to enhance the body's immune response to cancer.

Our focus on using our proprietary technology to screen for and identify product candidates targeting cellular metabolism may not result in the discovery and development of commercially viable medicines to treat cancer or RGDs. Any medicines that we develop may not effectively correct metabolic pathways or alter the metabolic state of immune cells. If we are able to develop a product candidate that targets cellular metabolism in preclinical studies, we may not succeed in demonstrating safety and efficacy of the product candidate in human clinical trials. In addition, even if we obtain marketing approval for one of our product candidates, we can provide no assurance that commercialization of such product candidate will be successful.

We are reliant on Celgene for the successful development and commercialization of IDHIFA®. If Celgene does not successfully commercialize IDHIFA® for the treatment of adult patients with R/R AML and an IDH2 mutation, our future prospects may be substantially harmed.

In August 2017, the FDA approved IDHIFA® for the treatment of adult patients with R/R AML and an IDH2 mutation, on the basis of an NDA submitted by Celgene. Although IDHIFA® has received FDA approval in R/R AML with an IDH2 mutation, we and Celgene are still evaluating IDHIFA® in other clinical trials. Celgene maintains worldwide development and commercial rights to IDHIFA® and Celgene will fund the development and commercialization costs related to this program, although we have certain co-commercialization and co-promotion rights to IDHIFA®. Under the 2010 Agreement, Celgene is responsible for all development costs for IDHIFA®, and we are eligible to receive up to $95.0 million in milestone payments and a tiered royalty on any net sales of products containing IDHIFA®. Thus, our ability to generate product revenue from IDHIFA® will depend heavily on Celgene's successful development and eventual commercialization of the product.

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The development and commercialization of IDHIFA® could be unsuccessful if:

- IDHIFA® becomes no longer accepted as safe, efficacious, and cost-effective for the treatment of adult patients with R/R AML and an IDH2 mutation in the medical community and by third-party payors;
- Celgene fails to continue to apply the necessary financial resources and expertise to manufacturing, marketing and selling IDHIFA®;
- Celgene does not continue to develop and implement effective marketing, sales and distribution strategies and operations for development and commercialization of IDHIFA®;
- Celgene does not continue to develop, validate and maintain a commercially viable manufacturing process for IDHIFA® that is compliant with current good manufacturing practices;
- Celgene do not successfully obtain third party reimbursement and generate commercial demand that results in sales of IDHIFA®;
- we or Celgene encounter any third party patent interference, derivation, inter partes review, post-grant review, reexamination or patent infringement claims with respect to IDHIFA®;
- Celgene does not comply with regulatory and legal requirements applicable to the sale of IDHIFA®;
- competing drug products are approved for the same indications as IDHIFA®;
- new safety risks are identified;
- IDHIFA® does not demonstrate acceptable safety and efficacy in current or future clinical trials, or otherwise does not meet applicable regulatory standards for approval in indications other than for the treatment of adult patients with R/R AML and an IDH2 mutation;
- Celgene determines to re-prioritize its commercial or development programs and reduce or terminate its efforts on the development or commercialization of IDHIFA®; or
- Celgene does not maintain or defend intellectual property rights associated with IDHIFA®.

If we or Celgene experience significant delays or an inability to successfully commercialize IDHIFA®, our business would be materially harmed.

We may not be successful in our efforts to identify or discover potential product candidates.

A key element of our strategy is to identify and test compounds that target cellular metabolism in a variety of different types of cancer and RGDs, as well as in immune cells for the treatment of cancer. A significant portion of the research that we are conducting involves new compounds and drug discovery methods, including our proprietary technology. The drug discovery that we are conducting using our proprietary technology may not be successful in identifying compounds that are useful in treating cancer or RGDs. In addition, our efforts in the emerging field of metabolic immuno-oncology may not be as successful as our efforts to date in cancer metabolism and RGDs. Furthermore, our research programs may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development for a number of reasons, including:

- the research methodology used may not be successful in identifying appropriate biomarkers or potential product candidates; or
- potential product candidates may, on further study, be shown to have harmful side effects or other characteristics that indicate that they are unlikely to be medicines that will receive marketing approval and achieve market acceptance.

Research programs to identify new product candidates require substantial technical, financial and human resources. We may choose to focus our efforts and resources on a potential product candidate that ultimately proves to be unsuccessful.

If we are unable to identify suitable compounds for preclinical and clinical development, we will not be able to obtain product revenue in future periods, which likely would result in significant harm to our financial position and adversely impact our stock price.

We depend heavily on the success of our clinical product candidates. Clinical trials of our product candidates may not be successful. If we or our collaborators 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 identification of our clinical product candidates, which are TIBSOVO® (ivosidenib) and AG-881 for the treatment of hematological and solid tumors, AG-348 for

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the treatment of pyruvate kinase, or PK, deficiency, and AG-270 for the treatment of methylthioadenosine phosphorylase, or MTAP, deleted cancers. We have initiated clinical trials for all of these product candidates. In December 2017, we submitted an NDA to the FDA for TIBSOVO® (ivosidenib) for the treatment of patients with R/R AML and an IDH1 mutation, which was accepted with priority review and granted a PDUFA action date of August 21, 2018. We also plan to submit a Marketing Authorization Application, or MAA, to the European Medicines Agency, or EMA, for TIBSOVO® (ivosidenib) for IDH1 mutant-positive R/R AML in the fourth quarter of 2018. We have not commenced clinical trials for any of our other product candidates. Our ability to generate product revenue will depend heavily on the successful development and eventual commercialization of our product candidates.

The success of TIBSOVO® (ivosidenib) and our other product candidates will depend on many factors, including the following:

- successful enrollment in, and completion of, clinical trials;
- safety, tolerability and efficacy profiles that are satisfactory to the FDA, the EMA or any comparable foreign regulatory authority for marketing approval;
- timely receipt of marketing approvals from applicable regulatory authorities;
- establishing both clinical and commercial manufacturing capabilities or making arrangements with third-party manufacturers;
- the performance of any collaborators;
- obtaining and maintaining patent and trade secret protection and non-patent exclusivity for our medicines;
- launching commercial sales of the medicines, if and when approved, whether alone or in collaboration with others;
- acceptance of the medicines, if and when approved, by patients, the medical community and third-party payors;
- effectively competing with other therapies;
- continuing acceptable safety profile for the medicines following approval;
- enforcing and defending intellectual property rights and claims; and
- achieving desirable medicinal properties for the intended indications.

Many of these factors are beyond our control, including clinical development, the regulatory submission process, potential threats to our intellectual property rights and the manufacturing, marketing and sales efforts of any collaborator. If we or any collaborators do not achieve one or more of these factors in a timely manner or at all, we or such collaborators could experience significant delays or an inability to successfully commercialize our most advanced product candidates, which would materially harm our business.

If clinical trials of our product candidates fail to demonstrate safety and efficacy to the satisfaction of regulatory authorities or do not otherwise produce positive results, we may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates.

We, and any collaborators, are not permitted to commercialize, market, promote or sell any product candidate in the United States without obtaining marketing approval from the FDA. Foreign regulatory authorities, such as the EMA, impose similar requirements. We have not previously submitted similar drug approval filings to comparable foreign regulatory authorities for any of our product candidates. Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must complete preclinical development and then conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans. In December 2017, we submitted an NDA to the FDA for TIBSOVO® (ivosidenib) in IDH1 mutant-positive R/R AML, which was accepted with priority review and granted a PDUFA action date of August 21, 2018, and we plan to submit an MAA to the EMA for TIBSOVO® (ivosidenib) for IDH1 mutant-positive R/R AML in the fourth quarter of 2018. However, we can provide no assurance that we will receive regulatory approval of TIBSOVO® (ivosidenib) on the timeframe we expect, or at all.

Clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. We cannot guarantee that any clinical trials will be conducted as planned or completed on schedule, if at all. The clinical development of our product candidates is susceptible to the risk of failure inherent at any stage of product development, including failure to demonstrate efficacy in a clinical trial or across a broad population of patients, the occurrence of adverse events that are severe or medically or commercially unacceptable, failure to comply with protocols or applicable regulatory requirements and determination by the FDA or any comparable foreign regulatory

authority that a product candidate may not continue development or is not approvable. For instance, in December 2016, we withdrew our IND for AG-519, our second

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PKR activator, following verbal notification of a clinical hold from the FDA relating to a previously disclosed case of drug-induced cholestatic hepatitis which occurred in our phase 1 clinical trial of AG-519 in healthy volunteers. Although these decisions and this hepatic adverse event finding do not affect our ongoing global phase 2 clinical trial, also known as DRIVE PK, for AG-348, our first PKR activator, we cannot provide any assurances that there will not be similar or other treatment-related severe adverse events in DRIVE PK or our other clinical trials, that our other trials will not be placed on clinical hold in the future, or that patient recruitment for DRIVE PK or our other trials will not be adversely impacted.

It is possible that even if one or more of our product candidates has a beneficial effect, that effect will not be detected during clinical evaluation as a result of one or more of a variety of factors, including the size, duration, design, measurements, conduct or analysis of our clinical trials. Conversely, as a result of the same factors, our clinical trials may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any. Similarly, in our clinical trials we may fail to detect toxicity of or intolerability caused by our product candidates, or mistakenly believe that our product candidates are toxic or not well-tolerated when that is not in fact the case.

Any inability to successfully complete preclinical and clinical development could result in additional costs to us, or any future collaborators, and impair our ability to generate revenue from product sales, regulatory and commercialization milestones and royalties. Moreover, if we or our collaborators are required to conduct additional clinical trials or other testing of our product candidates beyond those that we currently contemplate, if we or our collaborators are unable to successfully complete clinical trials of our product candidates or other testing, if the results of these trials or tests are not positive or are only modestly positive or if there are safety concerns, we or our collaborators may:

- be delayed in obtaining marketing approval for our product candidates;
- not obtain marketing approval at all;
- 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, including boxed warnings;
- be subject to additional post-marketing testing requirements; or
- have the medicine removed from the market after obtaining marketing approval.

Our failure to successfully complete clinical trials of our product candidates and to demonstrate the efficacy and safety necessary to obtain regulatory approval to market any of our product candidates would significantly harm our business.

If we, or any collaborators, experience any of a number of possible unforeseen events in connection with clinical trials of our product candidates, potential clinical development, marketing approval or commercialization of our product candidates could be delayed or prevented.

We or our collaborators 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, including:

- regulators or institutional review boards may not authorize us, our collaborators or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- we or our collaborators may have delays in reaching or fail to reach agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites;
- clinical trials of our product candidates may produce negative or inconclusive results, and we or our collaborators may decide, or regulators may require us, to conduct additional clinical trials, including testing in more subjects, or abandon product development programs;
- the number of patients required for clinical trials of our product candidates may be larger than we anticipate; enrollment in these clinical trials, which may be particularly challenging for some of the orphan diseases we target in our RGD programs, may be slower than we anticipate; or participants may drop out of these clinical trials at a higher rate than we anticipate;
- third-party contractors used by us or our collaborators may fail to comply with regulatory requirements or meet their contractual obligations in a timely manner, or at all;
-

we or our collaborators might have to suspend or terminate clinical trials of our product candidates for various reasons, including a finding that the participants are being exposed to unacceptable health risks;

- regulators, institutional review boards, or the data safety monitoring board for such trials may require that we, our collaborators or our investigators suspend or terminate clinical research for various reasons, including

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noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks;

- the cost of clinical trials of our product candidates may be greater than anticipated;
- 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; and
- our product candidates may have undesirable side effects or other unexpected characteristics, causing us, our collaborators or our investigators, regulators or institutional review boards to suspend or terminate the trials.

Product development costs for us, or any collaborators, will increase if we, or they, experience delays in testing or pursuing marketing approvals and we, or they, may be required to obtain additional funds to complete clinical trials and prepare for possible commercialization of our product candidates. We do not know whether any preclinical tests or clinical trials will begin as planned, will need to be restructured, or will be completed on schedule or at all. Significant preclinical study or clinical trial delays also could shorten any periods during which we, or any future collaborators, may have the exclusive right to commercialize our product candidates or allow our competitors, or the competitors of any collaborators, to bring products to market before we, or any collaborators, do and impair our ability, or the ability of any collaborators, to successfully commercialize our product candidates and may harm our business and results of operations. In addition, many of the factors that lead to clinical trial delays may ultimately lead to the denial of marketing approval of any of our product candidates.

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

We or our collaborators may not be able to initiate or continue clinical trials for our product candidates if we or they are unable to locate and enroll a sufficient number of eligible patients to participate in these trials as required by the FDA or analogous regulatory authorities outside the United States. Enrollment may be particularly challenging for some of the orphan diseases we target in our RGD programs. In addition, some of our competitors may have ongoing clinical trials for product candidates that would treat the same indications as our product candidates, and patients who would otherwise be eligible for our clinical trials may instead enroll in clinical trials of our competitors' product candidates.

Patient enrollment is also affected by other factors including:

- severity of the disease under investigation;
- availability and efficacy of approved medications for the disease under investigation;
- eligibility criteria for the study in question;
- perceived risks and benefits of the product candidate under study;
- efforts to facilitate timely enrollment in clinical trials;
- patient referral practices of physicians;
- the ability to monitor patients adequately during and after treatment; and
- proximity and availability of clinical trial sites for prospective patients.

Utilizing our precision medicine approach, we focus our development activities on genetically or biomarker defined patients most likely to respond to our therapies. As a result, the potential patient populations for our clinical trials are narrowed, and we may experience difficulties in identifying and enrolling a sufficient number of patients in our clinical trials. In particular, the successful completion of our clinical development program for AG-348 for the treatment of PK deficiency is dependent upon our ability to enroll a sufficient number of patients with PK deficiency. PK deficiency is a rare disease with a small patient population. Further, there are only a limited number of specialist physicians that regularly treat patients with PK deficiency and major clinical centers that support PK deficiency are concentrated in a few geographic regions. The small population of patients, the nature of the disease and limited trial sites may make it difficult for us to enroll enough patients to complete our clinical trials for AG-348 for PK deficiency in a timely and cost-effective manner.

In addition, other companies are conducting clinical trials, or may in the future conduct clinical trials, which may have similar eligibility criteria as our current or future clinical trials. For example, Daiichi Sankyo Company, Ltd., with DS-1001b, Bayer AG, or Bayer, with BAY1436032, and Forma Therapeutics Holdings, LLC, with FT-2102, are conducting clinical trials in patients with IDH1 mutant positive-cancers, and Rocket Pharma LTD is in the preclinical

stages of development for a gene therapy targeting PK deficiency. As these companies and others initiate and conduct clinical trials, they may compete for eligible patients with our clinical trials of TIBSOVO® (ivosidenib), AG-881 or AG-348. Competition for these patients may make it particularly difficult for us to enroll enough patients to complete our clinical trials for TIBSOVO® (ivosidenib), AG-881 or AG-348 in a timely and cost-effective manner.

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Furthermore, we rely on contract research organizations, or CROs, and clinical trial sites to ensure the proper and timely conduct of our clinical trials and while we have agreements governing their committed activities, we have limited influence over their actual performance. Our or our collaborators' inability to enroll a sufficient number of patients for our clinical trials would result in significant delays or may 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, which would cause the value of our company to decline and limit our ability to obtain additional financing.

If serious adverse side effects or unexpected characteristics are identified during the development of our product candidates, we may need to abandon or limit our development of some of our product candidates.

With the exception of IDHIFA®, all of our most advanced product candidates are still in clinical stage development and their risk of failure is high. It is impossible to predict when or if any of our product candidates will prove effective or safe in humans or will receive marketing approval. Adverse events or undesirable side effects caused by, or other unexpected properties of, our product candidates could cause us, any future collaborators, an institutional review board or regulatory authorities to interrupt, delay or halt clinical trials of one or more of our product candidates and could result in a more restrictive label, or the delay or denial of marketing approval by the FDA or comparable foreign regulatory authorities. If adverse effects were to arise in patients being treated with any of our product candidates, it could require us to halt, delay or interrupt clinical trials of such product candidate or adversely affect our ability to obtain requisite approvals to advance the development and commercialization of such product candidate. If any of our product candidates is associated with adverse events or undesirable side effects or has properties that are unexpected, we, or any future collaborators, may need to abandon development or limit development of that product candidate to certain 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. Many compounds that initially showed promise in earlier stage testing for treating cancer, RGDs or other diseases have later been found to cause side effects that prevented further development of the compound. For instance, in December 2016, we withdrew our IND for AG-519, our second PKR activator, following verbal notification of a clinical hold from the FDA relating to a previously disclosed case of drug-induced cholestatic hepatitis which occurred in our phase 1 clinical trial of AG-519 in healthy volunteers. Although these decisions and this hepatic adverse event finding do not affect our ongoing global phase 2 clinical trial (DRIVE PK) for AG-348, our first PKR activator, we cannot provide any assurances that there will not be similar or other treatment-related severe adverse events in DRIVE PK or our other clinical trials, that our other trials will not be placed on clinical hold in the future, or that patient recruitment for DRIVE PK or our other trials will not be adversely impacted.

Results of preclinical studies and early clinical trials may not be predictive of results of future clinical trials.

The outcome of preclinical studies and early clinical trials may not be predictive of the success of later clinical trials, and interim results of clinical trials do not necessarily predict success in future clinical trials. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials after achieving positive results in earlier development, and we could face similar setbacks. The design of a clinical trial can determine whether its results will support approval of a product and flaws in the design of a clinical trial may not become apparent until the clinical trial is well advanced. We have limited experience in designing clinical trials and may be unable to design and execute a clinical trial to support marketing approval. In addition, preclinical and clinical data are often susceptible to varying interpretations and analyses. Many companies that believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval for the product candidates. Even if we, or future collaborators, believe that the results of clinical trials for our product candidates warrant marketing approval, the FDA or comparable foreign regulatory authorities may disagree and may not grant marketing approval of our product candidates.

In some instances, there can be significant variability in safety or efficacy results between different clinical trials of the same product candidate due to numerous factors, including changes in trial procedures set forth in protocols, differences in the size and type of the patient populations, changes in and adherence to the dosing regimen and other clinical trial protocols and the rate of dropout among clinical trial participants. If we fail to receive positive results in clinical trials of our product candidates, the development timeline and regulatory approval and commercialization

prospects for our most advanced product candidates, and, correspondingly, our business and financial prospects would be negatively impacted.

We may expend our limited resources to pursue a particular product candidate or indication and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success. Because we have limited financial and managerial resources, we focus on research programs and product candidates that we identify for specific indications. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial medicines or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable medicines. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases

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in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate.

If we are unable to successfully develop companion diagnostics for our product candidates, or experience significant delays in doing so, we may not realize the full commercial potential of our therapeutics.

Because we are focused on precision medicine, in which predictive biomarkers will be used to identify the right patients for our drug candidates, we believe that our success will depend, in part, on our ability to develop companion diagnostics, which are assays or tests to identify an appropriate patient population for these drug candidates. There has been limited success to date industry-wide in developing these types of companion diagnostics. To be successful, we need to address a number of scientific, technical and logistical challenges. We have little experience in the development of diagnostics and may not be successful in developing appropriate diagnostics to pair with any of our therapeutic product candidates that receive marketing approval. Companion diagnostics are subject to regulation by the FDA and similar regulatory authorities outside the United States as medical devices and require separate regulatory approval prior to commercialization. Given our limited experience in developing diagnostics, we rely and expect to continue to rely in part or in whole on third parties for their design and manufacture. We also depend on Celgene for the development of the FDA approved companion diagnostic for IDHIFA®, and may in the future depend on Celgene or other third parties for the development of other companion diagnostics for our cancer therapeutic product candidates. If any parties, including without limitation Celgene or us, or any third parties engaged by Celgene or us are unable to successfully develop companion diagnostics for our therapeutic product candidates, or experience delays in doing so:

- the development of our therapeutic product candidates may be adversely affected if we are unable to appropriately select patients for enrollment in our clinical trials;
- our therapeutic product candidates may not receive marketing approval if safe and effective use of a therapeutic product candidate depends on an in vitro diagnostic; and
- we may not realize the full commercial potential of any therapeutics that receive marketing approval if, among other reasons, we are unable to appropriately select patients who are likely to benefit from therapy with our medicines.

As a result of any of these events, our business would be harmed, possibly materially.

We may be unable to obtain, or may be delayed in obtaining, marketing approval for our product candidates.

In December 2017, we submitted an NDA to the FDA for TIBSOVO® (ivosidenib) in IDH1 mutant-positive R/R AML, which was accepted with priority review and granted a PDUFA action date of August 21, 2018, and we plan to submit an MAA to the EMA for TIBSOVO® (ivosidenib) for IDH1 mutant-positive R/R AML in the fourth quarter of 2018. It is possible that the FDA or EMA may refuse to accept our applications for substantive review, or that the FDA or EMA may conclude after review of our data that our application is insufficient to obtain marketing approval of TIBSOVO® (ivosidenib) in the United States and the European Union, or E.U., respectively. If the FDA does not approve our NDA for TIBSOVO® (ivosidenib) or the EMA does not accept or approve the MAA for TIBSOVO® (ivosidenib) that we plan to submit, we may be required to conduct additional clinical trials, preclinical studies or manufacturing validation studies and submit that data to regulators before our application will be reconsidered. Depending on the extent of these or any other FDA- or EMA-required trials or studies, approval of our NDA for TIBSOVO® (ivosidenib) or acceptance or approval of the MAA for TIBSOVO® (ivosidenib) that we plan to submit may be delayed by several years, or may require us to expend more resources than we have available. It is also possible that additional trials or studies, if performed and completed, may not be considered sufficient by the FDA to approve our NDA for TIBSOVO® (ivosidenib) or the EMA to accept or approve the MAA for TIBSOVO® (ivosidenib) that we plan to submit. Any delay in obtaining, or an inability to obtain, marketing approvals would prevent us from commercializing TIBSOVO® (ivosidenib) in the United States and/or abroad, generating revenue and achieving and sustaining profitability. If any of these outcomes occur, either to TIBSOVO® (ivosidenib) or to any future product candidate for which we may seek marketing approval, we may be forced to abandon our development efforts for TIBSOVO® (ivosidenib) or such future product candidates, which could significantly harm our business.

Even if any of our product candidates receives marketing approval, we or others may later discover that the product is less effective than previously believed or causes undesirable side effects that were not previously identified, which could compromise our ability, or that of any future collaborators, to market the product.

Clinical trials of our product candidates are conducted in carefully defined sets of patients who have agreed to enter into clinical trials. Consequently, it is possible that our clinical trials, or those of any future collaborator, may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any, or alternatively fail to identify undesirable side effects. If, following approval of a product candidate, we, or others, discover that the product is less effective than previously believed or causes undesirable side effects that were not previously identified, any of the following adverse events could occur:

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- regulatory authorities may withdraw their approval of the product or seize the product;
- we, or any future collaborators, may be required to recall the product, change the way the product is administered or conduct additional clinical trials;
- additional restrictions may be imposed on the marketing of, or the manufacturing processes for, the particular product;
- we may be subject to fines, injunctions or the imposition of civil or criminal penalties;
- regulatory authorities may require the addition of labeling statements, such as a “black box” warning or a contraindication, including, for example, the black box warning for differentiation syndrome on the label for IDHIFA®;
- we, or any future collaborators, may be required to create a Medication Guide outlining the risks of the previously unidentified side effects for distribution to patients;
- we, or any future collaborators, could be sued and held liable for harm caused to patients;
- the product may become less competitive; and
- our reputation may suffer.

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

IDHIFA®, or any of our product candidates that receive marketing approval in the future, may nonetheless fail to gain sufficient market acceptance by physicians, patients, healthcare payors and others in the medical community. For example, current cancer treatments like chemotherapy and radiation therapy are well established in the medical community, and doctors may continue to rely on these treatments. If our product candidates do not achieve an adequate level of acceptance, we may not generate significant product revenue 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:

- efficacy and potential advantages compared to alternative treatments;
- the approval, availability, market acceptance and reimbursement for the companion diagnostic;
- the ability to offer our medicines for sale at competitive prices;
- 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;
- ensuring uninterrupted product supply;
- the strength of marketing and distribution support;
- sufficient third-party coverage or reimbursement; and
- the prevalence and severity of any side effects.

If we are unable to establish and maintain sales and marketing capabilities or enter into agreements with third parties to sell and market our product candidates, we may not be successful in commercializing our product candidates if and when they are approved.

We have little experience in the sale, marketing or distribution of pharmaceutical products. To achieve commercial success for any approved medicine for which we retain sales and marketing responsibilities, we must either develop a sales and marketing organization or outsource these functions to other third parties. Although we have established sales and marketing capabilities to support our co-promotion efforts for IDHIFA®, we are still building a sales and marketing infrastructure to sell, or participate in sales activities with our collaborators for, our other product candidates if and when they are approved.

There are risks involved with both establishing our own sales and marketing capabilities and entering into arrangements with third parties to perform these services. For example, recruiting and training a sales force is expensive and time consuming and could delay any product launch. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

Factors that may inhibit our efforts to commercialize our medicines on our own include:

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- our inability to recruit and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future medicines;
- the lack of complementary medicines to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

If we enter into arrangements with third parties to perform sales, marketing and distribution services, our product revenue or the profitability of product revenue to us are likely to be lower than if we were to market and sell any medicines that we develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to sell and market our product candidates or may be unable to do so on terms that are favorable to us. We likely will have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our medicines effectively. If we do not establish sales and marketing capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our product candidates.

We face substantial competition, which may result in others discovering, developing or commercializing products before or more successfully than we do.

The development and commercialization of new drug products is highly competitive. We face competition with respect to our current product candidates, and we and our collaborators will face competition with respect to any product candidates that we or they may seek to develop or commercialize in the future, from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide. There are a number of large pharmaceutical and biotechnology companies that currently market and sell products or are pursuing the development of products for the treatment of the disease indications for which we are developing our product candidates, such as AML and high risk myelodysplasia. For example, Jazz Pharmaceuticals plc, Abbvie Inc. (in collaboration with Roche Holdings Inc., or Roche) and Bayer are each developing or marketing therapies to treat AML. Some competitive products and therapies are based on scientific approaches that are the same as or similar to our approach, and others are based on entirely different approaches, for example, in the area of RGDs. Potential competitors also include academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for research, development, manufacturing and commercialization.

We are developing most of our initial product candidates for the treatment of cancer. There are a variety of available drug therapies marketed for cancer. In many cases, these drugs are administered in combination to enhance efficacy, and cancer drugs are frequently prescribed off-label by healthcare professionals. Some of the currently approved drug therapies are branded and subject to patent protection, and others are available on a generic basis. Many of these approved drugs are well established therapies and are widely accepted by physicians, patients and third-party payors. Insurers and other third-party payors may also encourage the use of generic products. We expect that IDHIFA®, and other of our product candidates, if approved, will be priced at a significant premium over competitive generic products. This may make it difficult for us to achieve our business strategy of using our product candidates in combination with existing therapies or replacing existing therapies with our product candidates.

We are also pursuing product candidates to treat patients with RGDs. There are a variety of treatment options available, including a number of marketed enzyme replacement therapies, for treating patients with RGDs. In addition to currently marketed therapies, there are also a number of products that are either enzyme replacement therapies or gene therapies in various stages of clinical development to treat RGDs. These products in development may provide efficacy, safety, convenience and other benefits that are not provided by currently marketed therapies. As a result, they may provide significant competition for any of our product candidates for which we obtain marketing approval.

There are also a number of product candidates in preclinical or clinical development by third parties to treat cancer and RGDs by targeting cellular metabolism. These companies include large pharmaceutical companies, including AstraZeneca plc, Bayer, Eli Lilly and Company, Roche and its subsidiary Genentech, Inc., GlaxoSmithKline plc, Merck & Co., or Merck, Pfizer, Inc., and Genzyme, a Sanofi company. There are also biotechnology companies of various sizes that are developing therapies to target cellular metabolism, including BioMarin Pharmaceutical Inc.,

Calithera Biosciences, Inc., or Calithera, Cornerstone Pharmaceuticals, Inc., Daiichi Sankyo Company, Ltd. with its IDH1 mutant inhibitor DS-1001b, and Forma Therapeutics Holdings LLC with its IDH1 mutant inhibitor FT-2102. In addition, there are several companies developing immunotherapies, including metabolic immunotherapies, targeting cancer, including Arcus Biosciences, AstraZeneca PLC, Merck, Bristol-Myers Squibb Company, Calithera, Incyte Corporation, NewLink Gentics Corporation, Novartis, and Rheos Medicines. Our competitors may develop products that are more effective, safer, more convenient or less costly than any that we are developing or that would render our product candidates obsolete or non-competitive. In addition, our competitors may discover biomarkers that more efficiently measure metabolic pathways than our methods, which may give them a competitive advantage in

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developing potential products. Our competitors may also obtain marketing approval from the FDA or other regulatory authorities for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market.

Many of our competitors have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller and other clinical stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

If the FDA does not grant our products appropriate periods of data exclusivity before approving generic versions of our products, the sales of our products could be adversely affected.

With FDA approval of an NDA, the product covered by the application is specified as a “reference-listed drug” in the FDA’s publication, “Approved Drug Products with Therapeutic Equivalence Evaluations,” or the Orange Book. Manufacturers may seek approval of generic versions of reference-listed drugs through submission of abbreviated new drug applications, or ANDAs, in the United States. In support of an ANDA, a generic manufacturer need not conduct clinical trials. Rather, the applicant generally must show that its product has the same active ingredient(s), dosage form, strength, route of administration and conditions of use or labeling as the reference-listed drug and that the generic version is bioequivalent to the reference-listed drug, meaning it is absorbed in the body at the same rate and to the same extent. Generic products may be significantly less costly to bring to market than the reference-listed drug and companies that produce generic products are generally able to offer them at lower prices. Thus, following the introduction of a generic drug, a significant percentage of the sales of any reference-listed drug may be typically lost to the generic product.

The FDA may not approve an ANDA for a generic product until any applicable period of non-patent exclusivity for the reference-listed drug has expired. The Federal Food, Drug, and Cosmetic Act, or FDCA, provides a period of five years of non-patent exclusivity for a new drug containing a new chemical entity, or NCE. Specifically, in cases where such exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification that a patent covering the reference-listed drug is either invalid or will not be infringed by the generic product, in which case the applicant may submit its application four years following approval of the reference-listed drug. The FDCA also provides a period of three years of new clinical investigation, or NCI, data exclusivity in connection with the approval of a supplemental indication for the product for which a clinical trial is essential for approval.

In the event that a generic manufacturer is somehow able to obtain FDA approval without adherence to these periods of data exclusivity, the competition that our approved products may face from generic versions could negatively impact our future revenue, profitability and cash flows and substantially limit our ability to obtain a return on our investments in those product candidates.

Even if we or any collaborators are able to commercialize any product candidates, such products may become subject to unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, which would harm our business.

The commercial success of our product candidates will depend substantially, both domestically and abroad, on the extent to which the costs of our product candidates will be paid by third-party payors, including government health administration authorities and private health coverage insurers. If coverage and reimbursement is not available, or reimbursement is available only to limited levels, we, or any future collaborators, 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, or any future collaborators, to establish or maintain pricing sufficient to realize a sufficient return on our or their investments. In the United States, no uniform policy of coverage and reimbursement for products exists among third-party payors and coverage and reimbursement for products can differ significantly from payor to payor. As a result, the coverage determination process is often a time-consuming and costly process that will

require us to provide scientific and clinical support for the use of our products to each payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance. There is significant uncertainty related to third-party payor coverage and reimbursement of newly approved drugs. Marketing approvals, pricing and reimbursement for new drug products vary widely from country to country. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we, or any future collaborators, might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay

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commercial launch of the product, possibly for lengthy time periods, which may negatively impact the revenue we are able to generate from the sale of the product in that country. Adverse pricing limitations may hinder our ability or the ability of any future collaborators to recoup our or their investment in one or more product candidates, even if our product candidates obtain marketing approval.

Patients who are provided medical treatment for their conditions generally rely on third-party payors to reimburse all or part of the costs associated with their treatment. Therefore, our ability, and the ability of any future collaborators, to commercialize any of our product candidates will depend in part on the extent to which coverage and reimbursement for these products and related treatments will be available from third-party payors. Third-party payors decide which medications they will cover and establish reimbursement levels. The healthcare industry is acutely focused on cost containment, both in the United States and elsewhere. Government authorities and other third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications, which could affect our ability or that of any future collaborators to sell our product candidates profitably. These payors may not view our products, if any, as cost-effective, and coverage and reimbursement may not be available to our customers, or those of any future collaborators, or may not be sufficient to allow our products, if any, to be marketed on a competitive basis. Cost-control initiatives could cause us, or any future collaborators, to decrease the price we, or they, might establish for products, which could result in lower than anticipated product revenue. If the prices for our products, if any, decrease or if governmental and other third-party payors do not provide coverage or adequate reimbursement, our prospects for revenue and profitability will suffer.

There may also be delays in obtaining coverage and reimbursement for newly approved drugs, and coverage may be more limited than the indications for which the drug is approved by the FDA or comparable foreign regulatory authorities. Moreover, eligibility for reimbursement does not imply that any drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Reimbursement rates may vary, by way of example, according to the use of the product and the clinical setting in which it is used. Reimbursement rates may also be based on reimbursement levels already set for lower cost drugs or may be incorporated into existing payments for other services.

In addition, increasingly, third-party payors are requiring higher levels of evidence of the benefits and clinical outcomes of new technologies and are challenging the prices charged. We cannot be sure that coverage will be available for any product candidate that we, or any future collaborator, commercialize and, if available, that the reimbursement rates will be adequate. Further, the net reimbursement for drug products may be subject to additional reductions if there are changes to laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. An inability to promptly obtain coverage and adequate payment rates from both government-funded and private payors for any of our product candidates for which we, or any future collaborator, obtain marketing approval could significantly harm our operating results, our ability to raise capital needed to commercialize products and our overall financial condition.

Product liability lawsuits against us or our collaborators could cause us or our collaborators to incur substantial liabilities and could limit commercialization of any medicines that we or they may develop.

We and our collaborators face an inherent risk of product liability exposure related to the testing of our product candidates in human clinical trials and will face an even greater risk as we or they commercially sell any medicines that we or they may develop. If we or our collaborators cannot successfully defend ourselves or themselves against claims that our product candidates or medicines caused injuries, we could incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for any product candidates or medicines that we may develop;
- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants;
- significant costs to defend the related litigation;
- substantial monetary awards to trial participants or patients;
- loss of revenue;
- reduced resources of our management to pursue our business strategy; and
- the inability to commercialize any medicines that we may develop.

Although we maintain product liability insurance coverage, it may not be adequate to cover all liabilities that we may incur. We anticipate that we will need to increase our insurance coverage as we advance or expand our clinical trials and if we successfully commercialize any medicine. Insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise. In addition, if one of our collaboration partners were to become subject to product liability claims or were unable to successfully defend themselves

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against such claims, any such collaboration partner could be more likely to terminate such relationship with us and therefore substantially limit the commercial potential of our products.

Our internal computer systems, or those of any collaborators or contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our product development programs.

Despite the implementation of security measures, our internal computer systems and those of third parties with which we contract are vulnerable to damage from cyber-attacks, computer viruses, worms and other destructive or disruptive software, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. System failures, accidents or security breaches could cause interruptions in our operations, and could result in a material disruption of our clinical and commercialization activities and business operations, in addition to possibly requiring substantial expenditures of resources to remedy. The loss of clinical trial data could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and our product research, development and commercialization efforts could be delayed. In addition, we may not have adequate insurance coverage to provide compensation for any losses associated with such events.

We could be subject to risks caused by misappropriation, misuse, leakage, falsification or intentional or accidental release or loss of information maintained in the information systems and networks of our company, including personal information of our employees. In addition, outside parties may attempt to penetrate our systems or those of our vendors or fraudulently induce our employees or employees of our vendors to disclose sensitive information in order to gain access to our data. Like other companies, we may experience threats to our data and systems, including malicious codes and viruses, and other cyber-attacks. The number and complexity of these threats continue to increase over time. If a material breach of our security or that of our vendors occurs, the market perception of the effectiveness of our security measures could be harmed, we could lose business and our reputation and credibility could be damaged. We could be required to expend significant amounts of money and other resources to repair or replace information systems or networks. Although we develop and maintain systems and controls designed to prevent these events from occurring, and we have a process to identify and mitigate threats, the development and maintenance of these systems, controls and processes is costly and requires ongoing monitoring and updating as technologies change and efforts to overcome security measures become more sophisticated. Moreover, despite our efforts, the possibility of these events occurring cannot be eliminated entirely.

Risks Related to Our Dependence on Third Parties

We depend on our collaborations and may depend on collaborations with additional third parties for the development and commercialization of our product candidates. If those collaborations are not successful, we may not be able to capitalize on the market potential of these product candidates.

We are party to several collaboration agreements, including the 2010 Agreement, the AG-881 Agreements and the 2016 Agreement. These collaborations involve complex allocations of rights, provide for milestone payments to us based on the achievement of specified clinical development, regulatory and commercial milestones, provide us with royalty-based revenue if certain product candidates are successfully commercialized and provide for cost reimbursements of certain development activities. We cannot predict the success of these collaborations.

We may seek other third-party collaborators for the development and commercialization of our product candidates. Our likely collaborators for any collaboration arrangements include large and mid-size pharmaceutical companies, regional and national pharmaceutical companies and biotechnology companies. If we enter into any such arrangements with any third parties, we will likely have limited control over the amount and timing of resources that our collaborators dedicate to the development or commercialization of our product candidates. Our ability to generate revenue from these arrangements will depend on our collaborators' abilities to successfully perform the functions assigned to them in these arrangements.

Collaborations involving our product candidates, including our collaborations with Celgene, pose the following risks to us:

- Collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations. Under the 2010 Agreement, the AG-881 Agreements and programs under a co-development and

co-commercialization agreement pursuant to the 2016 Agreement, development and commercialization plans and strategies for licensed programs, such as IDHIFA®, will be conducted in accordance with a plan and budget approved by a joint committee comprised of equal numbers of representatives from each of us and Celgene, as to which Celgene may have final decision-making authority. For example, Celgene has elected not to participate in our planned perioperative study of TIBSOVO® (ivosidenib) and AG-881 in patients with low grade glioma and, pursuant to the AG-881 Agreements, we will fund the trial ourselves.

- Collaborators may not pursue development and commercialization of our product candidates or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the

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collaborator's strategic focus or available funding or external factors such as an acquisition that diverts resources or creates competing priorities. For example, under the 2016 Agreement, it is possible for Celgene to elect not to progress into preclinical development a product candidate that we have nominated and the joint research committee confirmed, without triggering a termination of the collaboration arrangement.

- Collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing, which may result in a need for additional capital to pursue further development or commercialization of the applicable product candidate. For example, under the 2010 Agreement and the 2016 Agreement, it is possible for Celgene to terminate the agreement, upon 90 days prior written notice, with respect to any product candidate at any point in the research, development and clinical trial process, without triggering a termination of the remainder of the collaboration arrangement.
- Collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our medicines or product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours.
- Collaborators with marketing and distribution rights to one or more medicines may not commit sufficient resources to the marketing and distribution of such medicine or medicines.
- Collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our proprietary information or expose us to potential litigation. For example, under specified circumstances Celgene has the first right to maintain or defend our intellectual property rights with respect to IDHIFA® under the 2010 Agreement and, although we may have the right to assume the maintenance and defense of our intellectual property rights if Celgene does not, our ability to do so may be compromised by Celgene's actions.
- Disputes may arise between the collaborators and us that result in the delay or termination of the research, development or commercialization of our medicines or product candidates or that result in costly litigation or arbitration that diverts management attention and resources.
- We may lose certain valuable rights under circumstances identified in our collaborations, including, in the case of our agreements with Celgene, if we undergo a change of control.
- Collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates. For example, Celgene can terminate its agreements with us, in their entirety or with respect to IDHIFA® under the 2010 Agreement or any program under the 2016 Agreement, upon 90 days' notice and can terminate each entire agreement with us in connection with a material breach of the agreement by us that remains uncured for a period ranging from 60 to 90 days.
- Collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner or at all.
- If a present or future collaborators of ours were to be involved in a business combination, the continued pursuit and emphasis on our product development or commercialization program under such collaboration could be delayed, diminished or terminated.
- We may seek to establish additional collaborations, and, if we are not able to establish them on commercially reasonable terms, we may have to alter our development and commercialization plans.
- Our drug development programs and the potential commercialization of our product candidates will require substantial additional cash to fund expenses. For some of our product candidates, we may decide to collaborate with additional pharmaceutical and biotechnology companies for the development and potential commercialization of those product candidates.
- We face significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. Those factors may include the design or results of clinical trials, the likelihood of approval by the FDA or similar regulatory authorities outside the United States, the potential market for the subject product candidate, the costs and complexities of manufacturing and delivering such product candidate to patients, the potential of competing products,

the existence of uncertainty with respect to our ownership of technology, which can exist if there is a challenge to such ownership without regard to the merits of the challenge, and industry and market conditions generally. The collaborator may also consider alternative product candidates or

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technologies for similar indications that may be available to collaborate on and whether such collaboration could be more attractive than the one with us for our product candidate.

We may also be restricted under existing collaboration agreements from entering into future agreements on certain terms with potential collaborators. For example, during the discovery phase of the 2016 Agreement, we may not directly or indirectly develop, manufacture or commercialize, except pursuant to the agreement, any medicine or product candidate with specified activity against certain metabolic targets except in connection with certain third-party collaborations or with respect to certain targets the rights to which have reverted back to us pursuant to the terms of the 2016 Agreement. Following the discovery phase until termination or expiration of the 2010 Agreement, either in its entirety or with respect to the relevant program, we may not directly or indirectly develop, manufacture or commercialize, outside of the collaboration, any medicine or product candidate with specified activity against any collaboration target that is within a licensed program or against any former collaboration target against which Celgene is conducting an independent program under the agreement. Following the discovery phase of the 2016 Agreement until termination or expiration of the applicable co-development and co-commercialization agreement or license agreement under the 2016 Agreement, we may not directly or indirectly develop, manufacture or commercialize, outside of the collaboration, any medicine or product candidate with specified activity against the collaboration target that is the subject of such co-development and co-commercialization agreement or license agreement, except in connection with certain third-party collaborations or with respect to certain targets the rights to which have reverted back to us pursuant to the terms of the 2016 Agreement.

Collaborations are complex and time-consuming to negotiate and document. In addition, there have been a significant number of business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators.

We may not be able to negotiate collaborations on a timely basis, on acceptable terms, or at all. If we are unable to do so, we may have to curtail the development of the product candidate for which we are seeking to collaborate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or 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 increase our expenditures to fund development or commercialization activities on our own, we may need to obtain additional capital, which may not be available to us on acceptable terms or at all. If we do not have sufficient funds, we may not be able to further develop our product candidates or bring them to market and generate product revenue.

We rely and expect to continue to rely on third parties to conduct our clinical trials and some aspects of our research and preclinical testing, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials, research or testing.

We do not independently conduct clinical trials of any of our product candidates. We rely and expect to continue to rely on third parties, such as CROs, clinical data management organizations, medical institutions and clinical investigators, to conduct our clinical trials. In addition we currently rely and expect to continue to rely on third parties to conduct some aspects of our research and preclinical testing. Any of these third parties may terminate their engagements with us, some in the event of an uncured material breach and some at any time. If any of our relationships with these third parties terminate, we may not be able to enter into arrangements with alternative third-parties or to do so on commercially reasonable terms. Switching or adding additional third parties involves additional cost and requires management time and focus. In addition, there is a natural transition period when a new third party commences work. As a result, delays may occur in our product development activities. Although we seek to carefully manage our relationships with our CROs, we could encounter similar challenges or delays in the future and these challenges or delays could have a material adverse impact on our business, financial condition and prospects.

Our reliance on 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 are responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol, and legal, regulatory and scientific standards, and our reliance on third parties does not relieve us of our responsibility to comply with any such standards. We and these third parties are required to comply with current good clinical practices, or cGCP, which are regulations and guidelines enforced

by the FDA, the Competent Authorities of the Member States of the European Economic Area and comparable foreign regulatory authorities for all of our products in clinical development. Regulatory authorities enforce these cGCPs through periodic inspections of trial sponsors, principal investigators and trial sites. If we or any of these third parties fail to comply with applicable cGCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA, the EMA, or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials comply with cGCP regulations. In addition, our clinical trials must be conducted with product produced under current good manufacturing practices, or cGMP, regulations. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process. We also are required to register ongoing clinical trials and post the results of

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completed clinical trials on a U.S. government-sponsored database, clinicaltrials.gov, within certain timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

Furthermore, third parties on whom we rely may also have relationships with other entities, some of which may be our competitors. In addition, these third parties are not our employees, and except for remedies available to us under our agreements with such third parties, we cannot control whether or not they devote sufficient time and resources to our on-going clinical, nonclinical and preclinical programs. If these third parties do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols, regulatory requirements or for other reasons, our clinical trials may be extended, delayed or terminated and we may not be able to 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 medicines. As a result, our results of operations and the commercial prospects for our medicines would be harmed, our costs could increase and our ability to generate revenue could be delayed.

We also rely and expect to continue 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 medicines, producing additional losses and depriving us of potential product revenue.

We contract with third parties for the manufacture of our product candidates for preclinical and clinical testing and expect to continue to do so for late-stage clinical trials and for commercialization. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or medicines or that such supply will not be available to us at an acceptable cost, which could delay, prevent or impair our development or commercialization efforts.

We do not have any manufacturing facilities. We currently rely, and expect to continue to rely, on third-party manufacturers for the manufacture of our product candidates for preclinical and clinical testing and for commercial supply of any of these product candidates for which we or our collaborators obtain marketing approval. To date, we have obtained materials for our product candidates for our ongoing preclinical and clinical testing from third-party manufacturers. Although we have long-term supply agreements in place for commercial supply of TIBSOVO® (ivosidenib) with third-party manufacturers, we purchase the rest of our required drug supply on a purchase order basis.

We may be unable to establish any further long-term supply agreements with third-party manufacturers or to do so on acceptable terms. Even if we are able to establish agreements with third-party manufacturers, reliance on third-party manufacturers entails additional risks, including:

- reliance on the third party for regulatory compliance and quality assurance;
- the possible breach of the manufacturing agreement by the third party;
- the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us; and
- reliance on the third party for regulatory compliance, quality assurance, environmental and safety and pharmacovigilance reporting.

Third-party manufacturers may not be able to comply with cGMP regulations or similar regulatory requirements on a global basis. Our failure, or the failure of our third-party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us, including fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or medicines, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our medicines and harm our business and results of operations.

Any medicines 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.

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 for bulk drug substance or

drug product. If any one of our current contract manufacturers cannot perform as agreed, we may be required to replace that manufacturer. Although we believe that there are several potential alternative manufacturers who could manufacture our product candidates, we may incur added costs and delays in identifying and qualifying any such replacement.

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

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Risks Related to Our Intellectual Property

If we are unable to obtain and maintain patent or trade secret protection for our medicines and technology, or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize medicines and technology similar or identical to ours, and our ability to successfully commercialize our medicines and technology may be adversely affected.

Our success depends in large part on our ability to obtain and maintain patent protection in the United States and other countries with respect to our proprietary medicines and technology. We seek to protect our proprietary position by filing patent applications in the United States and abroad related to our novel technologies and medicines that are important to our business. We do not yet have issued patents for all our most advanced product candidates in all markets we intend to commercialize.

The patent prosecution process is expensive and time-consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. Although we enter into non-disclosure and confidentiality agreements with parties who have access to patentable aspects of our research and development output, such as our employees, corporate collaborators, outside scientific collaborators, contract research organizations, contract manufacturers, consultants, advisors and other third parties, any of these parties may breach the agreements and disclose such output before a patent application is filed, thereby jeopardizing our ability to seek patent protection.

We have licensed patent rights, and in the future may license additional patent rights, from third parties. These licensed patent rights may be valuable to our business, and we may not have the right to control the preparation, filing and prosecution of patent applications, or to maintain the patents, covering technology or medicines underlying such licenses. We cannot be certain that these patents and applications will be prosecuted and enforced in a manner consistent with the best interests of our business. If any such licensors fail to maintain such patents, or lose rights to those patents, the rights we have licensed may be reduced or eliminated and our right to develop and commercialize any of our products that are the subject of such licensed rights could be adversely affected. In addition to the foregoing, the risks associated with patent rights that we license from third parties also apply to patent rights we own.

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. 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 medicines or that effectively prevent others from commercializing competitive technologies and medicines. 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. The laws of foreign countries may not protect our rights to the same extent as the laws of the United States. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore we cannot be certain that 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.

Assuming the other requirements for patentability are met, prior to March 2013, in the United States, the first to make the claimed invention was entitled to the patent, while outside the United States, the first to file a patent application was entitled to the patent. Beginning in March 2013, the United States transitioned to a first inventor to file system in which, assuming the other requirements for patentability are met, the first inventor to file a patent application will be entitled to the patent. We may be subject to a third-party preissuance submission of prior art to the U.S. Patent and Trademark Office, or PTO, or become involved in opposition, derivation, revocation, reexamination, post-grant and inter partes 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 products and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize medicines without infringing third-party patent rights.

Even if our patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors or other third parties from competing with us or otherwise provide us with any competitive advantage. Our competitors or other third parties may be able to circumvent our patents by developing similar or alternative technologies or products in a non-infringing manner.

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our patents may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in loss of exclusivity or in patent claims being narrowed, invalidated or held unenforceable, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and medicines. 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

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result, our intellectual property may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

We may become involved in lawsuits to protect or enforce our patents and other intellectual property rights, which could be expensive, time consuming and unsuccessful.

Competitors may infringe our patents and other intellectual property rights. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming. In addition, in an infringement proceeding, a court may decide that a patent of ours is invalid or unenforceable, or may 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. An adverse result in any litigation proceeding could put one or more of our patents at risk of being invalidated or interpreted narrowly. 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 during this type of litigation.

Third parties may initiate legal proceedings alleging that we or our collaborators 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 and intellectual property of third parties. The biotechnology and pharmaceutical industries are characterized by extensive litigation regarding patents and other intellectual property rights. We have in the past and may in the future become party to, or threatened with, adversarial proceedings or litigation regarding intellectual property rights with respect to our medicines and technology, including interference proceedings before the PTO. For example, in 2011, The Leonard and Madlyn Abramson Family Cancer Research Institute at the Abramson Cancer Center of the University of Pennsylvania initiated a lawsuit against us, one of our founders, Craig B. Thompson, M.D., and Celgene, alleging misappropriation of intellectual property and, in 2012, the Trustees of the University of Pennsylvania initiated a similar lawsuit against us and Dr. Thompson. Each of these lawsuits was settled in 2012. We are not aware of any other legal proceedings having been filed against us to date. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future. If we or one of our collaborators are found to infringe a third party's intellectual property rights, we or they could be required to obtain a license from such third party to continue developing and marketing our medicines and technology. However, we or our collaborators may not be able to obtain any required license on commercially reasonable terms or at all. Even if we or our collaborators were able to obtain a license, it could be non-exclusive, thereby giving our competitors and other third parties access to the same technologies licensed to us. We or our collaborators could be forced, including by court order, to cease developing and commercializing the infringing technology or medicine. In addition, we or our collaborators could be found liable for monetary damages. A finding of infringement could prevent us or our collaborators from commercializing our product candidates or force us to cease some of our business operations, which could materially harm our business. Claims that we or our collaborators 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 have wrongfully used or disclosed alleged trade secrets of their former employers.

Many of our employees, consultants or advisors are currently or 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, consultants and advisors do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or these individuals have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such individual's current or former employer. Litigation may be necessary to defend against these claims. If we fail in 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 defending against such claims, litigation could result in substantial costs and be a distraction to our management. Intellectual property litigation 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 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 price of our common stock. 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 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 resources and more mature and developed intellectual property portfolios. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace.

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If we are unable to protect the confidentiality of our trade secrets, our business and competitive position would be harmed.

In addition to seeking patents for some of our technology and medicines, we also rely on trade secrets, including unpatented know-how, technology and other proprietary information, to maintain our competitive position. With respect to our proprietary cellular metabolism technology platform, we consider trade secrets and know-how to be our primary intellectual property. Trade secrets and know-how can be difficult to protect. In particular, we anticipate that with respect to this technology platform, these trade secrets and know-how will over time be disseminated within the industry through independent development, the publication of journal articles describing the methodology, and the movement of personnel skilled in the art from academic to industry scientific positions.

We seek to protect these trade secrets, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, corporate collaborators, outside scientific collaborators, contract research organizations, contract manufacturers, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. In addition, some courts inside and outside the United States are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor or other third party, we would have no right to prevent them from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor or other third party, our competitive position would be harmed.

Risks Related to Regulatory Approval of Our Product Candidates and Other Legal Compliance Matters

Even if we complete necessary preclinical studies and clinical trials, the marketing approval process is expensive, time-consuming and uncertain and may prevent us from obtaining approvals for the commercialization of some or all of our product candidates. If we or our collaborators are not able to obtain, or if there are delays in obtaining, required regulatory approvals, we or they will not be able to commercialize, or will be delayed in commercializing, our product candidates, and our ability to generate revenue will be materially impaired.

Our product candidates and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, record keeping, labeling, storage, approval, advertising, promotion, sale and distribution, export and import, are subject to comprehensive regulation by the FDA and other regulatory agencies in the United States and by the EMA and comparable regulatory authorities in other countries. With the exception of IDHIFA®, we and our collaborators have not received approval to market any of our product candidates from regulatory authorities in any jurisdiction. In December 2017, we submitted an NDA to the FDA for TIBSOVO® (ivosidenib) in IDH1 mutant-positive R/R AML, which was accepted with priority review and granted a PDUFA action date of August 21, 2018, and we plan to submit an MAA to the EMA for TIBSOVO® (ivosidenib) for IDH1 mutant-positive R/R AML in the fourth quarter of 2018. Failure to obtain marketing approval for a product candidate will prevent us from commercializing the product candidate. We have only limited experience in filing and supporting the applications necessary to gain marketing approvals and expect to rely on third-party contract research organizations to assist us in this process.

Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information to the various regulatory authorities for each therapeutic indication to establish the product candidate’s safety and efficacy. Securing regulatory approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the relevant regulatory authority. 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.

The process of obtaining marketing approvals, both in the United States and abroad, is expensive, may take many years if additional clinical trials are required, 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. 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 cause delays in the approval or rejection of an application. The FDA and comparable authorities in other countries have substantial discretion in the approval process and may refuse to accept any application we submit, or may decide that our data is insufficient for approval and require additional preclinical, clinical or other studies. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent marketing approval of a product candidate. Any marketing approval we or our collaborators ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved medicine not commercially viable.

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Accordingly, if we or our collaborators experience delays in obtaining approval or if we or they fail to obtain approval of our product candidates, the commercial prospects for our product candidates may be harmed and our ability to generate revenue will be materially impaired.

Failure to obtain marketing approval in foreign jurisdictions would prevent our medicines from being marketed in such jurisdictions.

In order to market and sell our medicines in the E.U. and many other jurisdictions, we or our 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. 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, a product must be approved for reimbursement before the product can be approved for sale in that country. We or our collaborators may not obtain approvals from regulatory authorities outside the United States on a timely basis, if at all. In particular, although we plan to file an MAA with EMA for TIBSOVO® (ivosidenib) in the future, we may not be successful in obtaining EMA approval of TIBSOVO® (ivosidenib) on a timely basis, or ever. Moreover, 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 medicines in any market.

Additionally, on June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the E.U., commonly referred to as Brexit. On March 29, 2017, the country formally notified the E.U. of its intention to withdraw pursuant to Article 50 of the Lisbon Treaty. Since a significant proportion of the regulatory framework in the United Kingdom is derived from E.U. directives and regulations, the referendum could materially impact the regulatory regime with respect to the approval of our product candidates in the United Kingdom or the E.U. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would prevent us from commercializing our product candidates in the United Kingdom and/or the E.U. and restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek regulatory approval in the United Kingdom and/or E.U. for our product candidates, which could significantly and materially harm our business.

A fast track designation by the FDA may not actually lead to a faster development or regulatory review or approval process, nor does it assure approval of the product candidate by FDA.

In the United States, IDHIFA® and TIBSOVO® (ivosidenib) received fast track designation for treatment of patients with AML that harbor an IDH2 and IDH1 mutation, respectively. If a drug is intended for the treatment of a serious or life-threatening disease or condition and the drug demonstrates the potential to address unmet medical needs for this disease or condition, the drug sponsor may apply for FDA fast track designation. The FDA has broad discretion whether or not to grant fast track designation, so even if we believe a particular product candidate is eligible for such designation, the FDA may decide not to grant it. Even if our product candidates receive fast track designation, we may not experience a faster development process, review or approval, if at all, 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.

We, or any future collaborators, may not be able to obtain orphan drug designation or orphan drug exclusivity for our drug candidates and, even if we do, that exclusivity may not prevent the FDA or the EMA from approving competing drugs.

Regulatory authorities in some jurisdictions, including the United States and Europe, may designate drugs and 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 annually in the United States.

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 EMA or the FDA from approving another marketing application for the same product for that time

period. The applicable period is seven years in the United States and ten years in Europe. The European exclusivity period can be reduced to six years if a product no longer meets the criteria for orphan drug designation or if the product 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 product to meet the needs of patients with the rare disease or condition. Moreover, even after an orphan drug is approved, the FDA can subsequently approve a different product for the same condition if the FDA concludes that the later product is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care.

On August 3, 2017, the Congress passed the FDA Reauthorization Act of 2017, or FDARA. FDARA, among other things, codified the FDA's pre-existing regulatory interpretation, to require that a drug sponsor demonstrate the clinical superiority of

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an orphan drug that is otherwise the same as a previously approved drug for the same rare disease in order to receive orphan drug exclusivity. The new legislation reverses prior precedent holding that the Orphan Drug Act unambiguously requires that the FDA recognize the orphan exclusivity period regardless of a showing of clinical superiority. The FDA may further reevaluate the Orphan Drug Act and its regulations and policies. We do not know if, when, or how the FDA may change the orphan drug regulations and policies in the future, and it is uncertain how any changes might affect our business. Depending on what changes the FDA may make to its orphan drug regulations and policies, our business could be adversely impacted.

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

Any product candidate for which we or our collaborators obtain marketing approval, along with the manufacturing processes, post-approval clinical data, labeling, advertising and promotional activities for such medicine, will be subject to continual requirements of and review 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 quality control and manufacturing, quality assurance and corresponding maintenance of records and documents, and requirements regarding the distribution of samples to physicians and record keeping. Even if marketing approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the medicine may be marketed or to the conditions of approval, or contain requirements for costly post-marketing testing and surveillance to monitor the safety or efficacy of the medicine, including the requirement to implement a risk evaluation and mitigation strategy.

The FDA and other agencies, including the Department of Justice, or the DOJ, closely regulate and monitor the post-approval marketing and promotion of products to ensure that they are marketed and distributed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA and DOJ impose stringent restrictions on manufacturers' communications regarding off-label use and if we do not market our medicines for their approved indications, we may be subject to enforcement action for off-label marketing. Violations of the Federal Food, Drug, and Cosmetic Act and other statutes, including the False Claims Act, relating to the promotion and advertising of prescription drugs may lead to investigations and enforcement actions alleging violations of federal and state health care 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 medicines, manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may yield various results, including:

- restrictions on such medicine, manufacturers or manufacturing processes;
- restrictions on the labeling or marketing of a medicine;
- restrictions on distribution or use of a medicine;
- requirements to conduct post-marketing studies or clinical trials;
- warning letters or untitled letters;
- withdrawal of the medicine from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of medicines;
- damage to relationships with any potential collaborators;
- unfavorable press coverage and damage to our reputation;
- fines, restitution or disgorgement of profits or revenue;
- suspension or withdrawal of marketing approvals;
- refusal to permit the import or export of our medicines;
- product seizure;
- injunctions or the imposition of civil or criminal penalties; and
- litigation involving patients using our medicines.

Non-compliance with E.U. 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 the E.U. requirements regarding the protection of personal information can also lead to significant penalties and sanctions.

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Our relationships with healthcare providers, physicians and third-party payors will be subject to applicable anti-kickback, fraud and abuse and other healthcare laws and regulations, which, in the event of a violation, 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 healthcare providers, physicians and third-party payors 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 medicines for which we obtain marketing approval. Restrictions under applicable 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 or arranging 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 through civil whistleblower or qui tam actions, against individuals or entities for, among other things, knowingly presenting, or causing to be presented, false or fraudulent claims for payment by a federal healthcare program or making a false statement or record material to payment of a false claim or avoiding, decreasing or concealing an obligation to pay money to the federal government, with potential liability including mandatory treble damages and significant per-claim penalties, currently set at $10,781.40 to $21,562.80 per false claim;
- 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;
- the federal Physician Payments Sunshine Act requires applicable manufacturers of covered drugs to report payments and other transfers of value to physicians and teaching hospitals; and
- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws and transparency statutes, 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 products 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 are 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.

Under the CURES Act and the Trump Administration's regulatory reform initiatives, the FDA's policies, regulations and guidance may be revised or revoked and that could prevent, limit or delay regulatory approval of our product

candidates, which would impact our ability to generate revenue.

In December 2016, the 21st Century Cures Act, or Cures Act, was signed into law. The Cures Act, among other things, is intended to modernize the regulation of drugs and spur innovation, but its ultimate implementation is unclear. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability, which would adversely affect our business, prospects, financial condition and results of operations.

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We also cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative or executive action, either in the United States or abroad. For example, certain policies of the Trump administration may impact our business and industry. Namely, the Trump administration has taken several executive actions, including the issuance of a number of Executive Orders, that could impose significant burdens on, or otherwise materially delay, the FDA's ability to engage in routine regulatory and oversight activities such as implementing statutes through rulemaking, issuance of guidance, and review and approval of marketing applications. An under-staffed FDA could result in delays in the FDA's responsiveness or in its ability to review submissions or applications, issue regulations or guidance, or implement or enforce regulatory requirements in a timely fashion or at all. Moreover, on January 30, 2017, President Trump issued an Executive Order, applicable to all executive agencies, including the FDA, which requires that for each notice of proposed rulemaking or final regulation to be issued in fiscal year 2017, the agency shall identify at least two existing regulations to be repealed, unless prohibited by law. These requirements are referred to as the "two-for-one" provisions. This Executive Order includes a budget neutrality provision that requires the total incremental cost of all new regulations in the 2017 fiscal year, including repealed regulations, to be no greater than zero, except in limited circumstances. For fiscal years 2018 and beyond, the Executive Order requires agencies to identify regulations to offset any incremental cost of a new regulation and approximate the total costs or savings associated with each new regulation or repealed regulation. In interim guidance issued by the Office of Information and Regulatory Affairs within OMB on February 2, 2017, the administration indicates that the "two-for-one" provisions may apply not only to agency regulations, but also to significant agency guidance documents. In addition, on February 24, 2017, President Trump issued an executive order directing each affected agency to designate an agency official as a "Regulatory Reform Officer" and establish a "Regulatory Reform Task Force" to implement the two-for-one provisions and other previously issued executive orders relating to the review of federal regulations, however it is difficult to predict how these requirements will be implemented, and the extent to which they will impact the FDA's ability to exercise its regulatory authority. If these executive actions impose constraints on the FDA's ability to engage in oversight and implementation activities in the normal course, our business may be negatively impacted.

Current and future legislation may increase the difficulty and cost for us and any future collaborators to obtain marketing approval and commercialize our drug candidates and affect the prices we, or they, 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, among other things, prevent or delay marketing approval of our drug candidates, restrict or regulate post-approval activities and affect our ability, or the ability of any future collaborators, to profitably sell any drugs for which we, or they, obtain marketing approval. We expect that current laws, 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, or any future collaborators, may receive for any approved drugs.

Among the provisions of the Patient Protection and Affordable Care Act, or ACA, of potential importance to our business and our drug candidates are the following:

- an annual, non-deductible 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 civil False Claims Act and the federal Anti-Kickback Statute, new government investigative powers and enhanced penalties for noncompliance;
- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices to eligible beneficiaries during their coverage gap period, as a condition for a manufacturer's outpatient drugs to be covered under Medicare Part D;
- extension of manufacturers' Medicaid rebate liability;
- expansion of eligibility criteria for Medicaid programs;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;
- new requirements to report certain financial arrangements with physicians and teaching hospitals;

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

Other legislative changes have been proposed and adopted since the PPACA was enacted. These changes include the Budget Control Act of 2011, which, among other things, led to aggregate reductions to Medicare payments to providers of up to 2% per

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fiscal year that started in 2013 and will stay in effect through 2024 unless additional Congressional action is taken, and the American Taxpayer Relief Act of 2012, which, among other things, reduced Medicare payments to several types of providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used. Further, there have been several recent U.S. congressional inquiries and proposed state and federal legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products.

We expect that these healthcare reforms, as well as other healthcare reform measures that may be adopted in the future, may result in additional reductions in Medicare and other healthcare funding, more rigorous coverage criteria, new payment methodologies and additional downward pressure on the price that we receive for any approved product and/or the level of reimbursement physicians receive for administering any approved product we might bring to market. Reductions in reimbursement levels may negatively impact the prices we receive or the frequency with which our products are prescribed or administered. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. Since enactment of the ACA, there have been numerous legal challenges and Congressional actions to repeal and replace provisions of the law. In May 2017, the U.S. House of Representatives passed legislation known as the American Health Care Act of 2017. Thereafter, the Senate Republicans introduced and then updated a bill to replace the ACA known as the Better Care Reconciliation Act of 2017. The Senate Republicans also introduced legislation to repeal the ACA without companion legislation to replace it, and a “skinny” version of the Better Care Reconciliation Act of 2017. In addition, the Senate considered proposed healthcare reform legislation known as the Graham-Cassidy bill. None of these measures was passed by the U.S. Senate.

The Trump Administration has also taken executive actions to undermine or delay implementation of the ACA. In January 2017, President Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. In October 2017, the President signed a second Executive Order allowing for the use of association health plans and short-term health insurance, which may provide fewer health benefits than the plans sold through the ACA exchanges. At the same time, the Administration announced that it will discontinue the payment of cost-sharing reduction (CSR) payments to insurance companies until Congress approves the appropriation of funds for such CSR payments. The loss of the CSR payments is expected to increase premiums on certain policies issued by qualified health plans under the ACA. A bipartisan bill to appropriate funds for CSR payments was introduced in the Senate, but the future of that bill is uncertain.

More recently, with enactment of the Tax Cuts and Jobs Act of 2017, which was signed by the President on December 22, 2017, Congress repealed the “individual mandate.” The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, will become effective in 2019. According to the Congressional Budget Office, the repeal of the individual mandate will cause 13 million fewer Americans to be insured in 2027 and premiums in insurance markets may rise. Further, each chamber of the Congress has put forth multiple bills designed to repeal or repeal and replace portions of the ACA. Although none of these measures has been enacted by Congress to date, Congress may consider other legislation to repeal and replace elements of the ACA. The Congress will likely consider other legislation to replace elements of the ACA, during the next Congressional session.

We will continue to evaluate the effect that the ACA and its possible repeal and replacement could have on our business. It is possible that repeal and replacement initiatives, if enacted into law, could ultimately result in fewer individuals having health insurance coverage or in individuals having insurance coverage with less generous benefits. While the timing and scope of any potential future legislation to repeal and replace ACA provisions is highly uncertain in many respects, it is also possible that some of the ACA provisions that generally are not favorable for the research-based pharmaceutical industry could also be repealed along with ACA coverage expansion provisions.

Accordingly, such reforms, if enacted, could have an adverse effect on anticipated revenue from product candidates that we may successfully develop and for which we may obtain marketing approval and may affect our overall financial condition and ability to develop or commercialize product candidates.

The costs of prescription pharmaceuticals in the United States has also been the subject of considerable discussion in the United States, and members of Congress and the Administration have stated that they will address such costs through new legislative and administrative measures. The pricing of prescription pharmaceuticals is also subject to governmental control outside the United States. 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 candidates to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our ability to generate revenues and become profitable could be impaired.

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

We are subject to U.S. and foreign anti-corruption and anti-money laundering laws with respect to our operations and non-compliance with such laws can subject us to criminal and/or civil liability and harm our business.

We are subject to the U.S. Foreign Corrupt Practices Act of 1977, as amended, or the FCPA, the U.S. domestic bribery statute contained in 18 U.S.C. § 201, the U.S. Travel Act, the USA PATRIOT Act, and possibly other state and national anti-bribery and anti-money laundering laws in countries in which we conduct activities. Anti-corruption laws are interpreted broadly and prohibit companies and their employees, agents, third-party intermediaries, joint venture partners and collaborators from authorizing, promising, offering, or providing, directly or indirectly, improper payments or benefits to recipients in the public or private sector. We may have direct or indirect interactions with officials and employees of government agencies or government-affiliated hospitals, universities, and other organizations. In addition, we may engage third party intermediaries to promote our clinical research activities abroad and/or to obtain necessary permits, licenses, and other regulatory approvals. We can be held liable for the corrupt or other illegal activities of these third-party intermediaries, our employees, representatives, contractors, partners, and agents, even if we do not explicitly authorize or have actual knowledge of such activities.

Noncompliance with anti-corruption and anti-money laundering laws could subject us to whistleblower complaints, investigations, sanctions, settlements, prosecution, other enforcement actions, disgorgement of profits, significant fines, damages, other civil and criminal penalties or injunctions, suspension and/or debarment from contracting with certain persons, the loss of export privileges, reputational harm, adverse media coverage, and other collateral consequences. If any subpoenas, investigations, or other enforcement actions are launched, or governmental or other sanctions are imposed, or if we do not prevail in any possible civil or criminal litigation, our business, results of operations and financial condition could be materially harmed. In addition, responding to any action will likely result in a materially significant diversion of management's attention and resources and significant defense and compliance costs and other professional fees. In certain cases, enforcement authorities may even cause us to appoint an independent compliance monitor which can result in added costs and administrative burdens.

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 have a material adverse effect on the success of 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 and radioactive 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.

Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, this insurance may not provide adequate coverage against potential liabilities. 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 research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

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

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

- different regulatory requirements for approval of drugs in foreign countries;
- reduced protection for intellectual property rights;
- unexpected changes in tariffs, trade barriers and regulatory requirements;
- economic weakness, including inflation, or political instability in particular foreign economies and markets;

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- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenue, and other obligations incident to doing business in another country;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geopolitical actions, including war and terrorism or natural disasters including earthquakes, typhoons, floods and fires.

Risks Related to Employee Matters and Managing Growth

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

We are highly dependent on the principal members of our management and scientific teams, each of whom is employed "at will," meaning we or they may terminate the employment relationship at any time. We do not maintain "key person" insurance for any of our executives or other employees. The loss of the services of any of these persons could impede the achievement of our research, development and commercialization objectives.

Recruiting and retaining qualified scientific, clinical, manufacturing and sales and marketing personnel will also be critical to our success. We may not be able to attract and retain these personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors, including our scientific co-founders, 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.

Our employees may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements, which could have a material adverse effect on our business.

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with FDA regulations, provide accurate information to the FDA, comply with manufacturing standards we have established, comply with federal and state healthcare fraud and abuse laws and regulations, report financial information or data accurately, disclose unauthorized activities to us, or comply with securities laws. Employee misconduct could also involve the improper use of information obtained in the course of clinical trials, including for illegal insider trading activities, which could result in regulatory sanctions and serious harm to our reputation. We have adopted a Code of Business Conduct and Ethics, but 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 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 expect to expand our development, regulatory and future sales and marketing 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 drug development, regulatory affairs and sales and marketing. 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 company with such anticipated growth, we may not be able to effectively manage the expected expansion of our operations or recruit and train additional qualified personnel. Moreover, the expected physical expansion of our operations may lead to significant costs and may divert our management and business development resources. Any inability to manage growth could delay the execution of our business plans or disrupt our operations.

We may engage in acquisitions that could disrupt our business, cause dilution to our stockholders or reduce our financial resources.

In the future, we may enter into transactions to acquire other businesses, products or technologies. Because we have not made any acquisitions to date, our ability to do so successfully is unproven. If we do identify suitable candidates, we may not be able to make such acquisitions on favorable terms, or at all. Any acquisitions we make may not strengthen our competitive position,

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and these transactions may be viewed negatively by customers or investors. We may decide to incur debt in connection with an acquisition or issue our common stock or other equity securities to the stockholders of the acquired company, which would reduce the percentage ownership of our existing stockholders. We could incur losses resulting from undiscovered liabilities of the acquired business that are not covered by the indemnification we may obtain from the seller. In addition, we may not be able to successfully integrate the acquired personnel, technologies and operations into our existing business in an effective, timely and non-disruptive manner. Acquisitions may also divert management attention from day-to-day responsibilities, increase our expenses and reduce our cash available for operations and other uses. We cannot predict the number, timing or size of future acquisitions or the effect that any such transactions might have on our operating results.

Risks Related to Our Common Stock and Other Matters

Provisions in our corporate charter documents and under Delaware law could make an acquisition of us, 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 corporate charter and our bylaws may discourage, delay or prevent a merger, acquisition or other change in control of us 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 not all members of the board are elected at one time;
- 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 the board;
- 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 shareholder rights plan, or so-called “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 75% of the votes that all our stockholders would be entitled to cast to amend or repeal certain provisions of our charter or bylaws.

Moreover, because we are incorporated in Delaware, 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.

If securities analysts do not publish research or reports about our business or if they publish negative, or inaccurate, evaluations of our stock, the price of our stock and trading volume could decline.

The trading market for our common stock relies in part on the research and reports that industry or financial analysts publish about us or our business. If one or more of the analysts covering our business downgrade their evaluations of our stock, the price of our stock could decline. If one or more of these analysts cease to cover our stock, we could lose visibility in the market for our stock, which in turn could cause our stock price and trading volume to decline.

An active trading market for our common stock may not be sustained.

Although our common stock is listed on the NASDAQ Global Select Market, an active trading market for our shares may not be sustained. If an active market for our common stock does not continue, it may be difficult for our stockholders to sell their shares without depressing the market price for the shares or to sell their shares at all. An inactive trading market for our common stock may also impair our ability to raise capital to continue to fund our

operations by selling shares and may impair our ability to acquire other companies or technologies by using our shares as consideration.

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The price of our common stock is likely to be volatile, which could result in substantial losses for purchasers of our common stock.

The trading price of our common stock has been, and may continue to be, volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control. For example, since January 1, 2014 the price of our common stock on the NASDAQ Global Select Market has ranged from $21.70 per share to $138.85 per share. The stock market in general and the market for biopharmaceutical 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:

- regulatory actions with respect to our product candidates or our competitors' products and product candidates;
- announcements by us or our competitors of significant acquisitions, strategic partnerships, joint ventures, collaborations or capital commitments;
- the timing and results of clinical trials of product candidates;
- commencement or termination of collaborations for our development programs;
- failure or discontinuation of any of our development programs;
- results of clinical trials of product candidates 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 develop additional product candidates or products;
- actual or anticipated changes in estimates as to financial results or development timelines;
- announcement or expectation of additional financing efforts;
- sales of our common stock by us, our insiders or other stockholders;
- variations in our financial results, including fluctuations in levels of royalties on sales of IDHIFA®, or results of companies that are perceived to be similar to us;
- changes in estimates or recommendations by securities analysts, if any, that cover our stock;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, industry and market conditions; and
- the other factors described in this "Risk Factors" section.

If any of the forgoing matters were to occur, or if our operating results fall below the expectations of investors or securities analysts, the price of our common stock could decline substantially. In the past, following periods of volatility in the market price of a company's securities, securities class-action litigation often has been instituted against that company. Such litigation, if instituted against us, could cause us to incur substantial costs to defend such claims and divert management's attention and resources, which could seriously harm our business, financial condition, results of operations and prospects.

Sales of a substantial number of shares of our common stock in the public market could cause our stock price to fall.

Certain stockholders hold a substantial number of shares of our common stock. If such stockholders sell, or indicate an intention to sell, substantial amounts of our common stock in the public market, the trading price of our common stock could decline.

In addition, shares of common stock that are either subject to outstanding options or reserved for future issuance under our stock incentive plans will become eligible for sale in the public market to the extent permitted by the provisions of various vesting schedules and Rule 144 and Rule 701 under the Securities Act of 1933, as amended, or the Securities Act, and, in any event, we have filed a registration statement permitting shares of common stock issued on exercise of options to be freely sold in the public market. If these additional shares of common stock are sold, or if it is perceived that they will be sold, in the public market, the trading price of our common stock could decline.

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Certain holders of our common stock are entitled to rights with respect to the registration of their shares under the Securities Act. Registration of these shares under the Securities Act would result in the shares becoming freely tradable without restriction under the Securities Act, except for shares held by affiliates. Any sales of securities by these stockholders who have exercised registration rights could have a material adverse effect on the trading price of our common stock.

Our executive officers, directors and principal stockholders maintain the ability to significantly influence all matters submitted to stockholders for approval.

As of March 31, 2018, our executive officers, directors and a small group of stockholders, in the aggregate, beneficially owned shares representing a significant percentage of our capital stock. As a result, if these stockholders were to choose to act together, they would be able to significantly influence 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, could significantly influence the election of directors and approval of any merger, consolidation or sale of all or substantially all of our assets. This concentration of voting power could delay or prevent an acquisition of our company on terms that other stockholders may desire.

Future sales and issuances of our common stock or rights to purchase common stock could result in additional dilution of the percentage ownership of our stockholders and could cause our stock price to fall.

We expect that significant additional capital will be needed in the future to continue our planned operations. To raise capital, we may sell common stock, convertible securities or other equity securities in one or more transactions at prices and in a manner we determine from time to time. If we sell common stock, convertible securities or other equity securities in more than one transaction, investors may be materially diluted by subsequent sales. Such sales may also result in material dilution to our existing stockholders, and new investors could gain rights, preferences and privileges senior to those of holders of our common stock.

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, or the IRC, if a company 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 and other pre-change tax attributes (such as research tax credits) to offset its post-change taxable income or taxes may be limited. Our prior equity offerings and other changes in our stock ownership, some of which are outside of our control, may have resulted or could in the future result in an ownership change. We completed a review of our changes in ownership through December 31, 2017, and determined that we had a qualified ownership change since our last review as of December 31, 2011. We do not expect that this or any previous changes of ownership will result in our net operating loss carryforwards or certain other tax attributes expiring unutilized. Future ownership changes under Section 382 may limit the amount of net operating loss and tax credit carryforwards that we could potentially utilize to reduce future tax liabilities.

The recently passed comprehensive tax reform bill could adversely affect our business and financial condition.

On December 22, 2017, President Trump signed into law new legislation that significantly revised the Internal Revenue Code of 1986, as amended. The newly enacted federal income tax law, among other things, contains significant changes to corporate taxation, including reduction of the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, limitation of the tax deduction for interest expense to 30% of adjusted earnings (except for certain small businesses), limitation of the deduction for net operating losses to 80% of current year taxable income and elimination of net operating loss carrybacks, one time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, elimination of U.S. tax on foreign earnings (subject to certain important exceptions), immediate deductions for certain new investments instead of deductions for depreciation expense over time, and modifying or repealing many business deductions and credits. Notwithstanding the reduction in the corporate income tax rate, the overall impact of the new federal tax law is uncertain and our business and financial condition could be adversely affected. In addition, it is uncertain how various states will respond to the newly enacted federal tax law. The impact of this tax reform on holders of our common stock is also uncertain and could be adverse. We urge our stockholders to consult with their legal and tax advisors with respect to this legislation and the potential tax consequences of investing in or holding our common stock.

Our effective tax rate may fluctuate, and we may incur obligations in tax jurisdictions in excess of accrued amounts. We are subject to taxation in numerous U.S. states and territories. As a result, our effective tax rate is derived from a combination of applicable tax rates in the various places that we operate. In preparing our financial statements, we estimate the amount of tax that will become payable in each of such places. Nevertheless, our effective tax rate may be different than experienced in the past due to numerous factors, including passage of the newly enacted federal income tax law, changes in the mix of our profitability from state to state, the results of examinations and audits of our tax filings, our inability to secure or sustain acceptable agreements with tax authorities, changes in accounting for income taxes and changes in tax laws. Any of these factors could cause us to experience an effective tax rate significantly different from previous periods or our current expectations and may result in tax obligations in excess of amounts accrued in our financial statements.

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

We have incurred and will continue to incur significant legal, accounting and other expenses as a public company. The Sarbanes-Oxley Act of 2002, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of The NASDAQ Global Select 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. Stockholder activism, the current political environment and the current high level of government intervention and regulatory reform may lead to substantial new regulations. Our management and other personnel will need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations increase our legal and financial compliance costs and make some activities more time-consuming and costly.

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

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, capital appreciation, if any, of our common stock will be the sole source of gain for our stockholders for the foreseeable future.

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Item 6. Exhibits

Exhibit Number	Description of Exhibit	Incorporated by Reference				Filed Herewith
		Form	File Number	Date of Filing	Exhibit Number	
3.1	Restated Certificate of Incorporation	8-K	001-36014	July 30, 2013	3.1	
3.2	Amended and Restated By-Laws	8-K	001-36014	July 30, 2013	3.2	
10.1#	Form of Restricted Stock Unit Agreement under 2013 Stock Incentive Plan (for employees)					X
31.1	Certification of principal executive officer pursuant to Rule 13a 14(a)/15d 14(a) of the Securities Exchange Act of 1934, as amended					X
31.2	Certification of principal financial officer pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934, as amended.					X
32.1	Certification of principal executive officer pursuant to 18 U.S.C. §1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.					X
32.2	Certification of principal financial officer pursuant to 18 U.S.C. §1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.					X
101.INS	XBRL Instance Document					X
101.SCH	XBRL Taxonomy Extension Schema Document					X
101.CAL	XBRL Taxonomy Calculation Linkbase Document					X
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document					X
101.LAB	XBRL Taxonomy Label Linkbase Document					X
101.PRE	XBRL Taxonomy Presentation Linkbase Document					X

# Indicates management contract or compensatory plan or arrangement.

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SIGNATURES

Pursuant to the requirements 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.

AGIOS PHARMACEUTICALS, INC.

Date: May 4, 2018 By: /s/ David P. Schenkein
David P. Schenkein
President and Chief Executive Officer
(principal executive officer)

Date: May 4, 2018 By: /s/ Andrew Hirsch
Andrew Hirsch
Chief Financial Officer
(principal financial officer)