

**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, 2019

OR

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

For the transition period from \_\_\_\_\_ to \_\_\_\_\_

Commission file number 001-38137

**Akcea Therapeutics, Inc.**

(Exact name of Registrant as specified in its charter)

**Delaware**  
(State or other jurisdiction of  
incorporation or organization)

**47-2608175**  
(IRS Employer  
Identification No.)

**22 Boston Wharf Road, 9<sup>th</sup> Floor, Boston, MA 02210**  
(Address of principal executive offices, including zip code)

**617-207-0202**  
(Registrant's telephone number, including area code)

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

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

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, smaller reporting company or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company" and "emerging growth company" in Rule 12b-2 of the Exchange Act:

Large accelerated filer	<input type="checkbox"/>	Accelerated filer	<input checked="" type="checkbox"/>
Non-accelerated filer	<input type="checkbox"/>	Smaller reporting company	<input type="checkbox"/>
		Emerging growth company	<input checked="" type="checkbox"/>

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

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12(b)-2 of the Securities Exchange Act of 1934). Yes  No

The number of shares of common stock outstanding as of May 2, 2019 was 92,770,397.

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock	AKCA	NASDAQ

**AKCEA THERAPEUTICS, INC.**  
**FORM 10-Q**  
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**TRADEMARKS**

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**AKCEA THERAPEUTICS, INC.**  
**CONDENSED CONSOLIDATED BALANCE SHEETS**  
(In thousands, except share and per share data)  
(Unaudited)

	March 31, 2019	December 31, 2018
<b>ASSETS</b>		
Current assets:		
Cash and cash equivalents	\$ 201,027	\$ 86,454
Short-term investments	120,765	166,155
Accounts receivable	10,269	4,597
Receivable from Ionis Pharmaceuticals, Inc.	7,206	—
Other current assets	11,618	10,029
Total current assets	350,885	267,235
Property, plant and equipment, net	5,336	5,696
Operating lease right-of-use-assets	11,602	—
Intangible assets, net	87,468	88,914
Deposits and other assets	3,426	3,416
Total assets	<u>\$ 458,717</u>	<u>\$ 365,261</u>
<b>LIABILITIES AND STOCKHOLDERS' EQUITY</b>		
Current liabilities:		
Accounts payable	\$ 6,153	\$ 12,068
Payable to Ionis Pharmaceuticals, Inc.	—	18,901
Accrued compensation	6,300	8,583
Accrued liabilities	17,255	14,787
Current portion of deferred revenue	21,539	25,354
Other current liabilities	1,863	968
Total current liabilities	53,110	80,661
Long-term portion of lease liabilities	15,018	4,442
Long-term portion of deferred revenue	1,725	3,434
Total liabilities	69,853	88,537
Stockholders' equity:		
Common stock, \$0.001 par value; 125,000,000 shares authorized at March 31, 2019 and December 31, 2018; 92,635,374 and 89,345,978 shares issued and outstanding at March 31, 2019 and December 31, 2018, respectively.	93	89
Additional paid-in capital	883,653	799,001
Accumulated other comprehensive loss	(27)	(324)
Accumulated deficit	(494,855)	(522,042)
Total stockholders' equity	388,864	276,724
Total liabilities and stockholders' equity	<u>\$ 458,717</u>	<u>\$ 365,261</u>

See accompanying notes.

**AKCEA THERAPEUTICS, INC.**  
**CONDENSED CONSOLIDATED STATEMENTS OF OPERATIONS**  
(In thousands, except for share and per share data)  
(Unaudited)

	Three Months Ended March 31,	
	2019	2018
<b>Revenue:</b>		
Product revenue, net	\$ 6,754	\$ —
Research and development and license revenue under collaborative agreement	157,062	17,108
Total revenue	<u>163,816</u>	<u>17,108</u>
<b>Expenses:</b>		
Cost of sales - product	1,041	—
Cost of sales - intangible asset amortization	1,403	—
Research and development	99,619	27,970
Selling, general and administrative	44,602	19,465
Net loss share from commercial activities under arrangement with Ionis Pharmaceuticals, Inc.	(9,056)	—
Total expenses	<u>137,609</u>	<u>47,435</u>
Income (loss) from operations	26,207	(30,327)
<b>Other income (expense):</b>		
Investment income	1,224	868
Other expense	(112)	(168)
Income (loss) before income tax expense	27,319	(29,627)
Income tax expense	(132)	—
Net income (loss)	<u>\$ 27,187</u>	<u>\$ (29,627)</u>
Net income (loss) per share of common stock owned by Ionis, basic	<u>\$ 0.35</u>	<u>\$ (0.44)</u>
Weighted-average shares of common stock outstanding owned by Ionis, basic	<u>68,581,967</u>	<u>45,447,879</u>
Net income (loss) per share of common stock owned by others, basic	<u>\$ 0.15</u>	<u>\$ (0.44)</u>
Weighted-average shares of common stock outstanding owned by others, basic	<u>22,126,363</u>	<u>21,171,372</u>
Net income (loss) per share of common stock owned by Ionis, diluted	<u>\$ 0.34</u>	<u>\$ (0.44)</u>
Weighted-average shares of common stock outstanding owned by Ionis, diluted	<u>68,581,967</u>	<u>45,447,879</u>
Net income (loss) per share of common stock owned by others, diluted	<u>\$ 0.15</u>	<u>\$ (0.44)</u>
Weighted-average shares of common stock outstanding owned by others, diluted	<u>25,545,975</u>	<u>21,171,372</u>

See accompanying notes.

**AKCEA THERAPEUTICS, INC.**  
**CONDENSED CONSOLIDATED STATEMENTS OF COMPREHENSIVE INCOME (LOSS)**  
**(In thousands)**  
**(Unaudited)**

	<b>Three Months Ended</b>	
	<b>March 31,</b>	
	<b>2019</b>	<b>2018</b>
Net income (loss)	\$ 27,187	\$ (29,627)
Unrealized gains (losses) on investments, net of tax	212	(45)
Currency translation adjustment	85	28
Comprehensive income (loss)	<u>\$ 27,484</u>	<u>\$ (29,644)</u>

See accompanying notes.

**AKCEA THERAPEUTICS, INC.**  
**CONDENSED CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY**  
(In thousands, except share amounts)  
(Unaudited)

For the Three Months Ended March 31, 2019

Description	Common Stock		Additional Paid In Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount				
<b>Balance at December 31, 2018</b>	89,346	\$ 89	\$ 799,001	\$ (324)	\$ (522,042)	\$ 276,724
Net income	—	—	—	—	27,187	27,187
Change in unrealized gains (losses), net of tax	—	—	—	212	—	212
Currency translation adjustment	—	—	—	85	—	85
Exercise of common stock options	434	1	4,205	—	—	4,206
Issuance of common stock in connection with employee stock purchase plan	18	0	382	—	—	382
Issuance of common stock in connection with Ionis sublicense fee	2,837	3	74,997	—	—	75,000
Distribution to Ionis	—	—	(13,492)	—	—	(13,492)
Stock-based compensation expense	—	—	18,560	—	—	18,560
<b>Balance at March 31, 2019</b>	<u>92,635</u>	<u>\$ 93</u>	<u>\$ 883,653</u>	<u>\$ (27)</u>	<u>\$ (494,855)</u>	<u>\$ 388,864</u>

For the Three Months Ended March 31, 2018

Description	Common Stock		Additional Paid In Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount				
<b>Balance at December 31, 2017</b>	66,542	\$ 67	\$ 464,430	\$ (451)	\$ (296,221)	\$ 167,825
Net loss	—	—	—	—	(29,627)	(29,627)
Change in unrealized gains (losses), net of tax	—	—	—	(45)	—	(45)
Currency translation adjustment	—	—	—	28	—	28
Exercise of common stock options	246	0	1,617	—	—	1,617
Issuance of common stock in connection with employee stock purchase plan	16	0	118	—	—	118
Stock-based compensation expense	—	—	6,384	—	—	6,384
<b>Balance at March 31, 2018</b>	<u>66,804</u>	<u>\$ 67</u>	<u>\$ 472,549</u>	<u>\$ (468)</u>	<u>\$ (325,848)</u>	<u>\$ 146,300</u>

See accompanying notes.

**AKCEA THERAPEUTICS, INC.**  
**CONDENSED CONSOLIDATED STATEMENTS OF CASH FLOWS**  
(In thousands)  
(Unaudited)

	Three Months Ended March 31,	
	2019	2018
<b>Operating activities:</b>		
Net income (loss)	\$ 27,187	\$ (29,627)
Adjustments to reconcile net income (loss) to net cash provided by (used in) operating activities:		
Depreciation	207	27
Amortization of intangibles	1,446	30
Amortization of discount/premium on investment securities, net	(229)	149
Non-cash sublicensing expense	75,000	—
Stock-based compensation expense	18,560	6,384
Changes in operating assets and liabilities:		
Accounts receivable	(5,672)	5,413
Other current and long-term assets	(1,269)	(4,326)
Accounts payable	(4,673)	197
Payable/receivable to/from Ionis Pharmaceuticals, Inc.	(26,165)	13,372
Accrued compensation	(2,283)	(310)
Accrued liabilities	2,063	5,833
Income taxes payable	(56)	63
Deferred revenue	(5,524)	(13,968)
Net cash provided by (used in) operating activities	78,592	(16,763)
<b>Investing activities:</b>		
Purchases of short-term investments	(13,858)	(9,906)
Proceeds from sale of short-term investments	59,689	36,447
Purchase of property, plant and equipment	(1,031)	—
Net cash provided by investing activities	44,800	26,541
<b>Financing activities:</b>		
Proceeds from exercise of common stock options and employee stock purchase plan issuances	4,588	1,724
Distribution to Ionis	(13,492)	—
Net cash provided by (used in) financing activities	(8,904)	1,724
Effect of exchange rates on cash	85	38
Net increase (decrease) in cash and cash equivalents	114,573	11,540
Cash, cash equivalents and restricted cash at beginning of period	88,838	58,367
Cash, cash equivalents and restricted cash at end of period	\$ 203,411	\$ 69,907
<b>Supplemental disclosures of non-cash financing activities:</b>		
Unpaid deferred offering costs	\$ —	\$ 450

See accompanying notes.

The following table presents the line items and amounts of cash, cash equivalents and restricted cash reported within the condensed consolidated balance sheets:

	<u>March 31,</u> <u>2019</u>	<u>March 31,</u> <u>2018</u>
Cash and cash equivalents	\$ 201,027	\$ 69,907
Restricted cash included in deposits and other assets	2,384	—
Total cash, cash equivalents and restricted cash	<u>\$ 203,411</u>	<u>\$ 69,907</u>

See accompanying notes.

**AKCEA THERAPEUTICS, INC.**  
**NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS**  
**March 31, 2019**

**1. Organization and Basis of Presentation**

We were incorporated in Delaware in December 2014. We were organized by Ionis Pharmaceuticals, Inc., or Ionis, to focus on developing and commercializing drugs to treat patients with rare and serious diseases. On July 19, 2017, we completed our initial public offering, or IPO. As of March 31, 2019, Ionis owned approximately 76% of our common stock and is our majority shareholder. Prior to our IPO, we were wholly owned by Ionis.

The accompanying condensed consolidated financial statements have been prepared in conformity with accounting principles generally accepted in the United States of America, or U.S. GAAP.

The condensed consolidated financial statements include the accounts of Akcea Therapeutics, Inc. and our wholly owned subsidiaries ("we," "our," and "us"). All intercompany transactions and balances were eliminated in consolidation. We included all normal recurring adjustments in the financial statements, which we considered necessary for a fair presentation of our financial position and our operating results and cash flows for the interim periods ended March 31, 2019 and 2018. Results for the interim periods are not necessarily indicative of the results for the entire year. For more complete financial information, these financial statements, and notes thereto, should be read in conjunction with the audited financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2018.

In accordance with Accounting Standard Codification, or ASC, 205-40, *Going Concern*, we evaluated whether there are conditions and events, considered in the aggregate, that raise substantial doubt about our ability to continue as a going concern within one year after the date that the condensed consolidated financial statements are issued. We have incurred losses since our inception and have funded our cash flow deficits primarily through the issuance of capital stock and the proceeds from licensing and collaboration agreements. As of March 31, 2019, we had an accumulated deficit of \$494.9 million. During the three months ended March 31, 2019, we generated income of \$27.2 million and provided \$78.6 million of cash from operations. We expect to generate operating losses and negative operating cash flows for the foreseeable future. The transition to sustained profitability is dependent upon the successful development, approval, and commercialization of our products and product candidates and the achievement of a level of revenue adequate to support our cost structure. We believe that our currently available funds of \$321.8 million as of March 31, 2019, cash expected to be generated from sales of TEGSEDI, which has been approved in the U.S., the EU and Canada, and cash expected to be generated from sales of WAYLIVRA, which has received conditional approval in the EU, will be sufficient to fund our operations through at least the next 12 months from the issuance of this Quarterly Report on Form 10-Q. Management's belief with respect to its ability to fund operations is based on estimates that are subject to risks and uncertainties. If actual results are different from management's estimates, we may need to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and commercialize our drugs even if we would otherwise prefer to develop and commercialize the drugs ourselves.

**2. Summary of Significant Accounting Policies**

The accounting policies followed in the preparation of the interim condensed consolidated financial statements are consistent in all material respects with those presented in Note 2 to our financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2018.

***Use of Estimates***

The preparation of financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities, the disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of revenue and expenses during the reporting periods. Significant estimates and assumptions reflected in these financial statements include, but are not limited to, revenue recognition, the accrual for research and development expenses and prior to our IPO, the valuation of common stock. Estimates are periodically reviewed in light of changes in facts, circumstances and experience. Changes in estimates are recorded in the period in which they become known. Actual results could differ from those estimates.

***Translation of Foreign Currency***

For our foreign subsidiaries that report in a functional currency other than U.S. dollars, we translate their assets and liabilities into U.S. dollars using the exchange rate at the balance sheet date. We translate revenue and expenses at the monthly average exchange rates for the period. We translate transactions in our capital accounts at the historic exchange rate in effect at the date of the transaction. We include foreign currency translation adjustments as a component of accumulated other comprehensive income (loss) within the condensed consolidated statements of comprehensive income (loss).

## **Revenue Recognition**

### *Collaboration and License Revenue*

In May 2014, the Financial Accounting Standards Board, or FASB, issued Accounting Standards Update, or ASU, No. 2014-09, which amended the guidance for accounting for revenue from contracts with customers. Under Topic 606, an entity recognizes revenue when its customer obtains control of promised goods or services in an amount that reflects the consideration which the entity expects to receive in exchange for those goods or services.

To determine revenue recognition for arrangements that an entity determines are within the scope of Topic 606, the entity performs the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) the entity satisfies a performance obligation. At contract inception, once the contract is determined to be within the scope of Topic 606, we assess the goods or services promised within each contract and determine those that are performance obligations, then assess whether each promised good or service is distinct. When we offer options for additional goods or services, such as an option to license a drug in the future or for additional goods or services to be provided in the future, we evaluate whether such options are material rights that should be treated as additional performance obligations. We typically have concluded that the option to license a drug or the options for additional goods or services that may be requested in the future under our collaboration agreement are not material rights as the amounts attributable to such options represent standalone selling price, and therefore no consideration is allocated to these items at the inception of an agreement. When a partner exercises its option to license a drug or requests the additional goods or services, a new performance obligation is created for that item. Once performance obligations are identified, we then recognize as revenue the amount of the transaction price that we allocated to the respective performance obligation when (or as) each performance obligation is satisfied, either at a point in time or over time. If the performance obligation is satisfied over time, we recognize revenue based on the use of an output or input method. As of March 31, 2019, we have three revenue agents: our strategic collaboration, option and license agreement, or collaboration agreement, with Novartis Pharma AG, or Novartis, which we entered into in January 2017, our collaboration and license agreement with PTC Therapeutics International Limited, or PTC Therapeutics, which we entered into in August 2018, and commercial product revenue related to TEGSEDI sales subsequent to product launch in the fourth quarter of 2018. For a complete discussion of the accounting related to our revenue streams, see Note 6, *Strategic Collaboration with Novartis*, Note 8, *Collaboration and License Agreement with PTC Therapeutics*, and the section below entitled Product Revenue, Net.

### *Product Revenue, Net*

Subsequent to regulatory approval in Europe on July 11, 2018 and FDA approval in the U.S. on October 5, 2018, in the fourth quarter of 2018, we began to sell TEGSEDI in the U.S. and Europe. In the U.S., the product is distributed through an exclusive distribution agreement with a third-party logistics (3PL) company that takes title to the product and represents our sole customer in the U.S. Our U.S. customer distributes TEGSEDI to a specialty pharmacy and a specialty distributor (collectively referred to as “wholesalers”), who then distribute the product to health care providers and patients. In Europe, the product is currently distributed through a non-exclusive distribution model with a 3PL that takes title to the product and currently is our sole customer in Europe. Our customer then distributes TEGSEDI to hospitals and pharmacies in Europe.

Revenue from product sales are recognized when the customer obtains control of our product, which occurs upon transfer of title to the customer. We record shipping and handling costs within cost of goods sold on our consolidated statement of operations. We classify payments to customers or other parties in the distribution channel for services that are distinct and priced at fair value as selling, general and administrative expenses in our consolidated statements of operations. Payments to customers or other parties in the distribution channel that do not meet those criteria are classified as a reduction of revenue, as discussed further below. Taxes collected from customers relating to product sales and remitted to governmental authorities are excluded from revenue. We have elected not to adjust consideration for the effects of a significant financing component when the period between the transfer of a promised good or service to the customer and when the customer pays for that good or service will be one year or less. Our payment terms are generally between thirty to ninety days.

### *Reserves for Variable Consideration*

Revenues from product sales are recorded at the net sales price (transaction price), which includes estimates of variable consideration for which reserves are established and which result from discounts, returns, chargebacks, rebates, co-pay assistance and other allowances that are offered within contracts between us and our customers, wholesalers, health care providers and other indirect customers relating to the sale of TEGSEDI. These reserves are based on the amounts earned or to be claimed on the related sales and are classified as reductions of accounts receivable (if the amount is payable to the customer) or a current liability (if the amount is payable to a party other than the customer). Where appropriate, these estimates take into consideration a range of possible outcomes that are probability-weighted for relevant factors such as our historical experience, current contractual and statutory requirements, specific known market events and trends, industry data and forecasted customer buying and payment patterns. Overall, product

revenue net of these reserves reflect our best estimates of the amount of consideration to which we are entitled based on the terms of the contract. The amount of variable consideration that is included in the transaction price may be constrained and is included in the net sales price only to the extent that it is considered probable that a significant reversal in the amount of the cumulative revenue recognized will not occur in a future period. Actual amounts of consideration ultimately received may differ from our estimates. If actual results in the future vary from our estimates, we will adjust these estimates, which would affect net product revenue and earnings in the period such variances become known.

The following are the components of variable consideration related to product revenue:

*Chargebacks:* In the U.S., we estimate obligations resulting from contractual commitments with the government and other entities to sell products to qualified healthcare providers at prices lower than the list prices charged to our U.S. customer. Our U.S. customer charges us for the difference between what they pay for the product and the selling price to the qualified healthcare providers. We record reserves for these chargebacks related to product sold to our U.S. customer during the reporting period, as well as our estimate of product that remains in the distribution channel at the end of the reporting period that we expect will be sold to qualified healthcare providers in future periods.

*Government rebates:* We are subject to discount obligations under government programs, including Medicaid programs and Medicare in the United States and we record reserves for government rebates based on statutory discount rates and estimated utilization in the period in which revenue is recognized. We estimate Medicaid and Medicare rebates based upon estimated payer mix. These reserves are recorded in the same period the related revenue is recognized, resulting in a reduction of product revenue and the establishment of a liability that is included in accrued expenses on our consolidated balance sheet. For Medicare, we also estimate the number of patients in the prescription drug coverage gap for whom we will owe an additional liability under the Medicare Part D program. On a quarterly basis, we update our estimates and record any adjustments in the period that we identify the adjustments.

*Trade discounts and allowances:* We provide customary invoice discounts on TEGSEDI sales to our U.S. customer for prompt payment that are recorded as a reduction of revenue in the period the related product revenue is recognized. In addition, we receive and pay for various distribution services from our U.S. customer and wholesalers in the U.S. distribution channel. For services that are either not distinct from the sale of our product or for which we cannot reasonably estimate the fair value, such fees are classified as a reduction of product revenue.

*Product Returns:* Our U.S. customer has return rights and the wholesalers have limited return rights primarily related to the product's expiration date. We estimate the amount of product sales that may be returned and record the estimate as a reduction of revenue and a refund liability in the period the related product revenue is recognized. Based on the distribution model for TEGSEDI, contractual inventory limits with our customer and wholesalers and the price of TEGSEDI, we believe there will be minimal returns. Our customer only takes title to the product once it receives an order from a hospital or pharmacy and therefore does not maintain any inventory of TEGSEDI. Therefore, there is limited return risk and the Company has not recorded any return estimate in the transaction price for TEGSEDI sold in Europe.

*Other incentives:* In the U.S., other incentives include co-payment assistance we provide to patients with commercial insurance that have coverage and reside in states that allow co-payment assistance. The calculation of the accrual for co-pay assistance is based on an estimate of claims and the cost per claim that we expect to receive associated with product that has been recognized as revenue. The estimate is recorded as a reduction of revenue in the same period the related revenue is recognized.

During the three months ended March 31, 2019, we recorded TEGSEDI product revenue, net, of \$6.8 million. The following table summarizes balances and activity in each of the product revenue allowance and reserve categories for the three months ended March 31, 2019 (in thousands):

	Chargebacks, discounts and fees	Government and other rebates	Returns	Total
Balance at December 31, 2018	\$ 50	\$ 293	\$ 5	\$ 348
Provision related to current period sales	155	375	52	582
Adjustment related to prior period sales	—	(30)	—	(30)
Credit or payments made during the period	(104)	—	—	(104)
Balance at March 31, 2019	<u>\$ 101</u>	<u>\$ 638</u>	<u>\$ 57</u>	<u>\$ 796</u>

## Leases

### *Topic 842 Adoption*

In February 2016, the FASB issued amended accounting guidance related to lease accounting. This guidance supersedes the lease requirements we previously followed in Accounting Standards Codification, or ASC, Topic 840, *Leases*, or Topic 840, and created a new lease accounting standard, Topic 842, *Leases*, or Topic 842. Under Topic 842, an entity will record all leases with a term longer than one year on its balance sheet. Further, an entity will record a liability with a value equal to the present value of payments it will make over the life of the lease (lease liability) and an asset representing the underlying leased asset (right-of-use asset). The new accounting guidance requires entities to determine if its leases are operating or financing leases. Entities will recognize expense for operating leases on a straight-line basis as an operating expense. If an entity determines a lease is a financing lease, it will record both interest and amortization expense and generally the expense will be higher in the earlier periods of the lease.

We adopted Topic 842 on January 1, 2019 and adjusted our opening balance sheet on that date to record our right-of-use operating lease assets and operating lease liabilities. We adopted Topic 842 using the available practical expedients permitted under the transition guidance within the new standard, which among other things, allowed us to carry forward historical lease classification of those leases we had in place as of January 1, 2019. The adoption did not have a significant impact on our financial statements. Results for the three months ended March 31, 2019 are presented under Topic 842. Results for the three months ended March 31, 2018 are presented in accordance with our historic accounting under Topic 840.

The impact of the adoption of Topic 842 on the accompanying Consolidated Balance Sheet as of January 1, 2019 was as follows (in thousands):

	December 31, 2018	Adjustment due to adoption of Topic 842	January 1, 2019
Operating lease right-of-use-assets	—	11,932	11,932
Other current liabilities	968	1,029	1,997
Long-term portion of lease liabilities	4,442	10,915	15,357

### *Leases*

We determine if an arrangement contains a lease at inception. We currently have operating leases. We recognize a right-of-use operating lease asset and associated short and long-term operating lease liability for operating leases greater than one year on our condensed consolidated balance sheet. We calculate our right-of-use operating lease asset and operating lease liability based on the present value of the future minimum lease payments we will pay over the lease term. We determine the lease term at the commencement date of the lease, and we include renewal options in the lease term if we are reasonably certain that we will exercise the option. As our current leases do not provide an implicit interest rate, we used our incremental borrowing rate, based on the information available at the date we adopted Topic 842, in determining the present value of future payments. We estimate the incremental borrowing rate based on the observed interest rates for secured debt issued by companies with similar credit ratings and with similar terms. Our right-of-use operating lease asset also includes any lease payments we made and excludes any tenant improvement allowances we received.

We recognize rent expense for the lease components of our operating leases on a straight-line basis over the term of our lease. We recognize non-lease components and non-components, such as common area maintenance expenses, in the period we incur the expense.

### *New Accounting Pronouncements - Recently Issued*

In June 2016, the FASB issued guidance that changes the measurement of credit losses for most financial assets and certain other instruments. If we have credit losses, this updated guidance requires us to record allowances for these instruments under a new expected credit loss model. This model requires us to estimate the expected credit loss of an instrument over its lifetime, which represents the portion of the amortized cost basis we do not expect to collect. The new guidance requires us to remeasure our allowance in each reporting period we have credit losses. The new standard is effective for annual and interim periods beginning after December 15, 2019. Early adoption is permitted for periods beginning after December 15, 2018. When we adopt the new standard, we will make any adjustments to beginning balances through a cumulative-effect adjustment to accumulated deficit on that date. We plan to adopt this guidance on January 1, 2020. We are currently assessing the effects it will have on our condensed consolidated financial statements and disclosures.

In August 2018, the FASB issued clarifying guidance on how to account for implementation costs related to hosted cloud-servicing arrangements. The guidance states that if these fees qualify to be capitalized and amortized over the service period, they need to be expensed in the same line item as the service expense and recognized in the same balance sheet category. The update can be applied either retrospectively or prospectively to all implementation costs incurred after the date of adoption. The updated guidance is effective for fiscal years beginning after December 15, 2019, and interim periods within those fiscal years. Early adoption is permitted in any interim period. We are currently assessing the effects this updated guidance could have on our condensed consolidated financial statements and timing of potential adoption.

In August 2018, the FASB updated its disclosure requirements related to Level 1, 2 and 3 fair value measurements. The update included deletion and modification of certain disclosure requirements and additional disclosure related to Level 3 measurements. The guidance is effective for fiscal years beginning after December 15, 2019 and early adoption is permitted. We adopted this updated guidance on January 1, 2019 and it did not have a significant impact on our disclosures.

In November 2018, the FASB issued clarifying guidance of the interaction between the collaboration accounting guidance and the new revenue recognition guidance we adopted on January 1, 2018 (Topic 606). Below is the clarifying guidance and how we will implement it (in italics):

1) When a participant is considered a customer in a collaborative arrangement, all of the associated accounting under Topic 606 should be applied

- *We will apply all of the associated accounting under Topic 606 when we determine a participant in a collaborative arrangement is a customer*

2) Adds “unit of account” concept to collaboration accounting guidance to align with Topic 606. The “unit of account” concept is used to determine if revenue is recognized or if a contra expense is recognized from consideration received under a collaboration

- *We will use the “unit of account” concept when we receive consideration under a collaboration to determine when we recognize revenue or a contra expense*

3) The clarifying guidance precludes us from recognizing revenue under Topic 606 when we determine a transaction with a collaborative partner is not a customer and is not directly related to the sales to third parties

- *When we conclude a collaboration partner is not a customer and is not directly related to the sales to third parties, we will not recognize revenue for the transaction*

The updated guidance is effective for public entities for fiscal years beginning after December 15, 2019, and interim periods within those fiscal years. Early adoption is permitted. We plan to adopt this guidance on January 1, 2020. We are currently assessing the effects it will have on our condensed consolidated financial statements and disclosures.

### 3. Investments and Fair Value Measurements

#### Investments

As of March 31, 2019 and December 31, 2018, we primarily invested our excess cash in debt instruments of the U.S. Treasury, financial institutions, corporations and U.S. government agencies with strong credit ratings and an investment grade rating at or above A-1, P-1 or F-1 by Moody's, S&P or Fitch, respectively. We have established guidelines relative to diversification and maturities that maintain safety and liquidity. We periodically review and modify these guidelines to maximize trends in yields and interest rates without compromising safety and liquidity.

The following is a summary of our investments at March 31, 2019 and December 31, 2018 (in thousands):

March 31, 2019	Cost	Gross Unrealized		Estimated Fair Value
		Gains	Losses	
Available-for-sale securities:				
Corporate debt securities	\$ 54,414	\$ 4	\$ (14)	\$ 54,404
Debt securities issued by U.S. government agencies	58,371	23	(2)	58,392
Total securities with a maturity of one year or less	\$ 112,785	\$ 27	\$ (16)	\$ 112,796
Debt securities issued by U.S. government agencies	7,961	8	—	7,969
Total securities with a maturity of one to two years	7,961	8	—	7,969
Total available-for-sale securities	\$ 120,746	\$ 35	\$ (16)	\$ 120,765

December 31, 2018	Cost	Gross Unrealized		Estimated Fair Value
		Gains	Losses	
Available-for-sale securities:				
Corporate debt securities	\$ 81,770	\$ —	\$ (151)	\$ 81,619
Debt securities issued by U.S. government agencies	85,578	—	(42)	85,536
Total securities with a maturity of one year or less	\$ 167,348	\$ —	\$ (193)	\$ 167,155

We recorded unrealized gains (losses) related to the securities listed above as of March 31, 2019 and December 31, 2018. We believe that the decline in value of some of our securities is temporary and primarily related to the change in market interest rates since purchase. We believe it is more likely than not that we will be able to hold our debt securities to maturity. Therefore, we anticipate a full recovery of the amortized cost basis of our debt securities at maturity.

All of our available-for-sale securities are available to us for use in our current operations. As a result, we categorized all of these securities as current assets even though the stated maturity of some individual securities may be one year or more beyond the balance sheet date.

### Fair Value Measurements

The following tables present the investments we held at March 31, 2019 and December 31, 2018 that are regularly measured and carried at fair value. The table segregates each security by the level within the fair value hierarchy of the valuation techniques we utilized to determine the respective securities' fair value (in thousands):

	At March 31, 2019	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Money market funds (1)	\$ 74,541	\$ 74,541	\$ —
Corporate debt securities	54,404	—	54,404
Debt securities issued by U.S. government agencies (3)	66,361	—	66,361
Total	\$ 195,306	\$ 74,541	\$ 120,765

	At December 31, 2018	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Money market funds (1)	\$ 82,343	\$ 82,343	\$ —
Corporate debt securities (2)	81,619	—	81,619
Debt securities issued by U.S. government agencies (3)	85,536	—	85,536
Total	\$ 249,498	\$ 82,343	\$ 167,155

- (1) Included in cash and cash equivalents on our condensed consolidated balance sheets.
- (2) At December 31, 2018, \$1.0 million was included in cash and cash equivalents on our condensed consolidated balance sheet, with the difference included in short-term investments on our condensed consolidated balance sheet.
- (3) Included in short-term investments on our condensed consolidated balance sheets.

#### 4. Property, Plant and Equipment

The following table presents property and equipment, at cost, and related accumulated depreciation (in thousands):

	<u>March 31,</u> <u>2019</u>	<u>December 31,</u> <u>2018</u>
Furniture and fixtures	\$ 1,611	\$ 1,611
Computer equipment and software	139	102
Leasehold improvements	4,013	4,213
Total property and equipment, at cost	5,763	5,926
Less accumulated depreciation and amortization	(427)	(230)
Total property and equipment, net	<u>\$ 5,336</u>	<u>\$ 5,696</u>

Total depreciation expense amounted to \$0.2 million and \$27 thousand for the three months ended March 31, 2019 and 2018, respectively. As part of the operating lease for our new corporate headquarters, the landlord has provided a tenant improvement allowance of \$3.6 million which is included in our leasehold improvements.

#### 5. Intangible Assets, net

The following table presents intangible assets (in thousands):

	<u>March 31,</u> <u>2019</u>	<u>December 31,</u> <u>2018</u>	<u>Estimated</u> <u>useful life</u>
Acquired and in-licensed rights	\$ 2,262	\$ 2,262	7 - 21 Years
Capitalized regulatory approval milestones	90,000	90,000	16 Years
Less accumulated amortization	(4,794)	(3,348)	
Total intangible assets, net	<u>\$ 87,468</u>	<u>\$ 88,914</u>	

The Company recorded \$1.4 million and \$30 thousand, respectively, in amortization expense related to intangible assets during the three months ended March 31, 2019 and 2018. Estimated future amortization expense for intangible assets as of March 31, 2019 is as follows (in thousands):

	<u>Total</u>
2019	\$ 4,417
2020	5,879
2021	5,861
2022	5,856
2023	5,843
Thereafter	59,612
	<u>\$ 87,468</u>

The weighted average remaining amortizable life of our patents was 12.39 years at March 31, 2019.

For additional detail of Akcea's license agreements with Ionis see Note 7, *License Agreements and Services Agreement with Ionis*.

## 6. Strategic Collaboration with Novartis

In January 2017, we initiated a strategic collaboration with Novartis for the development and commercialization of AKCEA-APO(a)-LRx and AKCEA-APOCIII-LRx. Under the Novartis collaboration, Novartis has an exclusive option to further develop and commercialize these drugs. We are responsible for completing a Phase 2 program, conducting an end-of-Phase 2 meeting with the United States Food and Drug Administration, or FDA, and providing initial quantities of the active pharmaceutical ingredient, or API, for each drug. If Novartis exercises its option for one of these drugs, Novartis will be responsible for all further global development, regulatory and co-commercialization activities and costs for such drug. We received a \$75.0 million upfront payment in the first quarter of 2017, of which we retained \$60.0 million and we paid Ionis \$15.0 million as a sublicense fee under our Cardiometabolic License Agreement with Ionis.

At commencement of our strategic collaboration, we identified the following four distinct performance obligations:

- Development activities for AKCEA-APO(a)-LRx;
- Development activities for AKCEA-APOCIII-LRx;
- API for AKCEA-APO(a)-LRx; and
- API for AKCEA-APOCIII-LRx.

The development activities and the supply of API are distinct because Novartis or another third party could provide these items without our assistance.

We determined the transaction price for the Novartis collaboration was \$108.4 million, comprised of the following:

- \$75.0 million from the upfront payment we received;
- \$28.4 million for the premium paid by Novartis, which represents the excess of the fair value Ionis received from Novartis' purchase of Ionis' stock at a premium in the first quarter of 2017; and
- \$5.0 million for the premium Novartis would have paid to purchase Ionis' stock if we did not complete our IPO within 15 months of the inception of the agreement.

We are recognizing the \$75.0 million upfront payment plus the premium paid by Novartis from its purchase of Ionis' stock and the premium associated with Novartis' obligation to purchase Ionis' stock if we did not complete our IPO because we are the party providing the services and API under the collaboration agreement.

None of the options or development or regulatory milestone payments under this agreement were included in the upfront transaction price determined in January 2017 as all payments are fully constrained. As part of our evaluation of the constraint, we considered numerous factors, including the fact that achievement of the milestones is outside of our control and contingent upon the success of our clinical trials, Novartis' efforts, and the receipt of regulatory approval. We will re-evaluate the transaction price, including estimated variable consideration included in the transaction price and all constrained amounts, in each reporting period and as uncertain events are resolved or other changes in circumstances occur.

Based on the distinct performance obligations under the Novartis collaboration, we allocated the \$108.4 million transaction price based on relative stand-alone selling prices of each of our performance obligations as follows:

- \$64.0 million for development services for AKCEA-APO(a)-LRx;
- \$40.1 million for development services for AKCEA-APOCIII-LRx;
- \$1.5 million for the delivery of AKCEA-APO(a)-LRx API; and
- \$2.8 million for the delivery of AKCEA-APOCIII-LRx API.

We are recognizing revenue related to each of our performance obligations as follows:

- We will satisfy the development services performance obligation for AKCEA-APO(a)-LRx as the research and development services are performed. A significant portion of the research and development services were completed by December 2018 with the remainder to be completed through mid-2019. We recognize revenue related to research and development services performed using an input method by calculating costs incurred at each period end relative to total costs expected to be incurred;
- We will satisfy the development services performance obligation for AKCEA-APOCIII-LRx as the research and development services are performed. We expect a significant portion of the research and development services to be completed by the end of December 2019 with the remainder through mid-2020. We recognize revenue related to research and development services performed using an input method by calculating costs incurred at each period end relative to total costs expected to be incurred;
- We recognized the amount attributed to the AKCEA-APO(a)-LRx API supply when we delivered API to Novartis in 2017; and
- We recognized the amount attributed to the AKCEA-APOCIII-LRx API supply when we delivered API to Novartis in May 2018.

Additionally, we and Ionis entered into a stock purchase agreement, or SPA, with Novartis. Under the SPA, in July 2017, Novartis purchased \$50.0 million of our common stock in a separate private placement concurrent with the completion of our IPO at a price per share equal to the IPO price.

On February 22, 2019, Novartis exercised its option to license AKCEA-APO(a)-LRx. We identified a separate performance obligation upon Novartis license of AKCEA-APO(a)-LRx because the license is distinct from our other performance obligations and recognized a license fee of \$150.0 million in the first quarter of 2019 because Novartis had full use of the license without any continuing involvement from us. Additionally, we did not have any further performance obligations related to the license after Novartis exercised its option to license AKCEA-APO(a)-LRx. Novartis is responsible for conducting and funding all future development, regulatory and commercialization activities for AKCEA-APO(a)-LRx, including a global pivotal cardiovascular outcomes study, for which planning and initiation activities are underway. In the first quarter of 2019, we issued 2,837,373 shares of our common stock to Ionis as payment of the \$75.0 million sublicense fee due to Ionis related to the option exercised by Novartis. For AKCEA-APO(a)-LRx, we are also eligible to receive up to \$675.0 million in milestone payments, including \$25.0 million for the achievement of a development milestone, up to \$290.0 million for the achievement of regulatory milestones and up to \$360.0 million for the achievement of commercialization milestones. In connection with Novartis' exercise of its option to exclusively license AKCEA-APO(a)-LRx, Akcea and Novartis established a more definitive co-commercialization framework under which we would negotiate the co-commercialization of AKCEA-APO(a)-LRx between us and Novartis in selected markets. Included in this framework is an option by which Novartis could solely commercialize AKCEA-APO(a)-LRx in exchange for Novartis paying us increased commercial milestone payments based on sales of AKCEA-APO(a)-LRx.

If Novartis exercises its option for AKCEA-APOCIII-LRx, Novartis will pay us a license fee equal to \$150.0 million. Half of this amount, or \$75.0 million, we will owe to Ionis as a sublicense fee. If Novartis exercises its option to license AKCEA-APOCIII-LRx, we are eligible to receive up to \$530.0 million in milestone payments, including \$25.0 million for the achievement of a development milestone, up to \$240.0 million for the achievement of regulatory milestones and up to \$265.0 million for the achievement of commercialization milestones. If Novartis licenses AKCEA-APOCIII-LRx, we may co-commercialize AKCEA-APOCIII-LRx through our specialized sales force in selected markets, under terms and conditions that we plan to negotiate with Novartis in the future.

We will earn the next milestone payment of \$25.0 million under this collaboration if Novartis reaches a specific level of enrollment related to the Phase 3 study for either drug. We are also eligible to receive tiered royalties in the mid-teens to low twenty percent range on net sales of AKCEA-APO(a)-LRx and AKCEA-APOCIII-LRx. Novartis will reduce these royalties upon the expiration of certain patents or if a generic competitor negatively impacts the product in a specific country. We will pay 50% of license fees, milestone payments and royalties under this agreement to Ionis as a sublicense fee.

During the three months ended March 31, 2019 and 2018, we earned revenue of \$157.1 million and \$17.1 million, respectively, from our strategic collaboration with Novartis, representing 100% of our research and development and license revenue. During the three months ended March 31, 2019 and 2018 we recognized \$5.5 million and \$17.1 million, respectively, of revenue from amounts that were in our beginning deferred revenue balance. Our consolidated balance sheet at March 31, 2019 and December 31, 2018 included deferred revenue of \$23.3 million and \$28.8 million, respectively, related to our strategic collaboration with Novartis.

## **7. License Agreements and Services Agreement with Ionis**

In December 2015, we entered into a development, commercialization and license agreement related to our cardiometabolic franchise and a services agreement with Ionis. In March 2018, we entered into a new development, commercialization, collaboration and license agreement related to our TTR franchise and amended the services agreement previously in place with Ionis. The following sections summarize these related party agreements with Ionis.

### ***Cardiometabolic Development, Commercialization and License Agreement***

Our development, commercialization and license agreement, or Cardiometabolic License Agreement, with Ionis granted exclusive rights to us to develop and commercialize WAYLIVRA, AKCEA-APO(a)-L Rx, AKCEA-APOCIII-LRx, and AKCEA-ANGPTL3-LRx, which are collectively referred to as the Lipid Drugs. Ionis granted us an exclusive license to certain patents to develop and commercialize products containing the Lipid Drugs. Ionis also granted us a non-exclusive license to the Ionis antisense platform technology for us to develop and commercialize products containing the Lipid Drugs. Ionis also granted us non-exclusive rights under its manufacturing technology to manufacture the Lipid Drugs in our own facility or at a contract manufacturer. As a part of this agreement both companies agreed not to work with any other parties to develop or commercialize other RNA-targeting drugs that are designed to inhibit any of the Lipid Drug targets so long as we are developing or commercializing the Lipid Drugs.

We and Ionis share development responsibilities for the Lipid Drugs, other than drugs licensed to Novartis. We pay Ionis for the research and development expenses it incurs on our behalf, which include both external and internal expenses. External research and development expenses include costs for contract research organizations, or CROs, costs to conduct nonclinical and clinical studies on our drugs, costs to acquire and evaluate clinical study data, such as investigator grants, patient screening fees and laboratory work, and fees paid to consultants. Internal research and development expenses include costs for the work that Ionis' research and development employees perform for us. Ionis charges us a full-time equivalent rate that covers personnel-related expenses, including salaries and benefits, plus an allocation of facility-related expenses, including rent, utilities, insurance and property taxes, for those development employees who work either directly or indirectly on the development of our drugs. We also pay Ionis for the API and drug product we use in our nonclinical and clinical studies for all of our drugs. Ionis manufactures the API for us and charges us a price per gram consistent with the price Ionis charges its pharmaceutical partners, which includes the cost for direct materials, direct labor and overhead required to manufacture the API. If we need the API filled in vials for our clinical studies and Ionis contracts with a third party to perform this work, Ionis will charge us for the resulting cost.

As we commercialize each of the Lipid Drugs, other than drugs licensed to Novartis, we will pay Ionis royalties from the mid-teens to the mid-twenty percent range on sales related to the Lipid Drugs that we sell. If we sell a Lipid Drug for a Rare Disease Indication (defined in the agreement as less than 500,000 patients worldwide or an indication that required a Phase 3 program of less than 1,000 patients and less than two years of treatment), we will pay a higher royalty rate to Ionis than if we sell a Lipid Drug for a Broad Disease Patient Population (defined in the agreement as more than 500,000 patients worldwide or an indication that required a Phase 3 program of 1,000 or more patients and two or more years of treatment). Other than with respect to the drugs licensed to Novartis under the collaboration agreement, if our annual sales reach \$500.0 million, \$1.0 billion and \$2.0 billion, we will be obligated to pay Ionis sales milestones in the amount of \$50.0 million for each sales milestone reached by each Lipid Drug. If and when triggered, we will pay Ionis each of these sales milestones over the subsequent 12 quarters in equal payments. We share 50% of payments we receive from Novartis with Ionis.

We may terminate this agreement if Ionis is in material breach of the agreement. Ionis may terminate this agreement if we are in material breach of the agreement. In each circumstance the party that is in breach will have an opportunity to cure the breach prior to the other party terminating this agreement.

In the first quarter of 2017, we entered into letter agreements with Ionis to reflect the agreed upon payment terms with respect to the upfront option payment that we received from Novartis and to allocate the premium that Novartis paid for Ionis' common stock in connection with our strategic collaboration with Novartis. For additional detail regarding our strategic collaboration with Novartis, see Note 6, *Strategic Collaboration with Novartis*.

### ***TTR Development, Commercialization, Collaboration and License Agreement***

On April 17, 2018, our stockholders, other than Ionis and its affiliates, approved the development, commercialization, collaboration and license agreement, or TTR License Agreement, and a stock purchase agreement, or Ionis SPA, with Ionis, our majority shareholder which was entered into on March 14, 2018. In addition, in connection with these agreements, we entered into an

amended and restated services agreement, or Amended Services Agreement, and an amended and restated investor rights agreement, or Amended Investor Rights Agreement, with Ionis.

We determined that the TTR License Agreement and Ionis SPA included provisions which required the approval of the agreements by our stockholders other than Ionis and its affiliates, which we deemed was not perfunctory in nature, therefore, we concluded that the approved date of the agreements for accounting purposes was April 17, 2018, the date on which such approval was received and the closing of the agreements took place.

In accordance with the terms and provisions of the TTR License Agreement, we received rights to:

- commercialize TEGSEDI following receipt of regulatory approval and perform certain other non-commercial activities with respect to TEGSEDI, in each case, in accordance with a global strategic plan;
- partner on the completion of all pivotal studies, of a follow-on drug to TEGSEDI, AKCEA-TTR-LRx and perform other non-commercial activities with respect to AKCEA-TTR-LRx;
- commercialize AKCEA-TTR-LRx following receipt of regulatory approval in accordance with a global strategic plan;
- share in profits and losses with respect to TEGSEDI and AKCEA-TTR-LRx;
- manufacture (including through a third party) each product following receipt of regulatory approval for such product; and
- sublicense the development and commercialization of either product to third parties or affiliates, with the consent of Ionis.

As consideration for the grant of rights under the TTR License Agreement, we paid an upfront licensing fee of \$150.0 million, which was paid through the issuance of 8 million shares of our common stock priced by reference to a trading average at the time of execution of the agreements. In addition, we are obligated to make milestone payments to Ionis in connection with the achievement of certain development, regulatory and commercialization events. These milestone payments include up to \$110.0 million, if all TEGSEDI regulatory approval milestones are met; up to \$145.0 million, if all AKCEA-TTR-LRx regulatory milestones are met; and a total of \$1.3 billion, in the form of seven milestone payments, if all sales milestones for the combined products are met. We can elect to pay each milestone payment in cash or shares of our common stock and Ionis may require payment in shares of common stock up until the achievement of the milestone event for aggregate worldwide annual net sales of \$750.0 million for the products. Subsequent to the achievement of the milestone event for aggregate worldwide annual net sales of \$750.0 million, all subsequent milestone payments must be paid in cash.

The TTR License Agreement will remain in effect until the expiration of all included payment obligations, or unless earlier terminated. The TTR License Agreement can be terminated by mutual consent of us and Ionis, by either us or Ionis upon certain events, by either party upon material breach, or by Akcea for convenience upon providing 90 days written notice to Ionis. Upon termination, all rights received under the TTR License Agreement will terminate.

To support the commercialization of TEGSEDI and AKCEA-TTR-LRx, Ionis purchased 10.7 million shares of our common stock for \$200 million.

In connection with the licensing transaction, we amended our Certificate of Incorporation to increase our authorized shares of common stock from 100,000,000 shares to 125,000,000 shares.

We determined that the upfront accounting for the TTR License Agreement should follow the accounting guidance for common control transactions given the nature of the relationship between us and Ionis, including the fact that Ionis maintains a controlling ownership position in us.

In addition, we assessed the identifiable assets that were acquired under the terms of the TTR License Agreement, including the licensed rights to TEGSEDI and AKCEA-TTR-LRx, certain batches of TEGSEDI materials, the transfer of a minimal number of employees from Ionis to us and certain manufacturing and clinical research agreements. We concluded that the licensed rights represented a group of similar identifiable assets and that substantially all of the fair value of the acquisition resides in the licensed rights. As such, we concluded that the acquired assets did not meet the definition of a business and that we should account for the TTR License Agreement as an asset acquisition under common control guidance. Accordingly, we recorded the carrying value of the licensed rights held by Ionis of \$0.6 million as an intangible asset at the date of acquisition and will amortize the amount over the remaining patent life.

In connection with the transaction, we also purchased \$4.7 million of commercial TEGSEDI inventory held by Ionis. In addition, during the three months ended March 31, 2019 we purchased \$13.5 million of clinical TEGSEDI material held by Ionis. Prospectively we will be responsible for the procurement of all additional inventory. The inventory and clinical material did not have a carrying value on the books of Ionis at the time of purchase. As such, in accordance with the accounting guidance for common control

transactions above, we recorded the purchase of this inventory and clinical material as a reduction of additional paid in capital. This amount represented a cash distribution to Ionis, therefore, we have included this distribution as a distribution to Ionis for purposes of income (loss) per share and we have applied the two-class method as discussed in Note 11, *Basic and Diluted Net Income (Loss) Per Share*.

We also determined that the TTR License Agreement represented a collaboration arrangement as defined by ASC 808. Prior to April 1, 2018, Ionis was responsible for all costs associated with TEGSEDI and for the period from April 1, 2018 to December 31, 2018, we were responsible for all costs associated with TEGSEDI. We and Ionis share all costs associated with AKCEA-TTR-LRx from January 1, 2018 forward on a 50/50 basis. We recorded \$3.1 million paid to Ionis for costs related to the period prior to the closing of the TTR License Agreement to equity, as these amounts were previously expensed in the financial statements of Ionis. This amount also represents a cash distribution to Ionis and was included as an adjustment to the net loss attributable to Ionis for purposes of applying the two-class method for loss per share as discussed in Note 11, *Basic and Diluted Net Income (Loss) Per Share*.

In addition, on July 11, 2018, we received marketing authorization, or MA, approval for TEGSEDI from the European Commission, or EC, for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis, or hATTR amyloidosis, in the European Union, or EU. As a result of the MA approval in the EU, on August 3, 2018, we issued 1,597,571 shares of our common stock to Ionis as payment of the \$40.0 million regulatory approval milestone for TEGSEDI. As a result of the marketing authorization in the EU, we capitalized this regulatory approval milestone payment as a licensed intangible asset on our condensed consolidated balance sheets as the amount is expected to be recoverable through future cash flows.

In addition, on October 5, 2018, we received regulatory approval for TEGSEDI from the FDA for the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults in the United States. As a result of the regulatory approval in the United States, on October 17, 2018 we issued 1,671,849 shares of our common stock to Ionis as payment of the \$50.0 million regulatory approval milestone for TEGSEDI. As a result of the FDA approval in the U.S., we capitalized this regulatory approval milestone payment as a licensed intangible asset on our condensed consolidated balance sheets as the amount is expected to be recoverable through future cash flows.

Both milestone payments are being amortized to cost of sales on a straight-line basis over the licensed assets expected useful life of approximately 16 years from the date of the initial regulatory approval milestone achievement. Amortization expense for the TTR milestone payments was \$1.4 million for the three months ended March 31, 2019. We did not record any amortization expense for the TTR milestone payments for the three months ended March 31, 2018.

#### *Profit Share*

Under the TTR License Agreement, we and Ionis agreed to share TEGSEDI and AKCEA-TTR-LRx profits and losses as follows: for TEGSEDI, beginning on the earlier of (i) the first day of the quarter after receipt of regulatory approval of TEGSEDI in the United States, or (ii) January 1, 2019, the parties will share profits and losses from the development and commercialization of TEGSEDI (A) on a 60/40 basis (60% to Ionis and 40% to us) through the end of the quarter in which the first commercial sale of AKCEA-TTR-LRx occurs, and (B) on a 50/50 basis commencing on the first day of the first quarter thereafter; and for AKCEA-TTR-LRx, beginning January 1, 2018, the parties will share all profits and losses from the development and commercialization of AKCEA-TTR-LRx on a 50/50 basis.

In the first quarter of 2019, the profit sharing provisions for TEGSEDI under the TTR License Agreement with Ionis became effective. As we are the principal for all commercial activities related to the TTR License Agreement, we record all commercial activities related to TEGSEDI on a gross basis in our statement of operations, including revenues, cost of sales and sales and marketing expenses. The Ionis share of commercialization costs for TEGSEDI is separately presented within operating expenses in our statement of operations under the caption “Net loss share from commercial activities under agreement with Ionis Pharmaceuticals, Inc.”. As we are a collaborator with Ionis for the execution of TTR development activities, we record all research and development expenses on a net basis representing our proportionate share of total costs incurred by Ionis and us. Accordingly, only our share of total costs incurred related to development activities under the TTR License Agreement is presented within research and development expense in our statement of operations.

A summary of the loss share related to the commercial activities under the TTR Agreement is as follows:

	<b>Three Months Ended March 31, 2019</b>
Net losses incurred by the collaboration related to the commercial activities under the TTR Agreement	\$ (15,098)
Ionis' share of commercial losses under the TTR Agreement reflected in our consolidated statements of operations	(9,056)
Akcea's share of commercial losses under the TTR Agreement reflected in our consolidated statements of operations	\$ (6,042)

A summary of the development expenses related to the TTR Agreement is as follows:

	<b>Three Months Ended March 31, 2019</b>
Total development expense incurred by the collaboration related to development activities under the TTR Agreement	\$ (14,380)
Akcea's share of TTR development expense reflected in research and development expense in our consolidated statements of operations	\$ (6,133)

We did not record any commercial or research and development expense related to the TTR License Agreement during the three months ended March 31, 2018

#### **Services Agreement**

We originally entered into a services agreement with Ionis in December 2015 in conjunction with the Cardiometabolic License Agreement. We entered into the Amended Services Agreement with Ionis in April 2018 in conjunction with the TTR License Agreement (collectively, the service agreements). The primary purpose of the Amended Services Agreement was to allow for the expansion of general and administrative services provided to us by Ionis to cover the TEGSEDI and AKCEA-TTR-LRx products under terms substantially similar to the prior services agreement.

Our services agreement with Ionis is designed to be flexible to adjust for our increasing capabilities in various functions. Under the services agreement, Ionis provides us certain services, including, without limitation, general and administrative support services and development support services. Ionis allocated a certain percentage of personnel to perform the services that it provides to us based on its good faith estimate of the required services. We pay Ionis for these allocated costs, which reflect the Ionis full-time equivalent, or FTE, rate for the applicable personnel, plus out-of-pocket expenses, such as occupancy costs, associated with the FTEs allocated to providing us these services. We do not pay a mark-up or profit on the external or internal expenses Ionis bills to us. Ionis invoices us quarterly for all amounts due under the services agreement and payments are due within 30 days of the receipt of an invoice.

In addition, as long as Ionis continues to consolidate our financials, we will comply with Ionis' policies and procedures and internal controls. As long as we are consolidated into Ionis' financial statements under U.S. GAAP, we may continue to access the following services from Ionis:

- investor relations services,
- human resources and personnel services,

- risk management and insurance services,
- tax related services,
- corporate record keeping services,
- financial and accounting services,
- credit services, and
- COO/CFO/CBO oversight.

However, if we wanted to provide the foregoing services internally, and doing so would not negatively impact Ionis' internal controls and procedures for financial reporting, we can negotiate in good faith with Ionis for a reduced scope of services related to the aforementioned services. When Ionis determines it should no longer consolidate our financials, we may mutually agree with Ionis in writing to extend the term of this arrangement in six-month increments.

We can establish our own benefits programs or continue to use Ionis' benefits, however we must provide Ionis a minimum advance notice to opt-out of using Ionis' benefits. We do not currently plan to establish our own benefits programs at this time or in the near future.

As of March 31, 2019, Ionis owed us \$7.21 million. As of December 31, 2018, we owed Ionis \$18.9 million.

The following table summarizes the amounts recorded related to transactions with Ionis including amounts related to the TTR licensing transaction for the following periods (in thousands):

	<b>Three Months Ended</b>	
	<b>March 31,</b>	
	<b>2019</b>	<b>2018</b>
<b>Operating expenses:</b>		
Services performed by Ionis	\$ 1,075	\$ 1,945
Active pharmaceutical ingredient manufactured by Ionis	—	5,229
Sublicensing expenses	75,000	—
Out-of-pocket expenses paid by Ionis	1,571	6,236
Less: commercial share of loss in connection with the TTR license transaction	(9,056)	—
Less: R&D share of loss in connection with the TTR license transaction	(796)	—
Total operating expenses generated by transactions with Ionis	67,794	13,410
Less: distribution to Ionis	13,492	—
Total charges generated by transactions with Ionis	81,286	13,410
Payable balance to Ionis at the beginning of the period	18,901	14,365
Less: total amounts paid to Ionis during the period	(32,393)	(38)
Less: non-cash sublicensing expenses	(75,000)	—
Total amount payable (receivable) to Ionis at period end	<u>\$ (7,206)</u>	<u>\$ 27,737</u>

## **8. Collaboration and License Agreement with PTC Therapeutics**

In August 2018, we entered into a collaboration and license agreement with PTC Therapeutics, or the PTC License Agreement, to commercialize TEGSEDI and WAYLIVRA in Latin America and certain Caribbean countries, or the PTC Territory.

We received a \$12.0 million upfront payment from PTC Therapeutics related to TEGSEDI in the third quarter of 2018 upon execution of the PTC License Agreement, of which we paid Ionis \$7.2 million as a sublicense fee related to the TTR License Agreement. PTC Therapeutics will pay us \$6.0 million as a result of WAYLIVRA approval by the European Commission, or EC. In addition, we are eligible to receive up to \$8.0 million for the achievement of regulatory milestones and royalties in the mid-twenty percent range on net sales of TEGSEDI and WAYLIVRA in the PTC Territory. PTC Therapeutics' obligation to pay royalties to us begins on the earlier of 12 months after the first commercial sale of a product in Brazil or the date that PTC Therapeutics recognized revenue of at least \$10.0 million in the PTC Territory. PTC Therapeutics will reduce these royalties upon the expiration of certain patents or if a generic competitor negatively impacts the market share of the product in the PTC Territory. Milestone payments and royalties that we are eligible to receive from PTC Therapeutics for TEGSEDI will be split 60% to Ionis and 40% to Akcea. All WAYLIVRA milestone payments and royalties that we are eligible to receive from PTC will be split 50/50 with Ionis. PTC Therapeutics is solely responsible for the commercialization of the products in the PTC Territory at its sole cost and expense, including the pursuit and maintenance of applicable regulatory approvals. Unless earlier terminated, the PTC License Agreement will continue in effect until the date on which the royalty term and all payment obligations with respect to all products in all countries in the PTC Territory have expired.

At the commencement of the PTC License Agreement, we identified two performance obligations, consisting of the transfer of (1) the license to TEGSEDI and related know-how and (2) the license to WAYLIVRA and related know-how, both of which were satisfied during the third quarter of 2018. In addition, we identified a customer option related to PTC Therapeutics option to purchase supply of product from us for its development and commercial needs. The option to purchase supply from us is subject to the terms of a supply agreement we entered with PTC in April 2019. We considered the manufacturing capabilities of PTC Therapeutics and the fact that manufacturing services are not proprietary and can be provided by other vendors, to conclude that the licenses have stand-alone functionality and are distinct. Further, the customer options for manufacturing of product is expected to be priced similar to other manufacturing options with similar customers and is therefore not considered a material right. As there were no remaining unsatisfied performance obligations as of September 30, 2018, the \$12.0 million upfront payment was recognized as license revenue upon contract execution in the third quarter of 2018. None of the regulatory milestones have been included in the upfront transaction price determined in August 2018, as all milestones were fully constrained. As part of our evaluation of the constraint as of March 31, 2019, we considered numerous factors, including that regulatory approvals are not within our control and accordingly the related milestones are fully constrained and excluded from the arrangement consideration until such regulatory approvals are received. Any consideration related to sales-based royalties will be recognized when the related sales occur.

## **9. Stock-Based Compensation**

### ***Stock Plans***

#### *2015 Equity Incentive Plan*

As of March 31, 2019, the aggregate number of shares of common stock that may be issued pursuant to stock awards under the 2015 Plan was 18,500,000 shares. The 2015 Plan also provides for the grant of nonstatutory stock options, or NSOs, incentive stock options, or ISOs, stock appreciation rights, restricted stock awards and restricted stock unit awards. At March 31, 2019, a total of 13,337,602 options were outstanding, of which 4,680,540 were exercisable, 36,455 restricted stock unit awards were outstanding, and 3,854,948 shares were available for future grant under the 2015 Plan.

#### *2017 Employee Stock Purchase Plan*

On January 1, 2019, 500,000 shares of common stock were added to the 2017 Employee Stock Purchase, or 2017 ESPP. In accordance with the provisions of our 2017 ESPP, the number of shares of our common stock reserved for issuance under the 2017 ESPP automatically increased on January 1 of each calendar year. As of March 31, 2019, the aggregate number of shares of common stock reserved under the 2017 ESPP was 1,500,000 and we had 1,450,709 shares available for future issuance under the 2017 ESPP. During the three months ended March 31, 2019, 17,740 shares were issued under our 2017 ESPP. At March 31, 2019, accrued liabilities included \$0.3 million of 2017 ESPP contributions for which the related shares will be issued on July 1, 2019.

### Stock-based Compensation Expense

The following table summarizes stock-based compensation expense for the three months ended March 31, 2019 and 2018 (in thousands):

	Three Months Ended March 31,	
	2019	2018
Cost of sales - product	\$ 118	\$ —
Research and development expenses	3,921	2,314
Selling, general and administrative expenses	14,521	4,070
Total	<u>\$ 18,560</u>	<u>\$ 6,384</u>

As of March 31, 2019, total unrecognized estimated non-cash stock-based compensation expense related to non-vested stock options was \$3.1 million.

### 10. Basic and Diluted Net Income (Loss) Per Share

In connection with the TTR License Agreement completed on April 17, 2018 with Ionis, we made distributions to Ionis representing the consideration to be paid in cash provided to Ionis in excess of the carrying value of the related assets acquired. These distributions are treated as dividends to Ionis; therefore, we have applied the two-class method of income (loss) per share to reflect the allocation of these distributions to the participating Ionis common shares.

The two-class method is an earnings allocation formula that determines income (loss) per share for each class of common stock and participating security according to dividends declared (or accumulated) and participation rights in undistributed earnings. For the purposes of calculating income (loss) per share under the two-class method, we have allocated the net income (loss) between common stock owned by Ionis and common stock owned by others.

Basic income (loss) per share for each class of stock is computed by dividing total distributable income (losses) applicable to common stock owned by Ionis and common stock owned by others by the weighted-average of common shares outstanding during the requisite period.

The following table summarizes the distributable income (losses) for the three months ended March 31, 2019 and 2018 (in thousands):

	Three Months Ended March 31,	
	2019	2018
Net income (loss)	\$ 27,187	\$ (29,627)
Distributions to Ionis	(13,492)	—
Distributable income (losses)	<u>\$ 13,695</u>	<u>\$ (29,627)</u>

The following table summarizes the reconciliation of weighted-average shares outstanding used in the calculation of basic income (loss) per share for the three months ended March 31, 2019 and 2018:

	Three Months Ended March 31,	
	2019	2018
Determination of shares:		
Weighted-average common shares outstanding owned by Ionis	68,581,967	45,447,879
Weighted-average common shares outstanding owned by others	22,126,363	21,171,372
Total weighted-average shares outstanding	<u>90,708,330</u>	<u>66,619,251</u>

The following table summarizes the calculation of basic income (loss) per share for the three months ended March 31, 2019 and 2018 (in thousands, except per share and share amounts):

	<b>Three Months Ended March 31,</b>	
	<b>2019</b>	<b>2018</b>
Income (losses) allocated to Ionis	\$ 10,354	\$ (20,212)
Plus: Distribution to Ionis	13,492	—
Income (losses) available to Ionis	\$ 23,846	\$ (20,212)
Weighted-average common shares outstanding owned by Ionis	68,581,967	45,447,879
Basic income (loss) per common share owned by Ionis	<u>\$ 0.35</u>	<u>\$ (0.44)</u>
Income (losses) allocated to common shares owned by others	\$ 3,341	\$ (9,415)
Weighted-average common shares outstanding owned by others	22,126,363	21,171,372
Basic income (loss) per common share owned by others	<u>\$ 0.15</u>	<u>\$ (0.44)</u>

For the three months ended March 31, 2018, we incurred a net loss; therefore, we did not include dilutive common equivalent shares in the computation of diluted net loss per share because the effect would have been anti-dilutive. Common stock from the following would have had an anti-dilutive effect on net loss per share:

- Options to purchase common stock;
- Unvested restricted stock units; and
- Employee Stock Purchase Plan.

For the three months ended March 31, 2019, we had net income available to Akcea common shareholders. As a result, we computed diluted net income per share using the weighted-average number of common shares owned by Ionis, weighted-average number of common shares owned by others and dilutive common equivalent shares outstanding during the period.

The following table summarizes the reconciliation of weighted-average shares outstanding and diluted common equivalent shares used in the calculation of diluted income (loss) per share for the three months ended March 31, 2019:

	<b>Three Months Ended March 31,</b>
	<b>2019</b>
Determination of shares:	
Weighted-average common shares outstanding owned by Ionis	68,581,967
Weighted-average common shares outstanding owned by others	22,126,363
Shares issuable upon exercise of stock options	3,370,817
Shares issuable upon restricted stock awards issuance	14,813
Shares issuable related to our ESPP	<u>33,982</u>
Weighted-average shares outstanding owned by others, plus assumed conversions	25,545,975
Total weighted-average shares outstanding	<u>94,127,942</u>

The following table summarizes the calculation of diluted income (loss) per share for the three months ended March 31, 2019 (in thousands, except per share amounts):

	<b>Three Months Ended March 31, 2019</b>
Income allocated to Ionis	\$ 9,978
Plus: Distribution to Ionis	13,492
Income available to Ionis	\$ 23,470
Weighted-average common shares outstanding owned by Ionis	68,581,967
Diluted income per common share owned by Ionis	<u>\$ 0.34</u>
Income allocated to common shares owned by others, plus assumed conversions	\$ 3,717
Weighted-average common shares outstanding owned by others, plus assumed conversions	25,545,975
Diluted income per common share owned by others	<u>\$ 0.15</u>

## 11. Contractual Obligations and Commitments

### *Operating Lease*

#### *Corporate Headquarters Lease*

On April 5, 2018, we entered into an operating lease agreement for 30,175 square feet of office space located in Boston, Massachusetts for our corporate headquarters. The lease commencement date was August 15, 2018 and we took occupancy in September 2018. We are leasing this space under a non-cancelable operating lease with an initial term ending after 123 months and an option to extend the lease for an additional five-year term. We did not include the extension option in our right-of-use asset and lease liability calculation as we did not consider it reasonably certain that we would exercise the option. Under the lease agreement, we received a three-month free rent period, which commenced on August 15, 2018, and a tenant improvement allowance up to \$3.8 million. We provided the lessor with a letter of credit to secure its obligations under the lease in the initial amount of \$2.4 million, to be reduced to \$1.8 million on the third anniversary of the rent commencement date and to \$1.2 million on the fifth anniversary of the rent commencement date if we meet certain conditions set forth in the lease at each such time. The letter of credit amount is included in deposits and other assets on the accompanying condensed consolidated balance sheets.

#### *Ionis Sublease*

On November 12, 2018 we entered into an operating lease agreement with Ionis Pharmaceuticals to sublease 4,723 square feet of office space located in Carlsbad, California. The commencement date was March 2018 and the term of the lease is 64 months with a four-month free rent period.

#### *Cambridge Lease*

We leased office space in a building in Cambridge, Massachusetts under an operating lease that commenced in April 2015 and was subsequently amended and expanded in February 2016 and March 2017. The lease was scheduled to expire in April 2020. We have subsequently terminated the lease effective April 2019.

When we determined our lease term for our operating lease right-of-use assets and lease liabilities for these leases we did not include extension option as we are not reasonably certain we will exercise the option.

### Other Operating Lease Information

Other information related to our operating leases were as follows (dollar amounts in thousands):

	At March 31, 2019
Right-of-use operating lease assets	\$ 11,602
Operating lease liabilities (1)	\$ 16,324
Weighted average remaining lease term	9.5 years
Weighted average discount rate	8%

- (1) Current portion of \$1.3 million included in other current liabilities and the difference of \$15 million included in long-term portion of lease liabilities on our condensed consolidated balance sheet.

Annual maturities of our operating lease liabilities as of March 31, 2019 are as follows (in thousands):

	Operating Leases
Remainder of 2019 Years ended December 31,	\$ 1,921
2020	2,422
2021	2,370
2022	2,403
2023	2,400
Thereafter	11,961
Total minimum lease payments	\$ 23,477
Less:	
Imputed interest	(7,153)
Total operating lease liability	\$ 16,324

Operating lease expense was \$0.5 million and \$0.2 million for the three months ended March 31, 2019 and 2018, respectively. Cash paid for amounts included in the measurement of lease liabilities for the three months ended March 31, 2019 was \$0.6 million and was included in net cash used in operating activities in our condensed consolidated statements of cash flows.

### Purchase Commitments

Purchase commitments include agreements to purchase goods or services that are enforceable and legally binding on us and that specify all significant terms, including, fixed or minimum quantities to be purchased; fixed, minimum or variable price provisions; and the approximate timing of the transaction. Such obligations are related principally to inventory purchase orders based on our current manufacturing needs and require significant lead times to be fulfilled by our vendors. Purchase commitments exclude agreements that are cancelable without penalty.

The following table summarizes the purchase commitments as of March 31, 2019 (in thousands):

Year Ending December 31,	Payments due by period		
	Total	Less than 1 year	1 to 2 years
Purchase commitments	7,173	5,811	1,362
Total	\$ 7,173	\$ 5,811	\$ 1,362

## 12. Subsequent Events

### PTC License Agreement Regulatory Milestone

On May 3, 2019, we received regulatory approval for WAYLIVRA from the European Commission, or EC, for the treatment of adult patients with genetically confirmed familial chylomicronemia syndrome, or FCS, in the EU. As a result we will be due a license fee of \$6.0 million from PTC as part of our PTC License Agreement discussed in Note 8, *Collaboration and License Agreement with PTC Therapeutics*, of which we will pay Ionis \$3.0 million as a sublicense fee related to the Cardiometabolic License Agreement.

## ITEM 2 MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

*In this Report on Form 10-Q, unless the context requires otherwise, "Akcea," "Company," "we," "our," and "us," means Akcea Therapeutics, Inc. and our subsidiaries.*

### Forward-Looking Statements

In addition to historical information contained in this Report on Form 10-Q, this Report includes forward-looking statements regarding our financial position, outlook, business, and the therapeutic and commercial launch of TEGSEDI™, WAYLIVRA™ and our other products in development. Any statement describing our goals, expectations, financial or other projections, intentions or beliefs, is a forward-looking statement and should be considered an at-risk statement. Words such as "may," "could," "should," "would," "believe," "expect," "expectation," "anticipate," "estimate," "intend," "seeks," "plan," "project," "continue," "predict," "will," "should," and other words or expressions of similar meaning are intended by us to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Such statements are subject to certain risks and uncertainties, particularly risks related to our financial condition and need for additional capital, the clinical development and regulatory review and approval of our drugs, the commercialization of our drugs, our dependence on third parties to develop and commercialize our drugs, our relationship with Ionis Pharmaceuticals, Inc., our controlling stockholder, and risks related to our business and industry generally, such as risks inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward-looking statements. Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those identified in this Quarterly Report on Form 10-Q and those discussed in the section titled "Risk Factors" set forth in Part II, Item 1A of this Quarterly Report on Form 10-Q and in our other Securities and Exchange Commission, or SEC, filings. You should not rely upon forward-looking statements as predictions of future events. Furthermore, such forward-looking statements, like all statements in the Report, speak only as of the date of this Report (unless another date is indicated). Except as required by law, we undertake no obligation to update any forward-looking statements to reflect events or circumstances after the date of such statements.

The following discussion and analysis should be read in conjunction with (1) our financial statements and accompanying notes included in this Quarterly Report on Form 10-Q, and (2) the audited financial statements and accompanying notes thereto and the related Management's Discussion and Analysis of Financial Condition and Results of Operations for the fiscal year ended December 31, 2018, which are contained in our Annual Report on the Form 10-K for the fiscal year ended on December 31, 2018 filed on March 1, 2019 with the SEC. Our consolidated financial information may not be indicative of our future performance.

### Overview

We are a commercial stage biopharmaceutical company developing and marketing drugs globally to treat patients with rare and serious diseases. We are bringing novel and transformative medicines to patients by driving clinical program execution, understanding patient and physician needs, preparing the market, creating market access, and commercializing our products on a global basis. As an affiliate of Ionis Pharmaceuticals, Inc., or Ionis, we have a robust portfolio of development-, registration- and commercial-stage drugs covering multiple targets and diseases using Ionis' antisense technology. Our immediate focus is on the commercial launch of our commercially approved therapies, TEGSEDI in the United States, or U.S., the European Union, or EU, and Canada, and WAYLIVRA in the E.U. TEGSEDI treats the polyneuropathy caused by hereditary transthyretin-mediated amyloidosis, or hATTR amyloidosis, in adults. WAYLIVRA is indicated as an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome, or FCS, and at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate.

WAYLIVRA was granted conditional marketing authorization in the E.U. on May 3, 2019. The approval of WAYLIVRA in the E.U. follows a positive recommendation by the Committee for Medical Products for Human Use, or CHMP, of the European Medicines Agency, or EMA. With this adoption of the positive opinion by the European Commission, or EC, which grants marketing authorization for medicines across the E.U., we plan to leverage our existing commercial infrastructure in Europe to market WAYLIVRA. FCS is an ultra-rare, devastating hereditary disease that causes unpredictable and potentially fatal acute pancreatitis, chronic complications due to permanent organ damage, and a severe impact on daily living. The hallmark of FCS is extremely elevated triglycerides. There are approximately 3,000 to 5,000 patients with FCS worldwide. We are advancing a mature pipeline of novel drugs with the potential to treat multiple diseases. TEGSEDI, WAYLIVRA and our pipeline drugs, AKCEA-APO(a)-L Rx, AKCEA-ANGPTL3-LRx, AKCEA-APOCIII-LRx and AKCEA-TTR-LRx, are all based on Ionis' antisense technology platform.

We are continuing to build our current commercial infrastructure to support TEGSEDI and, in the E.U., WAYLIVRA, and plan to use this infrastructure to support the other drugs in our pipeline, if approved, as we anticipate further commercialization in serious and rare diseases. A key element of our commercial strategy is to provide the specialized, patient-centric support required to successfully address rare disease patient populations. We believe our focus on treating patients with inadequately addressed rare and serious diseases will allow us to partner efficiently and effectively with the specialized medical community that supports these underserved patient communities. Our supply chain is fully operational in both the U.S. and E.U. To further support the hATTR amyloidosis community, Akcea and Ambry Genetics Corporation, or Ambry, a Konica Minolta company, launched hATTR Compass™ in the U.S. and Canada, a no-cost, confidential genetic testing and genetic counseling program for people with suspected hATTR amyloidosis. This program is intended to empower people with accurate genetic information, so they can make informed decisions about their healthcare.

Our efforts to treat people with serious and under-served rare diseases are focused on transthyretin amyloidosis, or ATTR amyloidosis, and cardiometabolic diseases.

### ***ATTR***

TEGSEDI is an antisense drug designed to reduce the production of the TTR protein. In patients with hATTR amyloidosis, a severe, rare and fatal genetic disease, both the hereditary and wild-type, or wt, TTR protein builds up as fibrils in tissues, such as the peripheral nerves, heart, gastrointestinal system, eyes, kidneys, central nervous system, thyroid and bone marrow. The presence of TTR fibrils interferes with the normal functions of these tissues. The progressive accumulation of TTR amyloid deposits in these tissues and organs leads to sensory, motor and autonomic dysfunction often having debilitating effects on multiple aspects of a patient's life and eventually leads to death.

We estimate that there are approximately 50,000 patients globally with hATTR amyloidosis, the majority of whom have symptoms of polyneuropathy.

TEGSEDI was discovered and developed by Ionis and was licensed by us in April 2018. In addition to TEGSEDI, we and Ionis are developing AKCEA-TTR-LRx for hereditary and wild-type forms of transthyretin amyloidosis, or ATTR amyloidosis. We initiated clinical development of AKCEA-TTR-LRx in December 2018.

### ***Cardiometabolic***

Our lipid/cardiometabolic drugs, WAYLIVRA, AKCEA-APO(a)-L Rx, AKCEA-ANGPTL3-LRx and AKCEA-APOCIII-LRx, are all based on antisense technology developed by Ionis. We are focused on commercial preparations for WAYLIVRA in the E.U. and on regulatory discussions for WAYLIVRA in the U.S. and Canada. WAYLIVRA was granted conditional marketing authorization in the E.U. on May 3, 2019. The approval of WAYLIVRA in the E.U. follows a positive recommendation by the CHMP of the EMA, as an adjunct to diet in adult patients with genetically confirmed FCS, who are at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate. With the adoption of the positive opinion by the EC, which grants marketing authorization for medicines across the EU, we plan to leverage our existing commercial infrastructure in Europe to market WAYLIVRA. On May 10, 2018, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted to support approval of WAYLIVRA for the treatment of people with FCS. On August 27, 2018, we and Ionis announced that we received a Complete Response Letter from the Division of Metabolism and Endocrinology Products of the FDA regarding the New Drug Application for WAYLIVRA. The FDA did not cite any new concerns beyond those described in the Advisory Committee briefing book, in which the main areas of focus were the dosing schedule and management of thrombocytopenia. We continue to feel strongly that WAYLIVRA demonstrates a favorable benefit/risk profile in people with FCS, as was reflected in the positive outcome from the Advisory Committee meeting. In November 2018, we received a Notice of Noncompliance withdrawal letter, or NON-W, from Health Canada for WAYLIVRA.

FCS is a severe and rare lipid disorder characterized by extremely elevated levels of triglycerides. FCS has life-threatening consequences such as acute pancreatitis and the lives of patients with this disease are impacted daily by the associated symptoms. In our clinical program, we have observed consistent and substantial (>70%) decreases in triglycerides and improvements in other manifestations of FCS, including pancreatitis attacks and abdominal pain. We believe the safety and efficacy data from the WAYLIVRA program demonstrate a favorable risk-benefit profile for patients with FCS. WAYLIVRA is also in Phase 3 clinical development for the treatment of familial partial lipodystrophy, or FPL. AKCEA-APO(a)-L Rx completed Phase 2 in 2018 and Novartis is currently working to initiate the Phase 3 program. Our other two lipid/cardiometabolic drugs are currently in Phase 2 clinical development.

## Commercial Infrastructure

We are continuing to build our global infrastructure as we commercialize TEGSEDI and, in the E.U., prepare to commercialize WAYLIVRA, and we have commercial teams in place in the U.S., E.U. and Canada. In addition, in August 2018, we entered into a licensing agreement with PTC Therapeutics International Limited, or PTC Therapeutics, to commercialize TEGSEDI and WAYLIVRA in Latin America and certain Caribbean countries. A key element of our commercial strategy is to provide the specialized, patient-centric support required to successfully address rare disease patient populations. We believe our focus on treating patients with inadequately addressed rare and serious diseases will allow us to partner efficiently and effectively with the specialized medical community that supports these underserved patient communities.

To maximize the commercial potential of two of the drugs in our pipeline, we initiated a strategic collaboration with Novartis Pharma AG, or Novartis, for the development and commercialization of AKCEA-APO(a)-LRx and AKCEA-APOCIII-LRx. In February 2019, Novartis exercised its option to license AKCEA-APO(a)-LRx. Novartis is currently preparing to initiate a Phase 3 study of AKCEA-APO(a)-LRx in patients with established cardiovascular disease, or CVD and elevated levels of lipoprotein(a), or Lp(a). We believe Novartis brings significant resources and expertise to the collaboration that can accelerate our ability to deliver these potential therapies to the large populations of patients who have high cardiovascular risk due to inadequately treated lipid disorders. As part of our collaboration, we received \$75.0 million in an upfront option payment, of which we retained \$60.0 million and paid \$15.0 million to Ionis as a sublicense fee. We also earned a \$150.0 million license fee when Novartis exercised its option to license AKCEA-APO(a)-LRx in February 2019. As a result of the option exercise, on March 29, 2019 we issued 2,837,373 shares of our common stock to Ionis as payment of a \$75.0 million sublicense fee. Novartis is now responsible for all future development and commercialization activities for AKCEA-APO(a)-LRx. We are eligible to receive license fees, milestone payments and royalties on sales of AKCEA-APO(a)-LRx from Novartis if and when it meets the development, regulatory and sales milestones specified in our agreement. In connection with Novartis' exercise of its option to exclusively license AKCEA-APO(a)-LRx, we and Novartis established a more definitive framework under which we will negotiate the co-commercialization of AKCEA-APO(a)-LRx between the two companies in selected markets. Included in this framework is an option by which Novartis could solely commercialize AKCEA-APO(a)-LRx in exchange for Novartis paying us increased commercial milestone payments based on sales of AKCEA-APO(a)-LRx. We will share any license fees, milestone payments and royalties equally with Ionis.

For AKCEA-APOCIII-LRx, under our agreement with Novartis, after we complete Phase 2 development and if Novartis exercises its option to license AKCEA-APOCIII-LRx, we would receive an additional \$150.0 million license fee which we would also share equally with Ionis. If exercised, Novartis would conduct and pay for a Phase 3 cardiovascular outcome study in patients with hypertriglyceridemia and prior cardiovascular risk. If approved, Novartis would commercialize AKCEA-APOCIII-LRx worldwide. Novartis will have 60 days plus additional time that could be required for Hart-Scott-Rodino, or HSR, filing and review following the end-of-Phase 2 meeting to exercise its option for AKCEA-APOCIII-LRx. As part of the collaboration, we may co-commercialize AKCEA-APOCIII-LRx in selected markets, on mutually agreed terms and conditions. Similar to AKCEA-APO(a)-LRx, we are eligible to receive license fees, milestone payments and royalties on sales of AKCEA-APOCIII-LRx from Novartis if and when it meets the development, regulatory and sales milestones specified in our agreement. We will share any license fees, milestone payments and royalties equally with Ionis.

Our strategic collaboration with Novartis has a potential aggregate transaction value of over \$1.0 billion, plus royalties, which we would generally be required to share equally with Ionis. The calculation of potential aggregate transaction value assumes that Novartis licenses, successfully develops and achieves regulatory approval for both AKCEA-APO(a)-LRx and AKCEA-APOCIII-LRx in the U.S., E.U. and Japan, and that Novartis achieves pre-specified sales targets with respect to both drugs. In addition to the \$150 million license fee that we have received for AKCEA-APO(a)-LRx we are eligible to receive up to \$675.0 million in milestone payments, including \$25.0 million for the achievement of a development milestone, up to \$290.0 million for the achievement of regulatory milestones and up to \$360.0 million for the achievement of commercialization milestones. In addition, for AKCEA-APOCIII-LRx we are eligible to receive up to \$530.0 million in milestone payments, including \$25.0 million for the achievement of a development milestone, up to \$240.0 million for the achievement of regulatory milestones and up to \$265.0 million for the achievement of commercialization milestones. We are also eligible to receive tiered royalties in the mid-teens to low twenty percent range on net sales of AKCEA-APO(a)-LRx and AKCEA-APOCIII-LRx, and Novartis will reduce these royalties upon the expiration of certain patents or if a generic competitor negatively impacts the product in a specific country. We will pay 50% of these license fees, milestone payments and royalties to Ionis as a sublicense fee. See Note 6, *Strategic Collaboration with Novartis*, to our condensed consolidated financial statements for additional information.

We began recognizing revenue under the collaboration with Novartis upon its initiation in 2017. Our collaboration and license revenue for the first three months of 2019 was \$157.1 million. In addition, we began to recognize TEGSEDI product revenue in late 2018. Our product revenue for the first three months of 2019 was \$6.8 million. Our total revenue for the first three months of 2019 was \$163.8 million. Our net income for the first three months of 2019 was \$27.2 million. Such net income has resulted from our revenues which was offset by costs incurred in developing TEGSEDI, WAYLIVRA and the other drugs in our pipeline, commercializing TEGSEDI and WAYLIVRA, and general and administrative activities associated with our operations. We expect to continue to generate operating losses and negative operating cash flows for the foreseeable future. The transition to profitability is dependent upon the successful development, approval, and commercialization of our products and product candidates and the achievement of a level of revenue adequate to support our cost structure. We incur meaningful expenses to support commercialization, including manufacturing, marketing, sales and distribution functions.

As of March 31, 2019, we had cash, cash equivalents and investments of \$321.8 million. We plan to use our cash, cash equivalents and investments on hand as of March 31, 2019 to further our commercialization efforts of TEGSEDI and WAYLIVRA and continue the advancement of our pipeline drugs.

### Our Relationship with Ionis

Ionis formed Akcea as a wholly owned subsidiary to complete development of and commercialize Ionis' drugs to treat lipid disorders. We began business operations in January 2015. We licensed our cardiometabolic franchise from Ionis at the beginning of 2015. Prior to licensing these drugs, Ionis' employees performed all of the development, regulatory and manufacturing activities for these drugs either themselves or through third-party providers. As such, Ionis incurred all of the expenses associated with these activities and reported them in its condensed consolidated financial statements. TEGSEDI and AKCEA-TTR-LRx were licensed from Ionis in April 2018. Prior to then, Ionis had been advancing these drugs in development and incurring the expenses for those activities. Under our license agreements with Ionis, Ionis continued and is continuing to conduct development, regulatory or manufacturing activities for our drugs and to charge us for this work. As of March 31, 2019, Ionis owned approximately 76 percent of our outstanding stock.

### Critical Accounting Policies

The accounting policies we followed in the preparation of our interim condensed consolidated financial statements appearing at the beginning of this Quarterly Report on Form 10-Q are consistent in all material respects with those included in Note 2 of our Annual Report on the Form 10-K for the fiscal year ended on December 31, 2018 and Note 2 in our condensed consolidated financial statements included in this Quarterly Report on Form 10-Q.

### Results of Operations

In order to analyze and compare our results of operations to other similar companies, we believe it is important to exclude non-cash stock-based compensation expense related to equity awards from our expenses. We believe non-cash stock-based compensation expense is not indicative of our operating results or cash flows from our operations. Further, we internally evaluate the performance of our operations excluding it. All numbers presented below exclude stock-based compensation expense unless otherwise indicated.

### Comparison of the three months ended March 31, 2019 and 2018

#### Revenue

The following table sets forth our revenue for the periods presented (in thousands):

	Three months ended March 31,	
	2019	2018
Product revenue	\$ 6,754	\$ —
Research and development and license revenue under collaboration agreement	157,062	17,108
Total revenue	\$ 163,816	\$ 17,108

*Product revenue.* Product revenue of \$6.8 million for the three months ended March 31, 2019 relates to sales of TEGSEDI globally. For the three months ended March 31, 2018, we did not generate any product revenue.

*Research and development revenue.* For the three months ended March 31, 2019, we recognized \$157.1 million compared to \$17.1 million for the three months ended March 31, 2018, in research and development and license revenue from our collaboration with Novartis. The increase in research and development revenue was primarily the result of the \$150 million license fee related to Novartis' exercise of its option to license AKCEA-APO(a)-LRx.

### Cost of sales and license expense

The following table sets forth our cost of sales and license expense for the periods presented (in thousands):

	Three months ended March 31,	
	2019	2018
Cost of sales - product	\$ 923	\$ —
Cost of sales - intangible asset amortization	1,403	—
Total cost of sales and license expenses, excluding non-cash stock-based compensation expense	2,326	—
Non-cash stock-based compensation expense	118	—
Total cost of sales and license expenses	<u>\$ 2,444</u>	<u>\$ —</u>

Cost of sales – product expense of \$0.9 million for the three months ended March 31, 2019, consists of period costs and certain fixed costs associated with the manufacturing of TEGSEDI. We do not expect fixed costs will increase in direct correlation to sales. Based on our policy, we expense costs associated with the manufacture of our products as research and development expense prior to regulatory approval. Certain product costs of TEGSEDI units recognized as revenue during the three months ended March 31, 2019, were incurred prior to the July 2018 EU approval, and therefore are not included in cost of sales during this quarter. We expect cost of sales to increase as we deplete inventories that were previously expensed prior to approval but are utilized for commercial sales. The cost of units sold during the period for which there was no cost basis was \$0.3 million for the three months ended March 31, 2019. No product cost of sales was recorded for the three months ended March 31, 2018. All amounts exclude non-cash compensation expense related to equity awards.

Cost of sales expense – intangible asset amortization of \$1.4 million for the three months ended March 31, 2019, consisted of amortization of intangible assets recorded as a result of the achievement of TEGSEDI regulatory milestones in the U.S. and E.U.

### Research and development expense

The following table sets forth our research and development expenses for the periods presented (in thousands):

	Three months ended March 31,	
	2019	2018
External TEGSEDI expenses	\$ 151	\$ —
External WAYLIVRA expenses	2,287	6,559
Other external research and development projects expenses	8,896	13,126
Research and development personnel and overhead expenses	9,364	5,971
Sublicensing expenses	75,000	—
Total research and development expenses, excluding non-cash stock-based compensation expense	95,698	25,656
Non-cash stock-based compensation expense	3,921	2,314
Total research and development expenses	<u>\$ 99,619</u>	<u>\$ 27,970</u>

Research and development expenses were \$95.7 million for the three months ended March 31, 2019 compared to \$25.7 million for the same period in 2018. The increase in research and development expenses was primarily due to development activities related to sublicensing expenses related to our collaboration with Novartis of \$75 million, development activities related to our Phase 2b studies for AKCEA-APOCIII-LRx and AKCEA-ANGPTL3-LRx which were initiated in the first quarter of 2018 and personnel and overhead expense to support our development efforts. This increase was offset primarily due to a decrease in development activities for AKCEA-APO(a)-LRx as the clinical study ended, finished data collection and reported topline results, as well as a decrease in development activities for WAYLIVRA. All amounts exclude non-cash compensation expense related to equity awards.

### *Selling, general and administrative expense*

The following table sets forth our selling, general and administrative expenses for the periods presented (in thousands):

	<b>Three months ended March 31,</b>	
	<b>2019</b>	<b>2018</b>
Selling, general and administrative expenses	\$ 30,081	\$ 15,395
Non-cash compensation expense related to equity awards	14,521	4,070
<b>Total Selling, general and administrative expenses</b>	<b>\$ 44,602</b>	<b>\$ 19,465</b>

Selling, general and administrative expenses were \$30.1 million for the three months ended March 31, 2019 compared to \$15.4 million for the three months ended March 31, 2018. Our selling, general and administrative expenses increased due to the ongoing buildout of our commercial organization and advancement of pre-commercialization and commercialization activities necessary to launch TEGSEDI in the U.S., the EU and Canada, and our anticipated launch of WAYLIVRA in the E.U. All amounts exclude non-cash compensation expense related to equity awards.

### *Net Profit/Loss Share*

In the first quarter of 2019, the profit sharing provisions for TEGSEDI under the TTR License Agreement with Ionis became effective. As we are the principal for all commercial activities related to the TTR License Agreement, we record all commercial activities related to TEGSEDI on a gross basis in our statement of operations, including revenues, cost of sales and sales and marketing expenses. The Ionis share of commercialization costs for TEGSEDI is separately presented within operating expenses in our statement of operations under the caption "Net loss share from commercial activities under agreement with Ionis Pharmaceuticals, Inc.". For the three months ended March 31, 2019, we recorded \$9.1 million of cost share related to TEGSEDI commercial activities. We did not record any amounts of cost share for the three months ended March 31, 2018.

### *Other income and other expense*

*Investment income.* Investment income for the three months ended March 31, 2019 totaled \$1.2 million compared to \$0.9 million for the same period in 2018. The increase in investment income was primarily due to a higher average investment balance and an increase in the interest rates on high quality debt and U.S. government agencies investments during 2019 compared to 2018.

### *Net Income (Loss) and Net Income (Loss) Per Share*

Net income for the three months ended March 31, 2019 was \$27.2 million compared to a net loss of \$29.6 million for the same period in 2018. We realized net income during 2019 compared to the net loss incurred in 2018 primarily due to the \$150 million license fee related to Novartis' exercise of its option to license AKCEA-APO(a)-LRx offset by the development and pre-commercialization and commercial activities for TEGSEDI and WAYLIVRA, the increase in expenses related to development activities for our other drugs, and the ongoing global expansion of our company. Basic net income per common share owned by Ionis and owned by others for the three months ended March 31, 2019 was \$0.35 and \$0.15, respectively. Basic net loss per common share owned by Ionis and owned by others for the three months ended March 31, 2018 was \$0.44. Diluted net income per common share owned by Ionis and owned by others for the three months ended March 31, 2019 was \$0.34 and \$0.15, respectively. Diluted net loss per common share owned by Ionis and owned by others for the three months ended March 31, 2018 was \$0.44.

### **Liquidity and Capital Resources**

At March 31, 2019 we had cash, cash equivalents and investments of \$321.8 million and accumulated deficit of \$494.9 million.

We have funded our operating activities through a \$100.0 million cash contribution that we received from Ionis in 2015, \$75.0 million from initiating our collaboration with Novartis that we received in the first quarter of 2017 and \$106.0 million in drawdowns under our line of credit with Ionis that we received in the first and second quarters of 2017. Our borrowings under our line of credit agreement with Ionis converted into shares of our common stock at the IPO price in connection with the closing of our IPO in July 2017. We no longer have access to the line of credit. Additionally, in July 2017 we received \$182.3 million in net proceeds from our IPO, including \$25.0 million Ionis invested in our IPO and the Novartis concurrent private placement of \$50.0 million.

In April 2018, the stockholders other than Ionis and its affiliates approved the development, commercialization, collaboration and license agreement, or TTR License Agreement, pursuant to which we acquired an exclusive license from Ionis to TEGSEDI and AKCEA-TTR-LRx and a stock purchase agreement, or Ionis SPA, with Ionis, our majority shareholder, which we entered into on March 14, 2018. To support our commercialization of TEGSEDI and AKCEA-TTR-LRx, Ionis purchased 10.7 million shares of our common stock for \$200.0 million. As a result of the MA approval for TEGSEDI in the EU, on August 3, 2018 we issued 1,597,571 shares of our common stock to Ionis as payment of the \$40.0 million regulatory milestone for TEGSEDI, and as a result of the regulatory approval for TEGSEDI in the United States, on October 17, 2018 we issued 1,671,849 shares of our common stock to Ionis as payment of the \$50.0 million regulatory milestone for TEGSEDI.

On February 22, 2019, we earned a license fee of \$150.0 million related to Novartis' option exercise of AKCEA-APO(a)-LRx, for which we issued 2,837,373 shares of our common stock on March 29, 2019 to Ionis as payment of a \$75.0 million sublicense fee. See Note 6, *Strategic Collaboration with Novartis* and Note 7, *License Agreements and Services Agreement with Ionis*, to our condensed consolidated financial statements included in this Form 10-Q for more information about our collaboration with Novartis and Cardiometabolic licensing agreement with Ionis.

At March 31, 2019, we had working capital of \$297.8 million compared to working capital of \$186.6 million at March 31, 2018. Working capital increased in 2019 primarily due to the increase in our cash, cash equivalents and investments as a result of our financing and revenue activities. This increase is offset by activities related to our normal course of business. As of March 31, 2019, our outstanding receivable from Ionis was \$7.2 million under our Amended Services Agreement with Ionis.

TEGSEDI is approved in the U.S., E.U. and Canada and we have begun our commercialization efforts in these three regions. We began to generate product revenue from TEGSEDI drug sales in the fourth quarter of 2018. We anticipate that we will continue to incur losses for the foreseeable future, and losses may continue to increase as we develop, seek regulatory approval for, and begin to commercialize our other pipeline drugs. We are subject to all of the risks incident in developing and commercializing new drugs and we may encounter unforeseen expenses, difficulties, complications, delays and other unknown factors that may adversely affect our business.

On February 22, 2019, Novartis exercised its option to license AKCEA-APO(a)-LRx as part of our strategic collaboration with Novartis discussed in Note 6, *Strategic Collaboration with Novartis*. As a result we earned a license fee of \$150.0 million. On March 29, 2019 we issued 2,837,373 shares of our common stock to Ionis as payment of the \$75.0 million sublicense fee.

### **Future Funding Requirements**

We expect that our cash, cash equivalents and investments of \$321.8 million as of March 31, 2019, and cash expected to be generated from sales of TEGSEDI, which has been approved in the U.S., the EU and Canada, and cash expected to be generated from sales of WAYLIVRA, which has received conditional approval in the EU, will be sufficient to fund our operations through at least the next 12 months from the issuance of this Quarterly Report on Form 10-Q. We expect to raise additional funding in the future to continue developing the drugs in our pipeline and to commercialize TEGSEDI and WAYLIVRA, or any other approved drug.

We may seek to obtain additional financing in the future through the issuance of our common stock, through other equity or debt financings or through collaborations or partnerships with other companies. We may not be able to raise additional capital on terms acceptable to us, or at all, and any failure to raise capital as and when needed could compromise our ability to execute on our business plan. Until such time, if ever, as we can generate substantial product revenue, we may finance our cash needs through additional financing in the future through the issuance of our common stock, through other equity or debt financings or through collaborations or partnerships with other companies. In any event, we may not generate significant revenue from product sales prior to the use of our existing cash, cash equivalents and investments. We do not have any committed external source of funds. Additional capital may not be available on reasonable terms, if at all. To the extent that we raise additional capital through the sale of stock 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 increased fixed payment obligations and covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures, declaring dividends, selling or licensing intellectual property rights and other operating restrictions that could adversely affect our ability to conduct our business. If we raise additional funds through collaborations or licensing arrangements with third parties, we may have to relinquish valuable rights to our drugs or grant licenses on terms that may not be favorable to us. If we cannot raise additional funds through stock offerings or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and commercialize our drugs even if we would otherwise prefer to develop and commercialize the drugs ourselves.

Our forecast of the period of time through which our financial resources will be adequate to support our operations involves risks and uncertainties, and actual results could vary as a result of a number of factors. We have based this estimate on assumptions that may prove to be wrong and we could use our available capital resources sooner than we currently expect. The amount and timing of future funding requirements, both near- and long-term, will depend on many factors, including, but not limited to:

- the cost of establishing and managing sales, marketing, manufacturing and distribution capabilities for our drugs;
- the revenue generated from commercial sales of our drugs for which we receive marketing authorization, which may be affected by market conditions, including obtaining coverage and adequate reimbursement of our drugs from third-party payors, including government programs and managed care organizations, and competition within the therapeutic class to which our drugs are assigned;
- the effect of competing technological and market developments;

- our strategic collaborators' success in developing and commercializing our drugs;
- the number and characteristics of drugs that we may pursue;
- the outcome, timing and cost of regulatory approvals by the FDA and comparable foreign regulatory authorities, including the potential for the FDA or comparable foreign regulatory authorities to require that we perform more studies than, or evaluate clinical endpoints other than, those that we currently expect;
- our need to expand our development activities, including our need and ability to hire additional employees;
- the design, initiation, progress, size, timing, costs and results of our clinical and nonclinical studies; and
- our need to add infrastructure, implement internal systems and hire additional employees to operate as a public company.

If we cannot expand our operations or otherwise capitalize on our business opportunities because we lack sufficient capital, our business, financial condition and results of operations could be materially adversely affected.

### ***Contractual Obligations and Commitments***

On February 22, 2019, Novartis exercised its option to license AKCEA-APO(a)-LRx as part of our strategic collaboration with Novartis discussed in Note 6, *Strategic Collaboration with Novartis* to our condensed consolidated financial statements included in this Form 10-Q. As a result, we earned a license fee of \$150.0 million. On March 29, 2019, we issued 2,837,373 shares of our common stock to Ionis as payment of the related \$75.0 million sublicense fee.

On May 3, 2019, we received regulatory approval for WAYLIVRA from the European Commission, or EC, for the treatment of adult patients with genetically confirmed familial chylomicronemia syndrome, or FCS, in the EU. As a result we will be due a license fee of \$6.0 million from PTC as part of our PTC License Agreement discussed in Note 8, *Collaboration and License Agreement with PTC Therapeutics*, of which we will pay Ionis \$3.0 million as a sublicense fee related to the Cardiometabolic License Agreement.

Other than the above, 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 our Annual Report on Form 10-K for the fiscal year ended December 31, 2018, as filed with the SEC on March 1, 2019.

### **Recently Issued Accounting Pronouncements**

We describe the recently issued accounting pronouncements that apply to us in Note 2, *Summary of Significant Accounting Policies*, to our condensed consolidated financial statements.

### **Off-balance Sheet Arrangements**

We did not have any off-balance sheet arrangements during the period presented, as defined in the rules and regulations of the SEC.

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

#### *Interest Rate Risk*

We are exposed to changes in interest rates primarily from our investments in certain short-term investments. We place our cash equivalents and short-term investments with reputable financial institutions. We primarily invest our excess cash in commercial paper and debt instruments of the U.S. Treasury, financial institutions, corporations, and U.S. government agencies with strong credit ratings and an investment grade rating at or above A-1, P-1 or F-1 by Moody's, Standard & Poor's, or Fitch, respectively. We have established guidelines relative to diversification and maturities that are designed to maintain safety and liquidity. We periodically review and modify these guidelines to maximize trends in yields and interest rates without compromising safety and liquidity. We typically hold our investments for the duration of the term of the respective instrument. We do not utilize derivative financial instruments, derivative commodity instruments or other market risk sensitive instruments, positions or transactions to manage exposure to interest rate changes. Accordingly, we believe that, while the securities we hold are subject to changes in the financial standing of the issuer of such securities, we are not subject to any material risks arising from changes in interest rates, foreign currency exchange rates, commodity prices, equity prices or other market changes that affect market risk sensitive instruments.

### *Foreign Exchange Risk*

Our results of operations are subject to foreign currency exchange rate fluctuations as we have foreign subsidiaries, Akcea Therapeutics UK Ltd., or Akcea UK, Akcea Therapeutics Canada, Inc., or Akcea Canada, Akcea Therapeutics France SAS, or Akcea France, Akcea Therapeutics Germany GmbH, or Akcea Germany, Akcea Therapeutics Ireland Limited, or Akcea Ireland, Akcea Therapeutics Portugal, Unipessoal Lda, or Akcea Portugal, Akcea Therapeutics Italia S.R.L., or Akcea Italy, and Akcea Therapeutics Spain, S.L., or Akcea Spain, with functional currencies other than the U.S. dollar. We created these foreign subsidiaries to support our initial pre-commercialization and commercial activities in North America and Europe and to serve as potential entities for future North American and European operations. We translate the foreign subsidiaries' functional currencies to our reporting currency, the U.S. dollar. As a result, our financial position, results of operations and cash flows can be affected by market fluctuations in the foreign currencies to U.S. dollar exchange rate which are difficult to predict. However, because the Akcea foreign subsidiaries currently have limited operations, the effect of fluctuations of the foreign currencies to U.S. dollar exchange rate on our condensed consolidated results is immaterial to our condensed consolidated financial statements. Our business strategy incorporates potentially significant international expansion, particularly with the recent conditional approval of WAYLIVRA in the E.U., therefore we expect that the impact of foreign currency exchange rate fluctuations may become more substantial in the future.

### *Inflation Risk*

We do not believe that inflation has had a material effect on our business, financial condition or results of operations. If our costs were to become subject to significant inflationary pressures, we may not be able to fully offset such higher costs through price increases. Our inability or failure to do so could harm our business, financial condition and results of operations.

## **Item 4. Controls and Procedures**

### *Evaluation of Disclosure Controls and Procedures*

We maintain disclosure controls and procedures that are designed to ensure that information we are required to disclose in our Exchange Act of 1934, as amended, or the Exchange Act, reports is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms, and that such information is accumulated and communicated to our management, including our Chief Executive Officer and Chief Financial Officer, as appropriate, to allow timely decisions regarding required disclosure. We design and evaluate our disclosure controls and procedures recognizing that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance and not absolute assurance of achieving the desired control objectives.

As of our most recently completed fiscal year and as of the end of the period covered by this Quarterly Report on Form 10-Q, we carried out an evaluation of the effectiveness of the design and operation of our disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer. Based on our evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective as of March 31, 2019. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to March 31, 2019.

We also performed an evaluation of any change in our internal control over financial reporting that occurred during our last fiscal quarter and that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting. We implemented internal controls in connection with our adoption of ASU 2016-02, Leases (Topic 842). We conducted this evaluation under the supervision of and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer. That evaluation did not identify any significant changes in our internal control over financial reporting that occurred during our latest fiscal quarter and that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

### *Inherent Limitations on Effectiveness of Controls*

Our management, including our Chief Executive Officer and Chief Financial Officer, believes that our disclosure controls and procedures and internal control over financial reporting are designed to provide reasonable assurance of achieving their objectives and are effective at the reasonable assurance level. However, our management does not expect that our disclosure controls and procedures or our internal control over financial reporting will prevent all errors and all fraud. A control system, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. Further, the design of a control system must reflect the fact that there are resource constraints, and the benefits of controls must be considered relative to their costs. Because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that all control issues and instances of fraud, if any, have been detected. These inherent limitations include the realities that judgments in decision making can be faulty, and that breakdowns can occur because of a simple error or mistake. Additionally,

controls can be circumvented by the individual acts of some persons, by collusion of two or more people or by management override of the controls. The design of any system of controls also is based in part upon certain assumptions about the likelihood of future events, and there can be no assurance that any design will succeed in achieving its stated goals under all potential future conditions; over time, controls may become inadequate because of changes in conditions, or the degree of compliance with policies or procedures may deteriorate. Because of the inherent limitations in a cost-effective control system, misstatements due to error or fraud may occur and not be detected.

## **PART II — OTHER INFORMATION**

### **ITEM 1. LEGAL PROCEEDINGS**

From time to time, we may be involved in various claims and legal proceedings relating to claims arising out of our operations. We are not currently a party to any legal proceedings that, in the opinion of our management, are likely to have a material adverse effect on our business. Regardless of outcome, litigation can have an adverse impact on us because of defense and settlement costs, diversion of management resources and other factors.

### **ITEM 1A. RISK FACTORS**

*Investing in our securities involves a high degree of risk. You should consider carefully the following information about the risks described below, together with the other information contained in this Report and in our other public filings in evaluating our business. If any of the following risks actually occur, our business could be materially harmed, and our financial condition and results of operations could be materially and adversely affected. As a result, the trading price of our securities could decline, and you might lose all or part of your investment. The risks and uncertainties described below are not the only ones we face. Additional risks and uncertainties not presently known to us or that we currently believe to be immaterial may also adversely affect our business. The risk factors set forth below with an asterisk (\*) next to the title are new risk factors or risk factors containing changes, which may be material, from the risk factors previously disclosed in Item 1A of our Annual Report on Form 10-K for the fiscal year ended December 31, 2018.*

#### **Risks Related to Our Financial Condition and Need for Additional Capital**

*We have a limited operating history and may never become sustainably profitable.*

Ionis Pharmaceuticals, Inc., or Ionis, incorporated us as a Delaware corporation in December 2014, and we have operated as an affiliate of Ionis since that time. As such, we have limited experience as a company, and no experience operating independently from Ionis, and have not yet demonstrated that we can successfully overcome many of the risks and uncertainties frequently encountered in new and rapidly evolving fields, particularly the biotechnology and pharmaceutical fields.

As a company, we have limited experience commercializing products. Our ability to generate substantial revenue and achieve profitability depends on our ability, alone or with strategic partners, to successfully develop our drugs, obtain the regulatory approvals necessary to commercialize our drugs, including WAYLIVRA™ (volanesorsen), AKCEA-APO(a)-LRx, AKCEA-TTR-LRx and our other drugs in development, launch WAYLIVRA in the E.U., and continue the commercialization of TEGSEDI™ (inotersen). Although we received our first revenue from product sales in the fourth quarter of 2018, if we are not successful in growing revenue and controlling costs, we will not achieve sustainably profitable operations or positive cash flow. Our ability to generate revenue sufficient to achieve profitability from product sales depends heavily on our and our current and future strategic partners' success in:

- completing clinical development of WAYLIVRA for additional indications and nonclinical and clinical development of AKCEA-APO(a)-L Rx, AKCEA-TTR-LRx, AKCEA-ANGPTL3-LRx and AKCEA-APOCIII-LRx;
- seeking and obtaining initial or additional regulatory and marketing authorizations for our drugs, including TEGSEDI, WAYLIVRA, AKCEA-APO(a)-LRx and our other drugs in development;
- managing supply and manufacturing relationships with third parties that can provide the amount and quality of products and services we need to continue to commercialize TEGSEDI and WAYLIVRA and to develop and, if approved, commercialize AKCEA-APO(a)-L Rx, AKCEA-TTR-LRx and our other drugs in development;
- launching and commercializing WAYLIVRA, AKCEA-ANGPTL3-L Rx and AKCEA-TTR-LRx and continuing the commercialization of TEGSEDI by managing a sales, marketing and distribution infrastructure;
- launching and co-commercializing AKCEA-APO(a)-LRx and AKCEA-APOCIII-LRx through our collaboration with Novartis Pharma AG, or Novartis, under terms that we may negotiate with Novartis in the future;

- educating physicians about our target patient populations, including the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adult patients in the United States, stage 1 or stage 2 polyneuropathy in adult patients with hereditary TTR Amyloidosis, or hATTR, in the EU or Canada, patients with familial chylomicronemia syndrome, or FCS, and patients with familial partial lipodystrophy, or FPL;
- obtaining market acceptance of TEGSEDI, WAYLIVRA, AKCEA-APO(a)-L Rx, AKCEA-TTR-LRx and our other drugs in development as viable treatment options;
- obtaining and maintaining adequate coverage and reimbursement from third-party payors for TEGSEDI, WAYLIVRA, AKCEA-APO(a)-L Rx, AKCEA-TTR-LRx and our other drugs in development;
- addressing any competing technological and market developments;
- negotiating favorable terms in any partnership, licensing or other arrangements into which we may enter;
- maintaining, protecting and expanding our portfolio of intellectual property rights, including patents, product trademarks and know-how;
- developing and commercializing WAYLIVRA, AKCEA-ANGPTL3-LRx, AKCEA-TTR-LRx and our other drugs in development and continuing the commercialization of TEGSEDI without infringing others' intellectual property rights; and
- attracting, hiring and retaining qualified personnel.

We may not successfully develop our products or generate product revenue sufficient to cover operating expenses or become sustainably profitable. If we cannot achieve or maintain profitability, it would depress the market price of our common stock and could impair our ability to raise capital, expand our business, diversify our product offerings or continue our operations. If the market price of our common stock declined, you could lose all or part of your investment.

***We have mostly incurred losses since our inception.***

Because drug development requires substantial lead-time and funding prior to commercialization, we have generally incurred expenses while generating limited revenue from our operating activities since our formation. Our net income was \$27.2 million for the three months ended March 31, 2019 compared to a net loss of \$29.7 million for the three months ended March 31, 2018. We realized a net income during 2019 compared to a net loss incurred in 2018 primarily due to the \$150 million license fee related to Novartis' exercise of its option to license AKCEA-APO(a)-L Rx. As of March 31, 2019, we had an accumulated deficit of approximately \$494.9 million. We expect to incur additional operating losses for the foreseeable future, and these losses may increase if we cannot generate substantial revenue.

***We will require substantial additional funding to achieve our goals. If we fail to obtain timely funding, we may need to curtail or abandon some of our programs. \****

All of our drugs are undergoing clinical studies. All of our drug programs, except TEGSEDI in the United States, E.U., and Canada, and WAYLIVRA in the E.U., will require additional nonclinical and/or clinical testing and/or marketing authorization prior to commercialization. We will need to spend significant additional resources to conduct these activities. Our expenses could increase beyond expectations if the U.S. Food and Drug Administration, or FDA, the European Medicines Agency, or EMA, or other regulatory authorities require us to perform clinical studies and other studies in addition to those that we currently anticipate. As of March 31, 2019, we had cash, cash equivalents and investments equal to \$321.8 million. Our operating expenses were \$137.6 million and \$47.4 million for the three months ended March 31, 2019 and March 31, 2018, respectively.

Prior to our IPO, we funded our operating activities through a \$100.0 million cash contribution we received from Ionis in 2015, \$75.0 million that we received from initiating our collaboration with Novartis and \$106.0 million in drawdowns under our line of credit with Ionis. The line of credit converted to our common stock when we closed our IPO. We no longer have access to the line of credit following the closing of our IPO and we do not have any firm commitment from Ionis to fund our cash flow deficits or provide other direct or indirect financial assistance to us. Additionally, in July 2017 we received \$182.3 million in net proceeds from our IPO including \$25.0 million that Ionis invested in our IPO and the Novartis concurrent private placement of \$50.0 million. In April 2018, we received \$200.0 million from the common stock we issued in connection with the licensing transaction with Ionis discussed in Note 7, *License Agreements and Services Agreement with Ionis*, to our condensed consolidated financial statements included in this Form 10-Q. We expect that we will need to raise additional funding to continue developing the drugs in our pipeline and to seek regulatory approval for and to commercialize TEGSEDI, WAYLIVRA and other drugs in our pipeline.

We have received marketing authorization approval for TEGSEDI from the FDA for the treatment of the polyneuropathy of hATTR in adult patients in the United States, from the European Commission, or EC, and from Health Canada for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hATTR, and we will continue to incur significant costs commercializing TEGSEDI. Further, on May 3, 2019, we received conditional marketing authorization approval for WAYLIVRA from the EC as an adjunct to diet in adult patients with genetically confirmed FCS who are at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate. Even if we obtain marketing authorizations to sell AKCEA-APO(a)-LRx or AKCEA-TTR-LRx, additional marketing authorizations for WAYLIVRA or marketing authorizations for WAYLIVRA in other indications, we will incur significant costs to commercialize the approved product. To date, only one of our product(s), TEGSEDI, has commercially launched, and even if we generate substantial revenue from the sale of approved products, we may not become sustainably profitable and would need to obtain additional funding to continue operations.

#### **Risks Related to Clinical Development, Regulatory Review and Approval of Our Drugs**

*If the results of clinical testing indicate that any of our drugs are not suitable for commercial use, we may need to abandon one or more of our drug development programs.*

Drug discovery and development has inherent risks and the historical failure rate for drugs is high. Antisense drugs are a relatively new approach to therapeutics. If we cannot demonstrate that our drugs are safe and effective for human use in the intended indication, we may need to abandon one or more of our drug development programs.

If any of our drugs in clinical studies, including WAYLIVRA, AKCEA-APO(a)-LRx, AKCEA-TTR-LRx and our other drugs in development, do not show sufficient safety and efficacy in patients with the targeted indication, it would negatively affect our development and commercialization goals for the drug and we would have expended significant resources with little or no benefit to us.

*Even if our drugs are successful in preclinical and earlier-stage clinical studies, the drugs may not be successful in later-stage clinical studies. \**

Successful results in preclinical or initial clinical studies, including the results of earlier studies for our drugs in development, may not predict the results of subsequent clinical studies, including the Phase 3 study of WAYLIVRA for the treatment of FPL and the Phase 3 study of AKCEA-APO(a)-LRx in patients with established cardiovascular disease and elevated levels of lipoprotein(a). There are a number of factors that could cause a clinical study to fail or be delayed, including:

- the clinical study may produce negative or inconclusive results;
- regulators may require that we hold, suspend or terminate clinical research for noncompliance with regulatory requirements;
- we, our partners, the FDA or foreign regulatory authorities could suspend or terminate a clinical study due to adverse side effects of a drug on people in the study;
- we or our partners may decide, or regulators may require us, to conduct additional preclinical testing or clinical studies;
- we or our partners may not identify, recruit and train suitable clinical investigators at a sufficient number of study sites;
- the institutional review board for a prospective site might withhold or delay its approval for the study;
- enrollment in our clinical studies may be slower than we anticipate;
- patients who enroll in the clinical study may later drop out due to adverse events, a perception they are not benefiting from participating in the study, fatigue with the clinical study process or personal issues;
- a clinical study site may deviate from the protocol for the study;
- the cost of our clinical studies may be greater than we anticipate;
- we or our partners may require additional capital to fund the clinical study;
- our partners may decide not to exercise any existing options to license and conduct additional clinical studies for our drugs; and
- the supply or quality of our drugs or other materials necessary to conduct the clinical studies may be insufficient, inadequate or delayed.

In addition, WAYLIVRA and AKCEA-APOCIII-L Rx have the same mechanism of action, TEGSEDI and AKCEA-TTR-LRx, also have the same mechanism of action and all of our current drugs, including WAYLIVRA, AKCEA-APO(a)-L Rx, AKCEA-ANGPTL3-LRx and AKCEA-APOCIII-LRx, are chemically similar to each other and the drugs Ionis and other companies are developing separately. As a result, a safety observation we, Ionis or other companies encounter with one of our or their drugs could have or be perceived by a regulatory authority to have an impact on a different drug we are developing. This could cause the FDA and other regulators to ask questions or take actions that could harm or delay our ability to develop and commercialize our drugs or increase our costs. For example, the FDA or other regulatory agencies could request, among other things, any of the following regarding one of our drugs: additional information or commitments before we can start or continue a clinical study, protocol amendments, increased safety monitoring, additional product labeling information, and post-approval commitments. For example, in connection with the conditional marketing approval for WAYLIVRA in the E.U., the EC is requiring us to conduct a post-authorization safety study to evaluate the safety of WAYLIVRA on thrombocytopenia and bleeding in FCS patients taking WAYLIVRA. Similarly, we have an ongoing Phase 3 study of WAYLIVRA in patients with FPL, an ongoing open label extension study of WAYLIVRA in patients with FCS and an open label extension study of TEGSEDI in patients with hATTR, and a n early access program, or EAP, for both WAYLIVRA and TEGSEDI. Adverse events or results from these studies or the EAPs could negatively impact our pending or future marketing approval applications for WAYLIVRA and TEGSEDI in patients with FCS or hATTR amyloidosis or the commercial opportunity for WAYLIVRA or TEGSEDI. In August 2018, we received a Complete Response Letter, or CRL, from the FDA regarding the new drug application for WAYLIVRA in which the FDA determined that the safety concerns identified with WAYLIVRA in our clinical development program outweighed the expected benefits of triglyceride lowering in patients with FCS. We also received a Notice of Noncompliance withdrawal letter, or Non-W, from Health Canada for WAYLIVRA in November 2018. We and Ionis are engaged with the FDA and plan to work with Health Canada to confirm a path forward for WAYLIVRA. As a result, we will need to submit additional data to FDA and may need to conduct additional clinical studies before obtaining marketing authorization, which in turn could delay or prevent us from generating any revenue or profit from the sale of WAYLIVRA. Any failure or delay in the clinical studies for any of our drugs in development could reduce the commercial potential or viability of our drugs.

***We may not have appropriately designed the planned and ongoing clinical studies for WAYLIVRA, AKCEA-APO(a)-L Rx, AKCEA-TTR-LRx and our other drugs in development to support submission of a marketing application to the FDA and foreign regulatory authorities or demonstrate safety or efficacy at the level required by the FDA and foreign regulatory authorities for product approval. \****

We completed a Phase 3 clinical program for WAYLIVRA for the treatment of FCS in 2018 and are conducting or plan to conduct additional clinical studies for WAYLIVRA in patients with FPL, as well as for AKCEA-TTR-LRx, AKCEA-APO(a)-L Rx, AKCEA-ANGPTL3-LRx and AKCEA-APOCIII-LRx.

Even if we achieve positive results on the endpoints for these clinical studies or any future clinical studies, the FDA or foreign regulatory authorities may believe the clinical studies do not show the appropriate balance of safety and efficacy in the indication being sought or may interpret the data differently than we do, and deem the results insufficient to demonstrate the appropriate balance of safety and efficacy at the level required for product approval. For example, in August 2018, we received a CRL from the FDA regarding the new drug application for WAYLIVRA in which the FDA determined that the safety concerns identified with WAYLIVRA in our clinical development program outweighed the expected benefits of triglyceride lowering in patients with FCS. We also received a Non-W from Health Canada for WAYLIVRA in November 2018. We and Ionis are engaged with the FDA and plan to work with Health Canada to confirm a path forward for WAYLIVRA. As a result, we will need to submit additional data to the FDA and may need to conduct additional clinical studies before obtaining marketing authorization, which in turn could delay or prevent us from generating meaningful revenue or profit from the sale of WAYLIVRA. The CHMP of the EMA adopted a positive opinion recommending conditional marketing authorization of WAYLIVRA as an adjunct to diet in adult patients with genetically confirmed FCS who are at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate. The positive opinion was subsequently referred to the EC, which grants marketing authorization for medicines in the European Union, as well as to European Economic Area members Iceland, Liechtenstein and Norway. The EC decided to adopt the CHMP's positive opinion and on May 3, 2019 we received conditional marketing authorization approval for WAYLIVRA from the EC as an adjunct to diet in adult patients with genetically confirmed FCS who are at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate. Despite this recent conditional marketing authorization from the EC, these risks that we may not have appropriately designed the planned and ongoing clinical studies for WAYLIVRA, AKCEA-APO(a)-L Rx, AKCEA-TTR-LRx and our other drugs in development are more likely to occur since we are developing our drugs against therapeutic targets or to treat diseases in which there is little or no clinical experience. In addition, these risks may be more likely to occur for WAYLIVRA since there were some patients in the Phase 3 program that experienced serious platelet events (grade 4 thrombocytopenia), a condition in which the patient has very low platelet levels, and additional patients experienced other adverse events in the program, including patients who discontinued participation in the APPROACH study due to platelet count declines. We believe that the enhanced monitoring we have implemented to support early detection and management of these issues can help manage these safety issues so that patients can continue treatment. Since implementation of the enhanced monitoring, serious platelet events have been infrequent.

We may make modifications to the clinical study protocols or designs of our ongoing clinical studies that delay enrollment or completion of such clinical studies and could delay additional regulatory approvals for WAYLIVRA and initial regulatory approvals for our other drugs in development. Any failure to obtain an approval for WAYLIVRA, AKCEA-APO(a)-L Rx, AKCEA-TTR-LRx and our other drugs in development on the timeline that we currently anticipate, or at all, would have a material and adverse impact on our business, prospects, financial condition and results of operations and could cause our stock price to decline.

***Clinical studies for WAYLIVRA, AKCEA-APO(a)-L Rx, AKCEA-TTR-LRx, AKCEA-ANGPTL3-LRx, AKCEA-APOCIII-LRx or our other drugs may not demonstrate safety or efficacy at the level required by the FDA and foreign regulatory authorities for product approval. \****

In January 2019, the CHMP of the EMA adopted a positive opinion recommending conditional marketing authorization of WAYLIVRA as an adjunct to diet in adult patients with genetically confirmed FCS who are at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate. The positive opinion was subsequently referred to the EC, which grants marketing authorization for medicines in the European Union, as well as to European Economic Area members Iceland, Liechtenstein and Norway. The EC decided to adopt the CHMP's positive opinion and on May 3, 2019, we received conditional marketing authorization approval for WAYLIVRA from the EC as an adjunct to diet in adult patients with genetically confirmed FCS patients who are at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate. Despite the recent conditional marketing authorization from the EC for WAYLIVRA, the FDA and Health Canada may continue to deem the results from our clinical studies for WAYLIVRA insufficient to demonstrate the appropriate balance of safety and efficacy at the level required for product approval. We and Ionis are conducting or intend to conduct clinical studies for AKCEA-APO(a)-LRx, AKCEA-TTR-LRx, AKCEA-ANGPTL3-LRx and AKCEA-APOCIII-LRx.

Even if positive results on the endpoints for the clinical studies are achieved, the FDA or foreign regulatory authorities may believe the clinical studies do not show the appropriate balance of safety and efficacy in the indication being sought or may interpret the data differently than we do, and may deem the results insufficient to demonstrate the appropriate balance of safety and efficacy at the level required for product approval. For example, in August 2018 we received a CRL from the FDA regarding the new drug application for WAYLIVRA in which the FDA determined that the safety concerns identified with WAYLIVRA in our clinical development program outweighed the expected benefits of triglyceride lowering in patients with FCS. We also received a Non-W from Health Canada for WAYLIVRA in November 2018. We and Ionis are engaged with the FDA and plan to work with Health Canada to confirm a path forward for WAYLIVRA. As a result, we will need to submit additional data to FDA and may need to conduct additional clinical studies before obtaining marketing authorization, which in turn could delay or prevent us from generating any revenue or profit from the sale of WAYLIVRA. As an additional example, the foreign regulatory authorities could claim that we have not tested WAYLIVRA for additional indications, AKCEA-APO(a)-L Rx, AKCEA-TTR-LRx, AKCEA-ANGPTL3-LRx and AKCEA-APOCIII-LRx in a sufficient number of patients to demonstrate that the drug is safe and effective in patients with other indications to support an application for marketing authorization for the applicable indication. In such a case, we may need to conduct additional clinical studies before obtaining marketing authorization, which would be expensive and delay the development and commercialization of the drug.

Any failure to obtain approvals for WAYLIVRA in other important markets outside of the United States, Canada and the European Union, on the timeline that we currently anticipate, or at all, would have a material and adverse impact on our business, prospects, financial condition and results of operations and could cause our stock price to decline.

***If we or our partners fail to obtain regulatory approval for our drugs, including AKCEA-APO(a)-LRx, AKCEA-TTR-LRx and our other drugs in development, or additional approvals for TEGSEDI and WAYLIVRA, we or our partners cannot sell them in the applicable markets. \****

We cannot guarantee that any of our drugs, including WAYLIVRA, AKCEA-APO(a)-L Rx, AKCEA-TTR-LRx and our other drugs in development, will be safe and effective, or will be approved or receive additional approvals for commercialization, as applicable. We and our partners must conduct time-consuming, extensive and costly clinical studies to demonstrate the safety and efficacy of each of our drugs, including WAYLIVRA, AKCEA-APO(a)-L Rx, AKCEA-TTR-LRx and our other drugs in development, before they can be approved, or receive additional approvals, for sale. We and our partners must conduct these studies in compliance with FDA regulations and with comparable regulations in other countries.

We or our partners may not obtain necessary regulatory approvals on a timely basis, if at all, for any of our drugs. It is possible that regulatory authorities will not approve TEGSEDI in additional markets or WAYLIVRA in additional markets or for additional indications or any of our other drugs, including AKCEA-APO(a)-LRx, AKCEA-TTR-LRx and our other drugs in development, for marketing. If the FDA or another regulatory authority believes that we or our partners have not sufficiently demonstrated the safety or efficacy of any of our drugs, including WAYLIVRA, AKCEA-APO(a)-L Rx, AKCEA-TTR-LRx and our other drugs in development, the authority will not approve the specific drug or will require additional studies, which can be time consuming and expensive and which will delay or harm our ability to successfully commercialize the drug. For example, in August 2018, we received a CRL from the FDA regarding the new drug application for WAYLIVRA in which the FDA determined that the safety concerns identified with WAYLIVRA in our clinical development program outweighed the expected benefits of triglyceride lowering in patients with FCS. We also received a Non-W from Health Canada for WAYLIVRA in November 2018. We and Ionis are engaged with the FDA and plan to work with Health Canada to confirm a path forward for WAYLIVRA. As a result, we will need to submit additional data to FDA and may need to conduct additional clinical studies before obtaining marketing authorization, which in turn could delay or prevent us from generating any meaningful revenue or profit from the sale of WAYLIVRA.

The FDA or other comparable foreign regulatory authorities can delay, limit or deny approval of a drug for many reasons, including:

- such authorities may disagree with the design or implementation of our clinical studies;
- we or our partners may be unable to demonstrate to the satisfaction of the FDA or other regulatory authorities that a drug is safe and effective for any indication;
- such authorities may not accept clinical data from studies conducted at clinical facilities that have deficient clinical practices or that are in countries where the standard of care is potentially different from the United States;
- we or our partners may be unable to demonstrate that our drug's clinical and other benefits outweigh its safety risks to support approval;
- such authorities may disagree with the interpretation of data from preclinical or clinical studies;
- such authorities may find deficiencies in the manufacturing processes or facilities of third-party manufacturers who manufacture clinical and commercial supplies for our drugs; and
- the approval policies or regulations of such authorities or their prior guidance to us or our partners during clinical development may significantly change in a manner rendering our clinical data insufficient for approval.

Failure to successfully develop WAYLIVRA, AKCEA-APO(a)-L Rx, AKCEA-TTR-LRx and our other drugs in development, or to receive marketing authorization for these drugs in important markets or delays in these authorizations would prevent or delay the commercial launch of the drug, and, as a result, would negatively affect our ability to generate revenue.

***We may not be able to benefit from orphan drug designation for WAYLIVRA, TEGSEDI or any of our other drugs.***

The FDA and EMA have granted orphan drug designation to TEGSEDI and to WAYLIVRA for the treatment of patients with FCS. In addition, the EMA has granted orphan drug designation to WAYLIVRA for the treatment of patients with FPL. The FDA, however, refused to grant our request for orphan drug designation for WAYLIVRA for the treatment of patients with FPL in the United States in 2017.

In the United States, under the Orphan Drug Act, the FDA may designate a drug as an orphan drug if it is intended to treat a rare disease or condition, which is generally defined as a patient population of fewer than 200,000 individuals in the United States. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process, but it can provide financial incentives, such as tax advantages and user-fee waivers, as well as longer regulatory exclusivity periods.

Even if approval is obtained on a drug that has been designated as an orphan drug, we may lose orphan drug exclusivity if the FDA determines that the request for designation was materially defective or if we cannot assure sufficient quantity of the applicable drug to meet the needs of patients with the rare disease or condition, or if a competitor is able to gain approval for the same drug in a safer or more effective form or that makes a major contribution to patient care.

Even if we maintain orphan drug exclusivity for TEGSEDI or WAYLIVRA for the treatment of patients with FCS or obtain orphan drug exclusivity for our other drugs, the exclusivity may not effectively protect the drug from competition because regulatory authorities still may authorize different drugs for the same condition.

***We may expend our limited resources to pursue a particular drug or indication and fail to capitalize on drugs or indications that may be more profitable or for which there is a greater likelihood of success.***

We will continue to dedicate a substantial amount of our resources to commercialize TEGSEDI and support the continued development of AKCEA-TTR-LRx. In addition, we may dedicate a substantial amount of our resources to commercialize WAYLIVRA to for patients with FCS and to develop and seek regulatory approval for WAYLIVRA to treat patients with FPL. As a result, we may forego or delay pursuit of opportunities with our other drugs 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 drugs or profitable market opportunities. Our spending on current and future research and development programs and drugs for specific indications may not yield any commercially viable drugs.

*Our drugs, including TEGSEDI, WAYLIVRA, AKCEA-APO(a)-L Rx, AKCEA-TTR-LRx and our other drugs in development, could be subject to regulatory limitations following approval. \**

Following approval of a drug, we and our partners must comply with comprehensive government regulations regarding the manufacture, marketing and distribution of drug products. Promotional communications regarding prescription drugs must be consistent with the information in the product's approved labeling. We and our partners may not obtain the labeling claims necessary or desirable to successfully commercialize our drug products, including TEGSEDI and WAYLIVRA for FCS in the European Union, and if approved, WAYLIVRA for additional indications, AKCEA-APO(a)-L Rx, AKCEA-TTR-LRx and our other drugs in development.

The FDA and foreign regulatory authorities can impose significant restrictions on an approved drug product through the product label and on advertising, promotional and distribution activities. For example:

- In the United States, TEGSEDI's label contains a boxed warning for thrombocytopenia and glomerulonephritis,
- TEGSEDI requires periodic blood and urine monitoring, and
- in the United States TEGSEDI is available only through a Risk Evaluation and Mitigation Strategy, or REMS, program.

In addition, when approved, the FDA or a foreign regulatory authority may condition approval on the performance of post-approval clinical studies or patient monitoring, which could be time consuming and expensive. For example, in connection with the conditional marketing approval for WAYLIVRA in the E.U., the EC is requiring us to conduct a post-authorization safety study to evaluate the safety of WAYLIVRA on thrombocytopenia and bleeding in FCS patients taking WAYLIVRA. If the results of such post-marketing studies are not satisfactory, the FDA, EC, or other foreign regulatory authority may withdraw marketing authorization or may condition continued marketing on commitments from us or our partners that may be expensive and/or time consuming to fulfill.

In addition, if we or others identify side effects after any of our drug products are on the market, if manufacturing problems occur subsequent to regulatory approval, or if we, our manufacturers or our partners fail to comply with regulatory requirements, we or our partners could be subject to:

- changes to the product label;
- restrictions on the marketing of a product;
- restrictions on product distribution;
- restrictions on such products' manufacturing processes;
- requirements to conduct post-marketing clinical studies;
- Untitled or Warning Letters;
- withdrawal of the products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of products;
- fines, restitution or disgorgement of profits or revenue;
- suspension or withdrawal of regulatory approvals;
- refusal to permit the import or export of our products;
- product seizure;
- injunctions;
- restrictions on our ability to conduct clinical studies, including full or partial clinical holds on ongoing or planned clinical studies; or
- imposition of civil or criminal penalties.

Any one or a combination of these events could prevent us from achieving or maintaining market acceptance of the affected drug product or could substantially increase the costs and expenses of commercializing such drug product, which in turn could delay or prevent us from generating any revenue or profit from the sale of the drug product.

*The development and commercialization of TEGSEDI and WAYLIVRA may place strain on our management team's time and attention and may divert our management team's attention from our other existing products. \**

Although we have personnel with experience commercializing drugs, we ourselves have limited experience commercializing products. We commercially launched TEGSEDI during the fourth quarter of 2018 and, following our receipt of conditional marketing authorization approval from the EC, we plan to commercially launch WAYLIVRA in the European Union during 2019 as an adjunct to diet in patients with genetically confirmed FCS who are at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate. The commercial launch of TEGSEDI will continue to and the commercial launch of WAYLIVRA will require significant efforts and the devotion of substantial resources, as we finalize regulatory submissions, manage the manufacturing of sufficient quantities of product to support long-term commercial sales and integrate, optimize or maintain, as applicable, the global sales, marketing, medical, for each of WAYLIVRA and TEGSEDI, and patient support infrastructure, which may place pressure on the management team's time and attention. These efforts may also divert the attention of the management team from our other business operations, such as the development or commercialization of our other pipeline products, including AKCEA-APO(a)-LRx, AKCEA-TTR-LRx, AKCEA-ANGPTL3-LRx and AKCEA-APOCIII-LRx. As a result, our business, results of operations, financial condition and prospects for future growth could be adversely impacted and the market price of our common stock may decline.

#### **Risks Related to Commercialization of Our Drugs**

*If we cannot effectively manage our marketing and sales capabilities or enter into agreements with third parties to market and sell our drug products, we may not generate product revenue.*

We commercially launched TEGSEDI in the fourth quarter of 2018 and plan to commercialize WAYLIVRA in the European Union in 2019. To successfully commercialize TEGSEDI and WAYLIVRA, we must effectively manage our marketing, sales and distribution capabilities or make arrangements with third parties to perform these services. We may not be successful in doing so. To commercialize WAYLIVRA in the initial indications we plan to pursue and to continue the commercialization of TEGSEDI, we will need to optimize and maintain specialty sales forces in the global regions where we currently market or expect to market TEGSEDI and WAYLIVRA, supported by case managers, reimbursement specialists, partnerships with specialty pharmacies, injection training, routine blood and urine monitoring and a medical affairs team. We may seek to further penetrate markets by expanding our sales forces or through strategic partnerships with other pharmaceutical or biotechnology companies or third-party sales organizations.

Even though certain members of our management team and other employees have significant experience commercializing drugs, as a company we have limited experience marketing, selling or distributing drugs, and there are significant risks involved in building and managing a commercial infrastructure. It is expensive and time consuming for us to maintain our own sales forces and related compliance protocols to market TEGSEDI and WAYLIVRA, and it will be increasingly expensive and time consuming as we commercially launch additional drugs, if approved. We may never successfully optimize or manage this capability and any failure could delay or preclude the commercial launch of WAYLIVRA or adversely affect TEGSEDI sales. We and our partners, if any, will have to compete with other companies to recruit, hire, train, manage and retain marketing and sales personnel. As a result of our receipt of a CRL from the FDA regarding the new drug application for WAYLIVRA, on September 6, 2018, we enacted a plan to reorganize our workforce to better align with the immediate needs of our business. In connection with this reorganization plan, we reduced our workforce by approximately 12%. If WAYLIVRA is subsequently approved in the United States, we will again need to increase our operations and expand our use of third-party contractors.

We have incurred expenses launching TEGSEDI in the E.U., Canada and U.S. and will incur expenses launching WAYLIVRA in the European Union and integrating and managing the marketing and sales infrastructure. If regulatory requirements or other factors cause the commercialization of TEGSEDI or WAYLIVRA to be less successful than expected in important markets, we would incur additional expenses for having invested in these capabilities prior to realizing any significant revenue from sales of TEGSEDI or WAYLIVRA. Our sales force and marketing teams may not successfully commercialize TEGSEDI.

To the extent we decide to rely on third parties to commercialize TEGSEDI or WAYLIVRA in a particular geographic market, we may receive less revenue than if we commercialized TEGSEDI or WAYLIVRA by ourselves. For example, in August 2018, we granted PTC Therapeutics International Limited, or PTC Therapeutics, the exclusive right to commercialize TEGSEDI and WAYLIVRA in Latin America and certain Caribbean countries, and will continue to rely on PTC Therapeutics to commercialize TEGSEDI and WAYLIVRA in those geographic markets. In addition, in August 2018 we entered into an agreement with Accredo Health Group, Inc., or Accredo, a subsidiary of Express Scripts, to be our specialty pharmacy partner for distribution of TEGSEDI in the U.S. Further, we have less control over the sales efforts of other third parties, including PTC Therapeutics and Accredo, involved in commercializing TEGSEDI or WAYLIVRA.

If we cannot effectively build and manage our distribution, medical affairs, market access, marketing and sales infrastructure, or find a suitable third party to perform such functions, the sales of TEGSEDI and commercial launch of WAYLIVRA may be adversely affected, which could have a material adverse effect on our business, prospects, financial condition and results of operations.

***If we are unable to rely on third-party specialty channels to distribute our drugs to patients we may be unable to generate adequate revenue***

We and our strategic partners have contracted with, rely on and will continue to rely on third-party specialty pharmacies to distribute our drugs to patients. A specialty pharmacy is a pharmacy that specializes in dispensing medications for complex or chronic conditions, a process that requires a high level of patient education and ongoing management. Our management team will need to devote a significant amount of its attention to optimizing and managing this distribution network. If we cannot effectively optimize and manage this distribution process, the commercial launch of WAYLIVRA, AKCEA-APO(a)-LRx and AKCEA-TTR-LRx and the sales of TEGSEDI will be adversely affected.

In addition, the use of specialty pharmacies involves certain risks, including, but not limited to, risks that these organizations will:

- not provide us with accurate or timely information regarding their inventories, the number of patients who are using our drugs or complaints regarding our drugs;
- not effectively sell or support TEGSEDI, WAYLIVRA, AKCEA-APO(a)-LRx, AKCEA-TTR-LRx or our other drugs;
- reduce or discontinue their efforts to sell or support TEGSEDI, WAYLIVRA, AKCEA-APO(a)-LRx, AKCEA-TTR-LRx or our other drugs;
- not devote the resources necessary to sell TEGSEDI, WAYLIVRA, AKCEA-APO(a)-LRx, AKCEA-TTR-LRx or our other drugs in the volumes and within the time frames that we expect;
- not satisfy financial obligations to us or others; or
- cease operations.

Any such events may result in decreased sales and lower revenue, which could have a material adverse effect on our business, prospects, financial condition and results of operations.

***If the market does not accept our drugs, including TEGSEDI, WAYLIVRA, AKCEA-TTR-LRx and our other drugs in development, we are not likely to generate substantial product revenue or become profitable. \****

Even though we have obtained marketing authorization approval from the FDA, the EC and Health Canada for TEGSEDI, conditional marketing authorization approval from the EC for WAYLIVRA and if we or our strategic partners obtain a marketing authorization for WAYLIVRA in the United States or Canada or for additional indications, AKCEA-APO(a)-LRx, AKCEA-TTR-LRx and our other drugs in development, our success will depend upon the medical community, patients and third-party payors accepting our drugs as medically useful, cost-effective, safe and convenient. Even if the FDA or foreign regulatory authorities authorize our drugs for commercialization, doctors may not prescribe our drugs to treat patients. We and our partners may not successfully commercialize additional drugs.

Additionally, in many of the markets where we or our partners may sell our drugs in the future, if we cannot agree with the government or other third-party payors regarding the price we can charge for our drugs, then we may not be able to sell our drugs in that market. Similarly, cost control initiatives by governments or third-party payors could decrease the price received for our drugs or increase patient coinsurance to a level that makes the continued commercializing of TEGSEDI and the commercializing of WAYLIVRA, AKCEA-APO(a)-LRx, AKCEA-TTR-LRx and our other drugs in development economically unviable.

The degree of market acceptance for TEGSEDI, WAYLIVRA, AKCEA-APO(a)-LRx, AKCEA-TTR-LRx and our other drugs in development depends upon a number of factors, including the:

- receipt and scope of marketing authorizations;
- establishment and demonstration in the medical and patient community of the efficacy and safety of our drugs and their potential advantages over competing products;
- cost and effectiveness of our drugs compared to other available therapies;
- patient convenience of the dosing regimen for our drugs; and
- reimbursement by government and third-party payors.

Based on the profile of our drugs, physicians, patients, patient advocates, payors or the medical community in general may not accept and/or use any drugs that we may develop.

For example, the product label for TEGSEDI in the United States has a boxed warning for thrombocytopenia and glomerulonephritis, requires periodic blood and urine monitoring, and TEGSEDI has a Risk Evaluation and Mitigation Strategy, or REMS, program. Our main competition in the U.S. market for TEGSEDI is ONPATTRO (patisiran), marketed by Alnylam Pharmaceuticals, Inc. Although ONPATTRO requires intravenous administration and pre-treatment with steroids, it does not have a boxed warning or REMS. Additionally, the product label for WAYLIVRA will require periodic blood monitoring. In each case, these label requirements could negatively affect our ability to attract and retain patients for these drugs. We believe that the enhanced monitoring we have implemented to support early detection and management of these issues can help manage these safety issues so that patients can continue treatment. Since implementation of the enhanced monitoring, serious platelet events have been infrequent. While we believe we can better maintain patients on TEGSEDI and WAYLIVRA through our patient-centric commercial approach where we plan to have greater involvement with physicians and patients, if we cannot effectively maintain patients on TEGSEDI and WAYLIVRA, we may not be able to generate substantial revenue from TEGSEDI and WAYLIVRA sales.

***The patient populations suffering from FCS and FPL are small and have not been established with precision. If the actual number of patients is smaller than we estimate, or if we cannot raise awareness of these diseases and diagnosis is not improved, our revenue and ability to achieve profitability from WAYLIVRA may be adversely affected.***

We estimate there are 3,000 to 5,000 FCS patients and an additional 3,000 to 5,000 FPL patients globally. Our estimates of the sizes of the patient populations are based on published studies as well as internal analyses. If the results of these studies or our analyses of them do not accurately reflect the number of patients with FCS and FPL, our assessment of the market potential for WAYLIVRA may be inaccurate, making it difficult or impossible for us to meet our revenue goals, or to obtain and maintain profitability. In addition, as is the case with most orphan diseases, if we cannot successfully raise awareness of these diseases and improve diagnosis, it will be more difficult or impossible to achieve profitability.

In addition, since the patient populations for FCS and FPL are small, the per-patient drug pricing must be priced appropriately in order to recover our development and manufacturing costs, fund adequate patient support programs and achieve profitability. For these initial indications, we may not maintain or obtain sufficient sales volume at a price that justifies our product development efforts and our sales and marketing and manufacturing expenses.

***The patient population suffering from hATTR amyloidosis is small and has not been established with precision. If the actual number of patients is smaller than we estimate, or if we cannot raise awareness of the disease and diagnosis is not improved, our revenue and ability to achieve profitability from either TEGSEDI or AKCEA-TTR-LRx may be adversely affected.***

Our estimate of the sizes of the patient populations are based on published studies as well as internal analyses. If the results of these studies or our analyses of them do not accurately reflect the number of patients with hATTR amyloidosis, our assessment of the market potential for either TEGSEDI or AKCEA-TTR-LRx may be inaccurate, making it difficult or impossible for us to meet our revenue goals, or to obtain and maintain profitability. In addition, as is the case with most orphan diseases, if we cannot successfully raise awareness of these diseases and improve diagnosis, it will be more difficult or impossible to achieve profitability. For these initial indications, we may not maintain or obtain sufficient sales volume at a price that justifies our product development efforts and our sales and marketing and manufacturing expenses.

***If we or our partners fail to compete effectively, WAYLIVRA, TEGSEDI and our other drugs in development will not contribute significant revenue.***

Our competitors engage in drug discovery throughout the world, are numerous and include, among others, major pharmaceutical companies and specialized biopharmaceutical firms. Our competitors may succeed in developing drugs that are:

- safer than our drugs;
- more effective than our drugs;
- priced lower than our drugs;
- reimbursed more favorably by government and other third-party payors than our drugs; or
- more convenient to use than our drugs.

These competitive developments could make our drugs, including WAYLIVRA, TEGSEDI, AKCEA-APO(a)-L Rx, AKCEA-TTR-LRx and our other drugs in development, obsolete or non-competitive. Further, all of our drugs are delivered by injection, which may render them less attractive to patients than non-injectable products offered by our current or future competitors.

Many of our competitors have substantially greater financial, technical and human resources than we do. In addition, many of these competitors have significantly greater experience than we do in conducting preclinical testing and human clinical studies, in obtaining FDA and other regulatory authorizations and in commercializing pharmaceutical products. Accordingly, our competitors may succeed in obtaining regulatory authorization for products earlier than we do. Marketing and sales capability is another factor relevant to the competitive position of our drugs, and many of our competitors will have greater marketing and sales capabilities than our capabilities.

There are several pharmaceutical and biotechnology companies engaged in the development or commercialization of products against targets that are also targets of drugs in our development pipeline. For example, WAYLIVRA could face competition from drugs like metreleptin and gemcabene. Metreleptin, produced by Novelson Therapeutics, Inc., is currently approved in the U.S. and E.U. for use in generalized lipodystrophy patients. WAYLIVRA may also compete with gemcabene, an oral small molecule that reduces apoC-III, that Gemphire Therapeutics, Inc. is developing to treat patients with triglycerides above 500 mg/dL.

As an additional example, TEGSEDI could face competition from drugs like ONPATTRO, marketed by Alnylam for hATTR amyloidosis with polyneuropathy in the U.S. and E.U., tafamidis, available in the E.U. for stage 1 hATTR amyloidosis with polyneuropathy and under review in the U.S. for ATTR with cardiomyopathy, and AG10, which is being developed by Eidos for patients with ATTR with cardiomyopathy. For example, ONPATTRO is approved in the United States and Europe for a similar and broader indication as TEGSEDI. AG10, which recently completed its Phase 2 dose-finding study, is an orally administered TTR tetramer stabilizer for ATTR amyloidosis. If WAYLIVRA, TEGSEDI or the other drugs in our pipeline cannot compete effectively with these and other products with common or similar indications to the drugs in our pipeline, we may not be able to generate substantial revenue from our product sales.

***If government or other third-party payors fail to provide adequate coverage and payment rates for TEGSEDI, WAYLIVRA, AKCEA-APO(a)-LRx, AKCEA-TTR-LRx and our other drugs in development, our revenue and prospects for profitability will be limited. \****

In both domestic and foreign markets, sales of our future products will depend in part upon the availability of coverage and reimbursement from third-party payors. The majority of patients in the United States who would fit within our target patient populations for our drugs have their healthcare supported by a combination of Medicare coverage, other government health programs such as Medicaid, managed care providers, private health insurers and other organizations. Coverage decisions may depend upon clinical and economic standards that disfavor new drug products when more established or lower cost therapeutic alternatives are already available or subsequently become available. Assuming coverage is approved, the resulting reimbursement payment rates might not be enough to make our drugs affordable. Accordingly, TEGSEDI and WAYLIVRA for FCS in the European Union and, if approved, WAYLIVRA in the United States or Canada and for additional indications, AKCEA-APO(a)-LRx, AKCEA-TTR-LRx and our other drugs in development, will face competition from other therapies and drugs for limited financial resources. We may need to conduct post-marketing studies to demonstrate the cost-effectiveness of any future products to satisfy third-party payors. These studies might require us to commit a significant amount of management time and financial and other resources. Third-party payors may never consider our future products as cost-effective. Adequate third-party coverage and reimbursement might not be available to enable us to maintain price levels sufficient to realize an appropriate return on investment in product development.

Third-party payors, whether foreign or domestic, or governmental or commercial, are developing increasingly sophisticated methods of controlling healthcare costs. In addition, in the United States, no uniform policy of coverage and reimbursement for drug products exists among third-party payors. Therefore, coverage and reimbursement for drug products can differ significantly from payor to payor. Further, we believe that future coverage and reimbursement will likely be subject to increased restrictions both in the United States and in international markets. For example, in the United States, recent health reform measures have resulted in reductions in Medicare and other healthcare funding, and there have been several recent U.S. Congressional inquiries and proposed federal legislation designed to, among other things, reform government program reimbursement methodologies for drug products and bring more transparency to drug pricing. Third-party coverage and reimbursement for our products or drugs may not be available or adequate in either the United States or international markets, which would negatively affect the potential commercial success of our products, our revenue and our profits.

***If we are found in violation of federal or state "fraud and abuse" laws or other healthcare laws and regulations, we may be required to pay a penalty and/or be suspended from participation in federal or state healthcare programs, which may adversely affect our business, financial condition and results of operation.***

We may be subject to various federal and state laws pertaining to healthcare "fraud and abuse," including anti-kickback laws and false claims laws. Anti-kickback laws, among other things, make it illegal for a prescription drug manufacturer to pay, or offer to pay, a healthcare provider to refer, purchase or prescribe a particular drug. Due to the breadth of the statutory and regulatory provisions, it is possible that government authorities and others might challenge our practices under anti-kickback or other fraud and abuse laws. Moreover, recent healthcare reform legislation has strengthened these laws. In addition, false claims laws prohibit anyone from knowingly and willingly presenting, or causing to be presented for payment, to government third-party payors, including Medicare and Medicaid claims for reimbursed drugs that are false or fraudulent, claims for items or services not provided as claimed, or claims for medically unnecessary items or services. Our activities relating to the sale and marketing of our products may be subject to scrutiny under these laws. If we violated fraud and abuse laws, we could face a combination of:

- criminal and civil sanctions, including fines and civil monetary penalties;

- the possibility of exclusion from federal healthcare programs, including Medicare and Medicaid; and
- corporate integrity agreements, which could impose rigorous operational and monitoring requirements on us.

Given the significant penalties and fines that the government can impose on companies and individuals if convicted, allegations of violations often result in settlements even if the company or individual being investigated admits no wrongdoing. Settlements often include significant civil sanctions, including fines and civil monetary penalties, and corporate integrity agreements. If the government were to allege or convict us or our executive officers of violating these laws, our business could be harmed. In addition, private individuals may bring similar actions under the False Claims Act. Our activities could be subject to challenge for the reasons discussed above and due to the broad scope of these laws and the increasing focus on these laws by law enforcement authorities. To the extent we have access to protected health information we could be subject to foreign and federal and state health information privacy and security laws, including without limitation, the Health Insurance Portability and Accountability Act of 1996, or HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, which governs the conduct of certain electronic healthcare transactions and protects the security and privacy of protected health information; and analogous foreign and state laws governing the privacy and security of health information, such as the General Data Protection Regulation, or GDPR in the E.U., and the California Consumer Privacy Act, or CCPA, in California, some of which are more stringent than HIPAA and many of which differ from each other in significant ways and may not have the same effect; and the Physician Payments Sunshine Act, which requires manufacturers of medicines, devices, biologic and medical supplies to report annually to the U.S. Department of Health and Human Services information related to payments and other transfers of value to physicians and teaching hospitals, and ownership and investment interests held by physicians and their immediate family members. Our failure to comply with applicable federal and state health information privacy and security laws could subject us to significant fines and multi-year corrective action plans. TEGSEDI commercially launched in the U.S. in the fourth quarter of 2018 and as such we are now required to report annually to Centers for Medicare and Medicaid Services certain information related to payments and other transfers of value we may provide to physicians and teaching hospitals. Further, an increasing number of state laws require manufacturers to make reports to states on pricing and marketing information. Many of these laws are unclear as to what is required to comply with the laws. Given the lack of clarity in laws and their implementation, our reporting actions could be subject to the penalty provisions of the pertinent state authorities.

Similar rigid restrictions related to anti-kickbacks and promoting and marketing medicinal products apply in the European Union and other countries. Authorities in these countries strictly enforce these restrictions. Even in those countries where we will not be directly responsible for promoting and marketing our products, inappropriate activity by any of our international commercialization partners we may have could harm us.

#### **Risks Related to Dependence on Third Parties**

*We plan to substantially depend on our collaboration with Novartis to develop and commercialize AKCEA-APO(a)-LRx and AKCEA-APOCIII-LRx.*

We have granted Novartis an exclusive option to exclusively license each of AKCEA-APO(a)-LRx and AKCEA-APOCIII-LRx pursuant to our strategic collaboration, option and license agreement with Novartis. In February 2019, Novartis exercised its option to license AKCEA-APO(a)-LRx. We plan to substantially depend on Novartis to further develop and commercialize AKCEA-APO(a)-LRx and potentially AKCEA-APOCIII-LRx. We initiated this collaboration primarily to have Novartis:

- conduct the cardiovascular outcome studies that are likely to be required for approval of AKCEA-APO(a)-LRx and AKCEA-APOCIII-LRx;
- seek and obtain regulatory approvals for AKCEA-APO(a)-LRx and AKCEA-APOCIII-LRx; and
- globally commercialize AKCEA-APO(a)-LRx and AKCEA-APOCIII-LRx.

Since Novartis has exercised its option to license AKCEA-APO(a)-LRx, we will rely on Novartis to further develop, obtain regulatory approvals for, and commercialize it. In general, we cannot control the amount and timing of resources that Novartis devotes to our strategic collaboration. If Novartis fails to use commercially reasonable efforts to further develop, obtain regulatory approvals for, or commercialize AKCEA-APO(a)-LRx, or if Novartis' efforts are not effective, our business may be negatively affected. Novartis could pursue other technologies or develop other drugs either on its own or in collaboration with others to treat the same diseases as we and Novartis plan to treat with AKCEA-APO(a)-LRx. Novartis could pursue these technologies and develop these other drugs at the same time as it is developing or commercializing AKCEA-APO(a)-LRx, and Novartis is not required to inform us of such activities.

If Novartis exercises its option to license AKCEA-APOCIII-LRx, we would rely on Novartis to further develop, obtain regulatory approvals for, and commercialize it. In general, we cannot control the amount and timing of resources that Novartis devotes to our strategic collaboration. If Novartis fails to use commercially reasonable efforts to further develop, obtain regulatory approvals for, or commercialize AKCEA-APOCIII-LRx, or if Novartis' efforts are not effective, our business may be negatively affected. Novartis could pursue other technologies or develop other drugs either on its own or in collaboration with others to treat the same disease as we and Novartis plan to treat with AKCEA-APOCIII-LRx. Novartis could pursue these technologies and develop these other drugs at the same time as it is developing or commercializing AKCEA-APOCIII-LRx and Novartis is not required to inform us of such activities.

Our strategic collaboration with Novartis may not continue for various reasons. Novartis can terminate our agreement at any time and is under no obligation to exercise the options we granted them. If Novartis stops developing or commercializing AKCEA-APO(a)-LRx, or does not exercise its option to license AKCEA-APOCIII-LRx, we will have to seek additional sources for funding and may have to delay or reduce our development and commercialization plans for these drugs.

In addition, following Novartis' exercise of its option to license AKCEA-APO(a)-LRx, and if Novartis exercises its option to license AKCEA-APOCIII-LRx, Novartis will be responsible for the long-term supply of drug substance and finished drug product for the licensed drug.

Our strategic collaboration with Novartis may not result in the successful commercialization of AKCEA-APO(a)-LRx or AKCEA-APOCIII-LRx. If Novartis does not successfully develop, manufacture or commercialize AKCEA-APO(a)-LRx or AKCEA-APOCIII-LRx, we may receive limited or no revenues for these drugs.

***We plan to substantially depend on our collaboration with PTC Therapeutics to commercialize TEGSEDI and WAYLIVRA in Latin America and certain Caribbean countries.***

In August 2018, we granted PTC Therapeutics International Limited the exclusive right to commercialize TEGSEDI and WAYLIVRA in Latin America and certain Caribbean countries. We plan to substantially depend on PTC to commercialize these drugs in those geographic markets.

In general, we cannot control the amount and timing of resources that PTC devotes to our strategic collaboration. If PTC fails to use commercially reasonable efforts to obtain regulatory approvals for, or commercialize these drugs, or if PTC's efforts are not effective, our business may be negatively affected. PTC could pursue other technologies or develop other drugs either on its own or in collaboration with others to treat the same diseases as we and PTC plan to treat with TEGSEDI and WAYLIVRA. PTC could pursue these technologies and develop these other drugs at the same time as it is developing or commercializing TEGSEDI and WAYLIVRA, and PTC is not required to inform us of such activities.

Our strategic collaboration with PTC may not continue for various reasons. If PTC stops commercializing a drug, we will have to seek additional sources for funding and may have to delay or reduce our commercialization plans for TEGSEDI and WAYLIVRA in Latin America or certain Caribbean countries.

Our strategic collaboration with PTC may not result in the successful commercialization of TEGSEDI or WAYLIVRA in Latin America or certain Caribbean countries. If PTC does not successfully commercialize TEGSEDI or WAYLIVRA, we may receive limited revenue for TEGSEDI or no revenue for WAYLIVRA in Latin America or certain Caribbean countries.

***AKCEA-APOCIII-LRx and AKCEA-ANGPTL3-LRx may compete with WAYLIVRA, which could reduce our expected revenues for WAYLIVRA.***

WAYLIVRA and AKCEA-APOCIII-LRx both inhibit the production of the same protein. We believe the enhancements we incorporated into AKCEA-APOCIII-LRx can provide greater patient convenience by allowing for significantly lower doses and less frequent administration compared to WAYLIVRA. As such, if Novartis exercises its option and successfully commercializes AKCEA-APOCIII-LRx while we are commercializing WAYLIVRA, to the extent physicians and patients elect to use AKCEA-APOCIII-LRx instead of WAYLIVRA, it will reduce the revenue we derive from WAYLIVRA. In addition, while AKCEA-ANGPTL3-LRx and WAYLIVRA use different mechanisms of action, if AKCEA-ANGPTL3-LRx can effectively lower triglyceride levels in FCS patients, it may likewise reduce the revenue we derive from WAYLIVRA.

***If we cannot manufacture our drugs or contract with a third party to manufacture our drugs at costs that allow us to charge competitive prices to buyers, we will not be able to operate profitably. \****

To successfully commercialize TEGSEDI, and WAYLIVRA for FCS in the European Union and, if approved, WAYLIVRA in the United States or Canada and for additional indications, AKCEA-TTR-LRx and our other drugs in development, we will need to optimize and manage large-scale commercial manufacturing capabilities either on our own or through a third-party manufacturer. In addition, as our drug development pipeline matures, we will have a greater need for clinical study and commercial manufacturing capacity. We have no direct experience manufacturing pharmaceutical products of the chemical class represented by our drugs, called oligonucleotides, on a commercial scale for the systemic administration of a drug. We currently rely and expect to rely for the foreseeable future on Ionis' manufacturing capacity and efficiency and the capacity and efficiency of third parties to produce our oligonucleotide drugs, and our business could be negatively affected if Ionis and these third parties ceased to provide us with this capability for any reason. In addition, there are a small number of suppliers for certain raw materials that we use to manufacture our drugs, and some of these suppliers will need to increase their scale of production to meet our projected needs for commercial manufacturing. Further, if we cannot continue to acquire raw materials from these suppliers on commercially reasonable terms or at all, we may be required to find alternative suppliers, which could be expensive and time consuming and negatively affect our ability to develop or commercialize our drugs in a timely manner or at all. We may not be able to manufacture our drugs at a cost or in quantities necessary to make commercially successful products.

We do not have long-term supply agreements for our drugs. We cannot guarantee that we will have a steady supply of drug to complete clinical studies, make registration batches for approval or satisfy market demand if commercialized at prices that are commercially acceptable. In addition, if we need to change manufacturers for any reason, we will need to verify that the new manufacturer maintains facilities and procedures that comply with quality standards and with all applicable regulations and guidelines. The delays associated with verifying a new manufacturer could negatively affect our ability to develop drugs in a timely manner or within budget.

Also, manufacturers must adhere to the FDA's current Good Manufacturing Practices regulations and similar regulations in foreign countries, which the applicable regulatory authorities enforce through facilities inspection programs. Our contract manufacturers may not comply or maintain compliance with Good Manufacturing Practices, or similar foreign regulations. Non-compliance could significantly delay or prevent receipt of marketing authorization for our drugs, including authorizations for WAYLIVRA, AKCEA-APO(a)-LRx, AKCEA-TTR-LRx and our other drugs in development, or result in enforcement action after authorization that could limit the commercial success of our drugs, including WAYLIVRA, TEGSEDI, AKCEA-APO(a)-LRx, AKCEA-TTR-LRx and our other drugs in development.

***We depend on Ionis and third parties to conduct our clinical studies for our drugs and any failure of those parties to fulfill their obligations could adversely affect our development and commercialization plans.***

We depend on Ionis and independent clinical investigators, contract research organizations and other third-party service providers to conduct the clinical studies for our drugs and expect to continue to do so in the future. For example, we use clinical research organizations for the clinical studies for WAYLIVRA, AKCEA-APO(a)-LRx, AKCEA-TTR-LRx and our other drugs in development. We rely heavily on these parties for successful execution of our clinical studies, but do not control many aspects of their activities. For example, the investigators are not our employees. However, we are responsible for ensuring that these third parties conduct each of our clinical studies in accordance with the general investigational plan, approved protocols for the study and applicable regulations. Ionis and third parties may not complete activities on schedule or may not conduct our clinical studies in accordance with regulatory requirements or our stated protocols. The failure of these parties to carry out their obligations or a termination of our relationship with these third parties could delay or prevent the development, marketing authorization and commercialization of our drugs, including authorizations for WAYLIVRA, AKCEA-APO(a)-LRx, AKCEA-TTR-LRx and our other drugs in development.

***We may seek to form additional partnerships in the future with respect to WAYLIVRA, and our other drugs in development, and we may not realize the benefits of such partnerships.***

Although we intend to develop and commercialize WAYLIVRA for patients with FCS and FPL ourselves, we may form partnerships, create joint ventures or collaborations or enter into licensing arrangements with third parties for the development and commercialization of our drugs in development. For example, we have granted PTC an exclusive license to commercialize WAYLIVRA in Latin America and certain Caribbean countries. We face significant competition in seeking appropriate strategic partners and the negotiation process is time-consuming and complex. Any delays in entering into new strategic partnership agreements related to our drugs could delay the development and commercialization of our drugs and reduce their competitiveness even if they reach the market. Moreover, we may not be successful in our efforts to establish other strategic partnerships or other collaborative arrangements for any additional drugs because the potential partner may consider that our development pipeline is not advanced enough to justify a collaborative effort, or that WAYLIVRA and our other drugs in development do not have the requisite potential to demonstrate safety and efficacy in the target populations in other geographic markets. In addition, we will need to mutually agree with Ionis on the terms of any additional sublicenses to a third party for WAYLIVRA and our other drugs in development. If we cannot

mutually agree on terms for a sublicense to a third party or if Ionis does not agree to a sublicense at all, it could delay our ability to develop and commercialize WAYLIVRA and our other drugs in development. Even if we are successful in establishing such a strategic partnership or collaboration, we cannot be certain that, following such a strategic transaction or collaboration, we will be able to progress the development and commercialization of the applicable drugs as envisioned, or that we will achieve the revenue that would justify such transaction. If we do not accurately evaluate the commercial potential or target market for a particular drug, we may relinquish valuable rights to that drug through future collaboration, licensing or other arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights.

### **Risks Related to Our Relationship with Ionis**

***Ionis controls the direction of our business, and the concentrated ownership of our common stock will prevent you and other stockholders from influencing significant decisions. \****

Ionis owns 70,221,338 shares of our common stock, or approximately 76 percent, of the economic interest and voting power of our outstanding common stock as of May 2, 2019, which ownership will be expected to increase further if we achieve certain milestone events and pay the associated milestone payment in shares of common stock pursuant to the payment election. As long as Ionis beneficially controls a majority of the voting power of our outstanding common stock, it will generally be able to determine the outcome of all corporate actions requiring stockholder approval, including the election and removal of directors. Even if Ionis were to control less than a majority of the voting power of our outstanding common stock, it may influence the outcome of such corporate actions so long as it owns a significant portion of our common stock. If Ionis continues to hold its shares of our common stock, it could remain our controlling stockholder for an extended period of time or indefinitely.

The licensing transaction with Ionis and the common stock issuances in connection with the achievement of the TEGSEDI regulatory milestones has increased Ionis' ownership percentage, and this increase, along with Ionis' increased reliance on Akcea as a commercialization partner, given that Akcea could now be commercializing at least two Ionis-developed products (WAYLIVRA and TEGSEDI), may increase the length of time during which Ionis will control us. As a general matter, the TEGSEDI license agreement and the related Investor Rights Agreement increased Ionis' control over our affairs. In addition, our TEGSEDI licensing agreement requires Ionis' consent to the budget related to the commercialization of TEGSEDI and AKCEA-TTR-LRx.

Ionis' interests may not be the same as, or may conflict with, the interests of our other stockholders. You will not be able to affect the outcome of any stockholder vote while Ionis controls the majority of the voting power of our outstanding common stock. As a result, Ionis can control, directly or indirectly and subject to applicable law, all matters affecting us, including:

- any determination with respect to our business strategy and policies, including the appointment and removal of officers and directors;
- any determinations with respect to mergers, business combinations or disposition of assets;
- our financing and dividend policy;
- compensation and benefit programs and other human resources policy decisions;
- termination of, changes to or determinations under our existing license agreements and services agreement with Ionis;
- changes to any other agreements that may adversely affect us; and
- determinations with respect to our tax returns.

Because Ionis' interests may differ from ours or yours, actions that Ionis takes with respect to us, as our controlling stockholder, may not be favorable to us or you.

***As a "controlled company" under the marketplace rules of the Nasdaq Stock Market, we may rely on exemptions from certain corporate governance requirements that provide protection to stockholders of companies that are subject to such requirements.***

Ionis beneficially owns more than 50% of the voting power of our outstanding common stock. As a result, we are a "controlled company" under the marketplace rules of the Nasdaq Stock Market, or Nasdaq, and eligible to rely on exemptions from Nasdaq corporate governance requirements generally obligating listed companies to maintain:

- A board of directors having a majority of independent directors;
- A compensation committee composed entirely of independent directors that approves the compensation payable to the company's chief executive officer and other executive officers; and
- A nominating committee composed entirely of independent directors that nominates candidates for election to the board of directors, or that recommends such candidates for nomination by the board of directors (or obligating the listed company to cause a majority of the board's independent directors to exercise this oversight of director nominations).

Currently, a majority of our board is made up of independent directors. As a controlled company, we have and in the future may avail ourselves of some of these exemptions. Accordingly, our stockholders may not have the same protections afforded to stockholders of companies that are subject to the Nasdaq corporate governance requirements described above.

***If Ionis sells a controlling interest in our company to a third party in a private transaction, you may not realize a change of control premium on shares of our common stock, and we may become subject to the control of a presently unknown third party.***

Ionis owns a significant equity interest in our company. This means that Ionis could choose to sell some or all of its shares of our common stock in a privately negotiated transaction, which, if sufficient in size, could result in a change of control of our company.

Ionis' ability to privately sell its shares of our common stock, with no requirement for a concurrent offer to be made to acquire your shares of our common stock, could prevent you from realizing any change of control premium on your shares of our common stock that may otherwise accrue to Ionis on its private sale of our common stock. Additionally, if Ionis privately sells its significant equity interest in our company, we may become subject to the control of a presently unknown third party. Such third party may have conflicts of interest with those of other stockholders. In addition, if Ionis sells a controlling interest in our company to a third party, such a sale could negatively impact or accelerate any future indebtedness we may incur, and negatively impact any other commercial agreements and relationships, all of which may adversely affect our ability to run our business as described herein and may have a material adverse effect on our operating results and financial condition.

***Certain of our directors and officers may have actual or potential conflicts of interest because of their positions with Ionis.***

Damien McDevitt, Chief Business Officer for Ionis, and B. Lynne Parshall, Senior Strategic Advisor and board member for Ionis, serve on our board of directors and retain their positions or engagements with Ionis. In addition, these individuals own Ionis equity and Ionis equity awards. Ionis common stock, options to purchase Ionis common stock and other Ionis equity awards represent a significant portion of these individuals' net worth. Their position at Ionis and the ownership of any Ionis equity or equity awards creates, or may create the appearance of, conflicts of interest when we ask these individuals to make decisions that could have different implications for Ionis than the decisions have for us. In addition, our certificate of incorporation provides for the allocation of certain corporate opportunities between us and Ionis. Under these provisions, neither Ionis or its other affiliates, nor any of their officers, directors, agents or stockholders, will have any obligation to present to us certain corporate opportunities. For example, a director of our company who also serves as a director, officer or employee of Ionis or any of its other affiliates may present to Ionis certain acquisitions, in-licenses, potential development programs or other opportunities that may be complementary to our business and, as a result, such opportunities may not be available to us. To the extent attractive corporate opportunities are allocated to Ionis or its other affiliates instead of to us, we may not be able to benefit from these opportunities.

***The resources Ionis provides us under the license agreements and the services agreement may not be sufficient for us to operate as a standalone company, and we may experience difficulty in separating our resources from Ionis.***

Because we have not operated separately from Ionis in the past, we may have difficulty doing so. We will need to acquire resources in addition to, and eventually in lieu of, those provided by Ionis to our company, and may also face difficulty in separating our resources from Ionis' resources and integrating newly acquired resources into our business. In addition, Ionis may prioritize its own research, development, manufacturing and other needs ahead of the services Ionis has agreed to provide us, or Ionis employees who conduct services for us may prioritize Ionis' interests over our interests. Our business, financial condition and results of operations could be harmed if we have difficulty operating as a standalone company, fail to acquire resources that prove to be important to our operations or incur unexpected costs in separating our resources from Ionis' resources or integrating newly acquired resources.

***We may not realize the benefits of the licensing transaction with Ionis if we are unable to successfully transition, integrate and support the development and commercialization of TEGSEDI and AKCEA-TTR-LRx.***

As a result of the licensing transaction with Ionis, we need to successfully transition, integrate and support the assets we acquired related to the commercialization and development of TEGSEDI and AKCEA-TTR-LRx if we are to realize any of the potential benefits of the licensing transaction. The failure to meet these integration challenges, including the addition of TEGSEDI commercial team and other employees from Ionis and the coordination across geographies between our headquarters in Massachusetts and our commercialization team in other locations, including major global markets, could seriously harm our results of operations. Our failure to implement an orderly integration could result in failure of, or delays in, the development or commercialization of TEGSEDI and AKCEA-TTR-LRx. Such failure or delay could adversely impact our business, results of operations, financial condition and prospects for future growth.

***We will incur incremental costs as a standalone company.***

Ionis currently performs or supports many important corporate functions for our company. Our condensed consolidated financial statements reflect charges for these services on an allocation basis. Under our services agreement with Ionis we can use these Ionis services for a fixed term established on a service-by-service basis. However, we generally will have the right to terminate a service earlier if we give notice to Ionis. Partial reduction in the provision of any service requires Ionis' consent. In addition, either party will be able to terminate the agreement due to a material breach of the other party, upon prior written notice, subject to limited cure periods.

We will pay Ionis mutually agreed upon fees for these services, based on Ionis' costs of providing the services. Since we negotiated the services agreement in the context of a parent subsidiary relationship, the terms of the agreement, including the fees charged for the services, may be higher or lower than those that would be agreed to by parties bargaining at arm's length for similar services and may be higher or lower than the costs reflected in the allocations in our historical condensed consolidated financial statements. Ionis will pass third party costs through to us at Ionis' cost. In addition, while Ionis provides us these services, our operational flexibility to modify or implement changes with respect to such services or the amounts we pay for them will be limited.

We may not be able to replace these services or enter into appropriate third-party agreements on terms and conditions, including cost, comparable to those that we will receive from Ionis under our services agreement. Additionally, after the agreement terminates, we may not sustain the services at the same levels or obtain the same benefits as when we were receiving such services and benefits from Ionis. When we begin to operate these functions separately, if we do not have our own adequate systems and business functions in place, or cannot obtain them from other providers, we may not operate our business effectively or at comparable costs, and our business may suffer. In addition, we have historically received informal support from Ionis, which may not be addressed in our services agreement. The level of this informal support will diminish and could end in the future.

***We may not be able to fully realize the expected benefits of our license agreements with Ionis.***

We have development, commercialization and license agreements with Ionis pursuant to which, subject to certain restrictions, we and Ionis will share development responsibilities for WAYLIVRA, TEGSEDI, AKCEA-APO(a)-L Rx, AKCEA-TTR-LRx and our other drugs in development. We are paying for research and development costs and reimbursing Ionis for Ionis' employees supporting our development activities. Until we build or acquire our own capabilities to replace those Ionis is providing to us, particularly development, regulatory and manufacturing services, we will be heavily dependent on Ionis.

While we and Ionis intend the license agreements, on the whole, to bolster our capabilities, certain terms of the license agreements and the other related agreements with Ionis may limit our ability to achieve the expected benefits of these transactions, including:

- a Joint Steering Committee, or JSC, having equal membership from us and Ionis, sets the development strategy for our drugs by mutual agreement. A Regulatory Sub-committee, established by the JSC and having equal membership from our company and Ionis, will set the regulatory strategy for each of our drugs by mutual agreement. If the JSC or the Regulatory Sub-committee cannot come to a mutual agreement, then this could delay our ability to develop and commercialize TEGSEDI, AKCEA-TTR-LRx and our other drugs in development. In the event of a disagreement at the JSC related to TEGSEDI or AKCEA-TTR-LRx, Ionis has final decision-making authority on decisions relating to development matters, Akcea has final decision making authority on decision relating to commercial matters, and the holder of the regulatory approvals for a product in a country has final decision making authority for regulatory affairs;
- we will need to mutually agree with Ionis on the terms of any additional sublicense to a third party for WAYLIVRA and AKCEA-ANGPTL-L Rx, and will need to obtain Ionis' consent prior to granting any sublicense to a third party for TEGSEDI or AKCEA-TTR-L Rx. If we cannot mutually agree on terms for a sublicense to a third party or if Ionis does not consent to a sublicense at all, it could delay or prevent our ability to develop and commercialize our drugs;
- we will need to obtain Ionis' approval to in-license a product, acquire a product or acquire another company, until the time Ionis ceases to hold at least 50% of our outstanding capital stock; and
- there is nothing in our agreements with Ionis to prevent Ionis from developing and commercializing drugs targeting RNAs that are not apoC-III, Apo(a) ANGPTL3 or TTR to pursue the same indications we are pursuing with our drugs.

Each of the foregoing terms and Ionis' other rights under the license agreements, could limit our ability to realize the expected benefits of the license agreements or otherwise limit our ability to pursue transactions or development efforts other stockholders may view as beneficial. Further, if Ionis does not continue to own a significant portion of our equity, Ionis' incentive to help us would be diminished. If we fail to achieve the expected benefits of our agreements with Ionis, it may be more difficult, time consuming or expensive for us to develop and commercialize WAYLIVRA, AKCEA-APO(a)-L Rx, AKCEA-TTR-LRx and our other drugs in development and continue the commercialization of TEGSEDI, or may result in our drugs being later to market than those of our competitors or prevent them from ever getting to market. If these events cause delays in new product development we could lose the first in class products in a given therapeutic area.

### **Risks Related to Our Intellectual Property**

***If we breach our obligations under any of our license agreements with Ionis, we could lose our rights to WAYLIVRA, TEGSEDI, AKCEA-TTR-L Rx and our other drugs in development.***

We obtained our rights to WAYLIVRA, TEGSEDI, AKCEA-TTR-L Rx and our other drugs in development under our license agreements with Ionis. If we breach our obligations under these license agreements and, as a result, Ionis subsequently exercises its right to terminate it, we generally would not be able to continue to develop or commercialize TEGSEDI, WAYLIVRA, AKCEA-TTR-L Rx and our other drugs in development that incorporate Ionis' intellectual property, and Ionis would receive a royalty-free, nonexclusive license to our improvements to those programs, meaning we would lose the benefits of our investment in these programs. If we breach our obligations under the license agreement with respect to AKCEA-APO(a)-LRx or AKCEA-APOCIII-LRx and, as a result, Ionis exercises its right to terminate it, then our strategic collaboration with Novartis would convert into a direct strategic collaboration between Novartis and Ionis, and Ionis would receive all of the revenue and other benefits associated with that strategic collaboration. Similarly, if we breach our obligations under the license agreement with respect to TEGSEDI or AKCEA-TTR-LRx and, as a result, Ionis exercises its right to terminate it, then our strategic collaboration with PTC in Latin America and certain Caribbean countries would convert into a direct strategic collaboration between PTC and Ionis, and Ionis would receive all of the revenue and other benefits associated with that strategic collaboration.

***If we cannot protect our patent rights or our other proprietary rights, others may compete more effectively against us.***

Our success depends to a significant degree upon whether we can continue to secure and maintain intellectual property rights that protect TEGSEDI, WAYLIVRA, AKCEA-APO(a)-LRx, AKCEA-TTR-LRx and our other drugs in development. However, patents may not issue from any of our pending patent applications in the United States or in other countries and we may not be able to obtain, maintain or enforce our owned or licensed patents and other intellectual property rights which could impact our ability to compete effectively. In addition, the scope of any of our owned or licensed patents may not be sufficiently broad to provide us with a competitive advantage. Furthermore, other parties may successfully challenge, invalidate or circumvent our issued patents or patents licensed to us so that our patent rights do not create an effective competitive barrier or revenue source.

Composition of matter patents on the active pharmaceutical ingredient for a product are generally considered to be the strongest form of intellectual property protection for pharmaceutical products, as such patents provide protection without regard to any method of use. Our WAYLIVRA patent portfolio currently includes:

- issued patent claims to the specific antisense sequence and chemical composition of WAYLIVRA in the United States, Australia, and Europe;
- issued patent claims in the United States and Australia drawn to the use of antisense compounds complementary to an active region of human apoC-III messenger ribonucleic acid, including the site targeted by WAYLIVRA;
- additional patent applications designed to protect the WAYLIVRA composition in Canada; and
- additional methods of use in jurisdictions worldwide for WAYLIVRA.

The natural term of the issued U.S. patent covering the WAYLIVRA composition of matter will expire in 2023, but we plan to seek to extend the U.S. patent expiration beyond 2023 based upon the development and regulatory review period in the United States. The natural term of the granted European and Australian patents covering WAYLIVRA will expire in 2024, but we plan to seek to extend each of these patents beyond 2024 based upon the development and regulatory review periods in Europe and Australia.

The natural term of the last expiring issued U.S. patent covering the composition of matter of TEGSEDI will expire in 2031. Patents issued in other countries will have the same natural term. We plan to seek to extend the term of one patent covering TEGSEDI in the U.S., and any other jurisdictions where such extension is available, based upon the development and regulatory review periods for TEGSEDI and in accordance with applicable laws.

We cannot be certain that the U.S. Patent and Trademark Office, or U.S. PTO, and courts in the United States or the patent offices and courts in foreign countries will consider the claims in our owned or licensed patents and applications covering WAYLIVRA, TEGSEDI, AKCEA-APO(a)-L Rx, AKCEA-TTR-LRx and our other drugs in development as patentable. Method-of-use patents protect the use of a product for the specified method. This type of patent does not prevent a competitor from making and marketing a product that is identical to our product for an indication that is outside the scope of the patented method. Moreover, even if competitors do not actively promote their product for our targeted indications, physicians may prescribe these products off-label. Although off-label prescriptions may infringe or contribute to the infringement of method-of-use patents, the practice is common and such infringement is difficult to prevent, including through legal action.

If we or any licensor partner loses or cannot obtain patent protection for TEGSEDI, WAYLIVRA, AKCEA-APO(a)-L Rx, AKCEA-TTR-LRx or our other drugs in development it could have a material adverse impact on our business.

***Intellectual property litigation could cause us to spend substantial resources and prevent us from pursuing our programs.***

From time to time we may have to defend our intellectual property rights. If we are involved in an intellectual property dispute, we may need to litigate to defend our rights or assert them against others. Disputes can involve arbitration, litigation or proceedings declared by the U.S. PTO or the International Trade Commission or foreign patent authorities. 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.

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

Our commercial success depends upon our ability and the ability of our strategic partners to develop, manufacture, market and sell our drugs and use our proprietary technologies without infringing the proprietary rights and intellectual property of third parties. Extensive litigation regarding patents and other intellectual property rights is common in the biotechnology and pharmaceutical industries. We may in the future become party to, or threatened with, adversarial proceedings or litigation regarding intellectual property rights with respect to our drugs and technology, including interference, derivation, reexamination, post-grant review, opposition, cancellation or similar proceedings before the U.S. PTO or its foreign counterparts.

Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future. For example, a potential competitor was issued a patent which they have broadly characterized in their annual report on Form 10-K for the year ended December 31, 2018 as being directed to single-stranded antisense polynucleotide molecules capable of inhibiting expression of the human transthyretin gene, and having certain combinations of structural features. This third party has also attempted to broadly characterize certain other patents that they hold. While we believe that we would have substantial defenses in the event this competitor brought a claim against us with respect to TEGSEDI or AKCEA-TTR-LRx, patent litigation is inherently uncertain, involves substantial cost and is a distraction to management. Moreover, our stock price may be impacted by the existence of or developments during a litigation, even developments that are preliminary in nature.

We may not be aware of all such intellectual property rights potentially relating to our drugs and their uses. If a third party claims that WAYLIVRA, TEGSEDI, AKCEA-APO(a)-LRx, AKCEA-TTR-LRx, our other drugs in development or our technology infringe its patents or other intellectual property rights, we or our partners may have to discontinue an important product or product line, alter our products and processes, pay license fees or cease certain activities. We may not be able to obtain a license to needed intellectual property on favorable terms, if at all. There are many patents issued or applied for in the biotechnology industry, and we may not be aware of patents or patent applications held by others that relate to our business. This is especially true since patent applications in the United States are filed confidentially for the first 18 months. Moreover, the validity and breadth of biotechnology patents involve complex legal and factual questions for which important legal issues remain. Thus, we do not know with certainty that our drugs or our intended commercialization thereof, does and will not infringe or otherwise violate any third party's intellectual property.

***We will not seek to protect our intellectual property rights in all jurisdictions throughout the world and we may not be able to adequately enforce our intellectual property rights even in the jurisdictions where we seek protection.***

Filing, prosecuting and defending patents on our drugs in all countries and jurisdictions throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States could be less extensive than those we could obtain in the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions.

Competitors may use our technologies in jurisdictions where we do not pursue and obtain patent protection to develop their own products. In addition, competitors may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our products and our patent rights or other intellectual property rights may not be effective or sufficient to prevent them from competing. Even if we pursue and obtain issued patents in particular jurisdictions, our patent claims or other intellectual property rights may not be effective or sufficient to prevent third parties from so competing.

The laws of some foreign countries do not protect intellectual property rights to the same extent as the laws of the United States. Many companies have encountered significant problems in protecting and defending intellectual property rights in certain foreign jurisdictions. The legal systems of some countries, particularly developing countries, do not favor the enforcement of patents and other intellectual property protection, especially those relating to biotechnology. This could make it difficult for us to stop competitors from infringing our patent rights or misappropriating our other intellectual property rights. For example, many foreign countries have compulsory licensing laws under which a patent owner must grant licenses to third parties. In addition, many countries limit our right to enforce our patent rights against third parties, including government agencies or government contractors. In these countries, patents may provide limited or no benefit. We must ultimately seek patent protection on a country-by-country basis, which is an expensive and time-consuming process with uncertain outcomes. Accordingly, we may choose not to seek patent protection in certain countries, and we will not have the benefit of patent protection in such countries.

In addition, proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patent rights at risk of being invalidated or interpreted narrowly, could put our owned or licensed patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

***If we do not obtain additional protection under the Hatch-Waxman Amendments and similar foreign legislation by extending the patent protection for TEGSEDI, WAYLIVRA, AKCEA-APO(a)-LRx, AKCEA-TTR-LRx, and our other drugs in development, our business may be materially harmed.***

Depending upon the timing, duration and specifics of the first FDA marketing authorization of TEGSEDI, WAYLIVRA, AKCEA-APO(a)-LRx, AKCEA-TTR-LRx, and our other drugs in development, a United States patent that we own or license may be eligible for limited patent term restoration under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Amendments. The Hatch-Waxman Amendments allow the owner of an approved product to extend patent protection for up to five years as compensation for patent term lost during product development and the FDA regulatory review process. During this period of extension, the scope of protection is limited to the approved product and approved uses.

In 2018 we applied for patent term extensions to U.S. patents covering the TEGSEDI compound, composition and uses to recapture a portion of the term lost during regulatory review. Although we have applied for patent term extension for TEGSEDI, and plan on seeking patent term restoration for our other products, we may not succeed if, for example, we fail to apply within applicable deadlines, fail to apply prior to expiration of relevant patents or otherwise fail to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we cannot obtain patent term restoration or the term of any such patent restoration is less than we request, our competitors may enter the market and compete against us sooner than we anticipate, and our ability to generate revenue could be materially adversely affected.

***Changes in United States patent law could diminish the value of patents in general, thereby impairing our ability to protect our products.***

Recent United States Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on decisions by the United States Congress, the federal courts, and the U.S. PTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

***If we and our partners do not adequately protect the trademarks and trade names for our products, then we and our partners may not be able to build name recognition in our markets of interest and our business may be adversely affected.***

Our competitors or other third parties may challenge, infringe or circumvent the trademarks or trade names for our products. We and our partners may not be able to protect these trademarks and trade names. In addition, if the trademarks or trade names for one of our products infringe the rights of others, we or our partners may be forced to stop using the trademarks or trade names, which we need for name recognition in our markets of interest. If we cannot establish name recognition based on our trademarks and trade names, we and our partners may not be able to compete effectively and our business may be adversely affected.

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

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations, and may not adequately protect our business, or permit us to maintain our competitive advantage. The following examples are illustrative:

- others may make compounds that are similar to our drugs but that are not covered by the claims of the patents that we own or have exclusively licensed;
- we, or our license partners or current or future strategic partners, might not have been the first to make the inventions covered by the issued patent or pending patent application that we own or have exclusively licensed;
- we, or our license partners or current or future strategic partners, might not have been the first to file patent applications covering our inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights;
- our pending licensed patent applications or those that we own in the future may not lead to issued patents;
- issued patents that we hold rights to may be held invalid or unenforceable, including as a result of legal challenges by our competitors;
- our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we may not develop additional proprietary technologies that are patentable; and
- the patents of others may have an adverse effect on our business.

Should any of these events occur, they could significantly harm our business, results of operations and prospects.

***Risks Related to Our Business and Industry\****

***We will need to significantly increase the size of our organization, and we may experience difficulties in managing growth.***

We are currently a small company. To continue the commercialization of TEGSEDI and commercialize our drugs in development that we are responsible for commercializing, we will need to increase our operations and expand our use of third-party contractors. We plan to continue to build our compliance, financial and operating infrastructure to ensure the maintenance of a well-managed company including hiring additional staff within our regulatory, clinical and medical affairs groups and an in-house commercial organization initially focused on marketing and selling TEGSEDI and WAYLIVRA. We have added a significant number of new employees to our sales and marketing capability to commercialize TEGSEDI.

We may also anticipate needs for growth that do not materialize. For example, in anticipation of WAYLIVRA's potential approval, we added a significant number of new employees to our sales and marketing capability to develop WAYLIVRA in the second half of 2017. However, as a result of our receipt of a complete response letter, or CRL, from the FDA regarding the new drug application for WAYLIVRA, on September 6, 2018, we enacted a plan to reorganize our workforce to better align with the immediate needs of our business. In connection with this reorganization plan, we reduced our workforce by approximately 12%. If WAYLIVRA is subsequently approved in the United States, we will again need to increase our operations and expand our use of third-party contractors. We cannot assure you that we will not build out our compliance, financial or operating infrastructure again in anticipation of developments that do not occur or that occur later than we anticipate.

The current and future growth will impose significant added responsibilities on our management, including the need to maintain, integrate, optimize and manage additional employees. In addition, to meet our obligations as a public company, we will need to increase our general and administrative capabilities. Our current management, personnel and systems may not be adequate to support this growth. Our future financial performance and our ability to commercialize our drugs and to compete effectively will depend, in part, on our ability to manage any future growth effectively. To that end, we must be able to:

- manage the manufacturing of our drugs for clinical and commercial use;
- integrate current and additional management, administrative, financial and sales and marketing personnel;
- optimize and manage a marketing and sales infrastructure;

- maintain personnel necessary to effectively commercialize TEGSEDI and WAYLIVRA and our other drugs in development;
- manage our clinical studies and the regulatory process effectively;
- develop our administrative, accounting and management information systems and controls; and
- hire and train additional qualified personnel.

Our staff, financial resources, systems, procedures or controls may be inadequate to support our operations and our management may be unable to successfully manage future market opportunities or our relationships with customers and other third parties.

***If we do not progress in our programs as anticipated, the price of our securities could decrease.***

For planning purposes, we estimate and may disclose the timing of a variety of clinical, regulatory and other milestones, such as when we anticipate a certain drug will enter into clinical trials, when we anticipate completing a clinical study, when we anticipate filing an application for marketing authorization, or when we or our partners plan to commercially launch a drug. We base our estimates on present facts and a variety of assumptions. Many underlying assumptions are outside of our control. If we do not achieve milestones in accordance with our or our investors' or securities analysts' expectations, including milestones related to WAYLIVRA, TEGSEDI, AKCEA-APO(a)-L Rx, AKCEA-TTR-LRx and our other drugs in development, the price of our securities could decrease.

***The loss of key personnel, or if we cannot attract and retain highly skilled personnel, could make it more difficult to run our business and reduce our likelihood of success.***

We are dependent on the principal members of our management and scientific staff. We do not have employment agreements with any of our executive officers that would prevent them from leaving us. The loss of management and key scientific employees might slow the achievement of important research and development goals. It is also critical to our success that we recruit and retain qualified scientific personnel to perform development work and marketing, sales and commercial support personnel to perform commercialization activities. We may not be able to attract and retain skilled and experienced scientific and commercial personnel on acceptable terms because of intense competition for experienced personnel among many pharmaceutical and health care companies, universities and non-profit research institutions. In addition, failure to successfully complete clinical studies, obtain regulatory approvals or effectively commercialize drugs may make it more challenging to recruit and retain qualified personnel.

***We are exposed to potential product liability claims, and insurance against these claims may not be available to us at a reasonable rate in the future or at all.***

Our business exposes us to potential product liability risks that are inherent in the testing, manufacturing, marketing and sale of therapeutic products, including potential product liability claims related to TEGSEDI, WAYLIVRA, AKCEA-APO(a)-L Rx, AKCEA-TTR-LRx and our other drugs in development. We have clinical study insurance coverage and commercial product liability insurance coverage. In addition, Novartis has agreed to indemnify us against specific claims arising from Novartis' development and commercialization of AKCEA-APO(a)-LRx and AKCEA-APOCIII-LRx, and PTC has agreed to indemnify us against specific claims arising from PTC's commercialization of TEGSEDI and WAYLIVRA in Latin America and certain Caribbean countries. However, this insurance coverage and indemnities may not be adequate to cover claims against us. Insurance may not be available to us at an acceptable cost, if at all. Regardless of their merit or eventual outcome, products liability claims may result in decreased demand for our drug products, injury to our reputation, withdrawal of clinical study volunteers and loss of revenue. Thus, whether or not we are insured or indemnified, a product liability claim or product recall may result in losses that could be material.

***Because we use biological materials, hazardous materials, chemicals and radioactive compounds, if we do not comply with laws regulating the protection of the environment and health and human safety, our business could be adversely affected.***

Our development and manufacturing activities involve the use of potentially harmful biological materials as well as materials, chemicals and various radioactive compounds that could be hazardous to human health and safety or the environment. We cannot completely eliminate the risk of contamination, which could cause:

- interruption of our development, manufacturing and distribution efforts;
- injury to our employees and others;
- environmental damage resulting in costly clean up; and
- liabilities under federal, state and local laws and regulations governing health and human safety, as well as the use, storage, handling and disposal of these materials and resultant waste products.

In such an event, we may be held liable for any resulting damages, and any liability could exceed our resources. Although we carry insurance in amounts and types that we consider commercially reasonable, we do not have insurance coverage for losses relating to an interruption of our development, manufacturing or commercialization efforts caused by contamination, and the coverage or coverage limits of our insurance policies may not be adequate. If our losses exceed our insurance coverage, our financial condition would be adversely affected.

***A variety of risks associated with operating our business and marketing our drugs internationally could materially adversely affect our business.***

In addition to our U.S. operations, we are commercializing TEGSEDI in Europe and Canada, we plan to commercialize WAYLIVRA in the European Union and, following approval, plan to establish operations to commercialize our products in other countries globally. We face risks associated with our current and planned international operations, including possible unfavorable regulatory, pricing and reimbursement, political, tax and labor conditions, which could harm our business. Because we have international operations we are subject to numerous risks associated with international business activities, including:

- compliance with differing or unexpected regulatory requirements for our drugs and foreign employees;
- complexities associated with managing multiple payor reimbursement regimes, government payors or patient self-pay systems;
- difficulties in staffing and managing foreign operations;
- in certain circumstances, increased dependence on the commercialization efforts and regulatory compliance of third-party distributors or strategic partners;
- foreign government taxes, regulations and permit requirements;
- U.S. and foreign government tariffs, trade restrictions, price and exchange controls and other regulatory requirements;
- anti-corruption laws, including the Foreign Corrupt Practices Act, or the FCPA, and its equivalent in foreign jurisdictions;
- economic weakness, including inflation, natural disasters, war, events of terrorism or political instability in particular foreign countries;
- fluctuations in currency exchange rates, which could result in increased operating expenses and reduced revenue, and other obligations related to doing business in another country;
- compliance with tax, employment, privacy, immigration and labor laws, regulations and restrictions for employees living or traveling abroad;
- workforce uncertainty in countries where labor unrest is more common than in the United States; and
- changes in diplomatic and trade relationships.

The United Kingdom's anticipated exit from the EU could increase these risks.

Our business activities outside of the United States are subject to the FCPA and similar anti-bribery or anti-corruption laws, regulations or rules of other countries in which we operate, including the United Kingdom's Bribery Act 2010. In many other countries, the healthcare providers who prescribe pharmaceuticals are employed by their government, and the purchasers of pharmaceuticals are government entities; therefore, any dealings with these prescribers and purchasers may be subject to regulation under the FCPA. There is no certainty that all employees and third-party business partners (including our distributors, wholesalers, agents, contractors and other partners) will comply with anti-bribery laws. In particular, we do not control the actions of manufacturers and other third-party agents, although we may be liable for their actions. Violation of these laws may result in civil or criminal sanctions, which could include monetary fines, criminal penalties, and disgorgement of past profits, which could have a material adverse impact on our business and financial condition.

***The impact on us of the vote by the United Kingdom to leave the European Union cannot be predicted. \****

On June 23, 2016, the United Kingdom, or the UK, voted to leave the EU in an advisory referendum, which is generally referred to as Brexit. On March 29, 2017, the UK delivered notice under Article 50 of the Lisbon Treaty of its intent to leave the EU, beginning a two year negotiation period for the UK and the 27 remaining members of the EU to reach agreement on the terms of Brexit. To date, no formal withdrawal agreement has been reached between the UK and the EU, despite the passage of the date on which it was expected that the UK's membership in the EU would automatically terminate. The deadline for negotiating a withdrawal agreement has been extended to October 31, 2019, and discussions between the UK and the EU continue to focus on withdrawal issues and transition agreements. However, limited progress has been made to date, and the disagreement and uncertainty within the government of the UK sustains the possibility that the UK may leave the EU without a withdrawal agreement and associated transition period in place, which is likely to cause significant market and economic disruption. The UK is a significant pharmaceutical market,

and Brexit may lead to legal uncertainty and potentially divergent laws and regulations between the UK and the EU as the UK determines which EU laws to replicate or replace. We cannot predict whether or not the UK will significantly alter its current laws and regulations in respect of the pharmaceutical industry and, if so, what impact any such alteration would have on us or our business.

As part of Brexit, the EMA, currently situated in London, is expected to relocate to Amsterdam. There is a risk that the relocation process will interrupt current administrative routines and occupy resources, which may generally adversely affect our dealings with the EMA. Further, there is considerable uncertainty resulting from a lack of precedent and the complexity of the UK and EU's intertwined legal regimes as to how Brexit will impact the life sciences industry in Europe, including our company, including with respect to ongoing or future clinical trials. The impact will largely depend on the model and means by which the UK's relationship with the EU is governed post-Brexit. For example, following Brexit, the UK will no longer be covered by the centralized procedures for obtaining EU-wide marketing authorization from the EMA and, unless a specific agreement is entered into, a separate process for authorization of drug products, including our product candidates, will be required in the UK, the potential process for which is currently unclear. Brexit may adversely affect and delay our ability to commercialize, market and sell our product candidates in the UK. Brexit may also result in a reduction of funding to the EMA if the UK no longer makes financial contributions to European institutions, such as the EMA. If UK funding is so reduced, it could create delays in the EMA issuing regulatory approvals for our product candidates and, accordingly, have a material adverse effect on our business, financial condition, results or prospects.

***If a natural or man-made disaster strikes our development or manufacturing facilities or otherwise affects our business, it could delay our progress developing and commercializing our drugs.***

We currently rely on Ionis to manufacture our clinical supplies in a manufacturing facility located in Carlsbad, California and third party contract manufacturing organizations to manufacture active pharmaceutical ingredient and finished drug product for TEGSEDI. The facilities and the equipment required to develop and manufacture our drugs would be costly to replace and could require substantial lead time to repair or replace. Natural or man-made disasters, including, without limitation, earthquakes, floods, fires and acts of terrorism may harm these facilities. If a disaster affects these facilities, our and our partners' development and commercialization efforts would be delayed. Although we possess insurance for damage to our property and the disruption of our business from casualties, this insurance may not be sufficient to cover all of our potential losses and may not continue to be available to us on acceptable terms, or at all. In addition, a shutdown of the U.S. government, including the FDA could harm or delay our development and commercialization activities.

***Our business and operations would suffer in the event of computer system failures.***

We are dependent upon our own or third-party information technology systems, infrastructure and data, including mobile technologies, to operate our business. The multitude and complexity of our computer systems may make them vulnerable to service interruption or destruction, disruption of data integrity, malicious intrusion, or random attacks. Likewise, data privacy or security incidents or breaches by employees or others may pose a risk that sensitive data, including our intellectual property, trade secrets or personal information of our employees, patients, customers or other business partners may be exposed to unauthorized persons or to the public. Cyber-attacks are increasing in their frequency, sophistication and intensity. Cyber-attacks could include the deployment of harmful malware, denial-of-service, social engineering and other means to affect service reliability and threaten data confidentiality, integrity and availability. Our business partners face similar risks and any security breach of their systems could adversely affect our security posture. A security breach or privacy violation that leads to disclosure or modification of or prevents access to patient information, including personally identifiable information or protected health information, could harm our reputation, compel us to comply with federal and/or state breach notification laws and foreign law equivalents, subject us to mandatory corrective action, require us to verify the correctness of database contents and otherwise subject us to litigation or other liability under laws and regulations that protect personal data, any of which could disrupt our business and/or result in increased costs or loss of revenue. Moreover, the prevalent use of mobile devices that access confidential information increases the risk of data security breaches, which could lead to the loss of confidential information, trade secrets or other intellectual property. While we have invested, and continue to invest, in the protection of our data and information technology infrastructure, there can be no assurance that our efforts will prevent service interruptions, or identify breaches in our systems, that could adversely affect our business and operations and/or result in the loss of critical or sensitive information, which could result in financial, legal, business or reputational harm to us. In addition, our liability insurance may not be sufficient in type or amount to cover us against claims related to security breaches, cyber-attacks and other related breaches.

***Risks Related to Our Common Stock***

***We are an "emerging growth company" and as a result of the reduced disclosure and governance requirements applicable to emerging growth companies, our common stock may be less attractive to investors.***

We are an "emerging growth company," as defined in the JOBS Act, and we may take advantage of certain exemptions from various reporting requirements that are applicable to other public companies that are not "emerging growth companies" including, but not limited to, the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act, reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements, and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved. We cannot predict if investors will find our common stock less attractive if we choose to rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

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

Prior to the completion of our IPO in July 2017, no public market for our common stock existed. An active public trading market for our common stock may not be sustained. The lack of an active market may impair your ability to sell your shares at the time you wish to sell them or at a price that you consider reasonable. The lack of an active market may also reduce the fair value of your shares. An inactive market may also impair our ability to raise capital to continue to fund operations by selling shares. Additionally, as of May 2, 2019, Ionis owns approximately 76 percent of our outstanding common stock. Ionis intends to hold its shares of our common stock for the foreseeable future, which could reduce the public market for our stock.

***The market price for our common stock may be volatile, which could contribute to the loss of your investment.***

Fluctuations in the price of our common stock could contribute to the loss of all or part of your investment. There has been a public market for our common stock for a limited period of time. The trading price of our common stock is likely to be highly volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control. Any of the factors listed below could have a material adverse effect on your investment in our common stock and our common stock may trade at prices significantly below your purchase price. In such circumstances the trading price of our common stock may not recover and may experience a further decline.

Factors affecting the trading price of our common stock may include:

- our failure to effectively develop and commercialize TEGSEDI, WAYLIVRA and our other drugs in development;
- Novartis' failure to exercise its option and/or effectively develop and commercialize AKCEA-APO(a)-LR<sub>x</sub> and AKCEA-APOCIII-LR<sub>x</sub> to the extent it exercises its option to license those drugs from us;
- PTC's failure to effectively commercialize TEGSEDI or WAYLIVRA in Latin America and certain Caribbean countries;
- changes in the market's expectations about our operating results;
- adverse results or delays in preclinical or clinical studies;
- our decision to initiate a clinical study, not to initiate a clinical study or to terminate an existing clinical study;
- adverse regulatory decisions, including failure to receive additional regulatory approvals for TEGSEDI, or regulatory approval for WAYLIVRA, AKCEA-APO(a)-LR<sub>x</sub>, AKCEA-TTR-LR<sub>x</sub> and our other drugs in development;
- success or failure of competitive products or antisense drugs more generally;
- adverse developments concerning our manufacturers or our strategic partnerships;
- inability to obtain adequate product supply for any drug for clinical studies or commercial sale or inability to do so at acceptable prices;
- the termination of a strategic partnership or the inability to establish additional strategic partnerships;
- unanticipated serious safety concerns related to the use of TEGSEDI, WAYLIVRA, AKCEA-APO(a)-LR<sub>x</sub>, AKCEA-TTR-LR<sub>x</sub> and our other drugs in development;
- adverse safety or other clinical results, such as those that have occurred in the past or that may occur in the future, related to drugs being developed by Ionis or other companies that are or may be perceived to be similar to our drugs;
- our ability to effectively manage our growth;
- the size and growth, if any, of the targeted market;
- our operating results do not meet the expectation of securities analysts or investors in a particular period;
- actual or anticipated fluctuations in our quarterly financial results or the quarterly financial results of companies perceived to be similar to us;
- securities analysts do not publish reports about us or our business or publish negative reports;
- changes in financial estimates and recommendations by securities analysts concerning our company, our market opportunity, or the biotechnology and pharmaceutical industries in general;
- operating and stock price performance of other companies that investors deem comparable to us;
- overall performance of the equity markets;
- announcements by us or our competitors of acquisitions, new drugs or programs, significant contracts, commercial relationships or capital commitments;

- our and our strategic partners' ability to successfully market TEGSEDI, WAYLIVRA, AKCEA-APO(a)-L Rx, AKCEA-TTR-LRx and our other drugs in development;
- changes in laws and regulations affecting our business, including but not limited to clinical study requirements for approvals;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain and maintain patent protection for TEGSEDI, WAYLIVRA, AKCEA-APO(a)-LRx, AKCEA-TTR-LRx and our other drugs in development;
- commencement of, or involvement in, litigation involving our company, our general industry, or both;
- changes in our capital structure, such as future issuances of securities or the incurrence of additional debt;
- the volume of shares of our common stock available for public sale;
- additions or departures of key scientific or management personnel;
- any major change in our board or management;
- changes in accounting practices;
- ineffectiveness of our internal control over financial reporting;
- significant changes in our relationship with Ionis;
- sales of substantial amounts of common stock by our directors, executive officers or significant stockholders or the perception that such sales could occur; and
- general economic and political conditions such as recessions, interest rates, fuel prices, elections, drug pricing policies, international currency fluctuations and acts of war or terrorism.

Broad market and industry factors may materially harm the market price of our common stock irrespective of our operating performance. The stock market in general, and NASDAQ and the market for biotechnology companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of the particular companies affected. The trading prices and valuations of these stocks, and of ours, may not be predictable. A loss of investor confidence in the market for biotechnology or pharmaceutical stocks or the stocks of other companies which investors perceive to be similar to us, the opportunities in the biotechnology and pharmaceutical market or the stock market in general, could depress our stock price regardless of our business, prospects, financial conditions or results of operations.

***Sales of a substantial number of shares of our common stock by our existing stockholders in the public market may cause our stock price to decline. \****

Sales of our common stock in the public market, or the perception that these sales may occur, could cause the market price of our common stock to decline. Novartis has agreed that it will not sell any of its shares until the earlier of January 5, 2020 or six months after we stop developing a drug under our agreement with Novartis. Thereafter, Novartis may only sell a limited number of shares each day. In addition, as of May 2, 2019 Ionis owns 70,221,338 shares, or approximately 76 percent, of our common stock. While the shares of common stock held by Ionis are eligible for sale in the public market, any sales by Ionis will be subject to volume limitations under Rule 144 under the Securities Act of 1933, as amended, or the Securities Act. In addition, 18,500,000 shares of common stock that are either subject to outstanding options or reserved for future issuance under our employee benefit plans are eligible for sale in the public market to the extent permitted by the provisions of various vesting schedules, the lock-up agreements and Rule 144 and Rule 701 under the Securities Act. To the extent the holders of these shares sell them into the market or our stockholders believe these sales might occur, the market price of our common stock could decline.

We cannot predict with certainty whether or when Ionis will sell a substantial number of shares of our common stock. Ionis' sale of a substantial number of shares, or a perception that such sales could occur, could significantly reduce the market price of our common stock.

***We do not expect to pay any cash dividends for the foreseeable future.***

You should not rely on an investment in our common stock to provide dividend income. We do not anticipate that we will pay any cash dividends to holders of our common stock in the foreseeable future. Instead, we plan to retain any earnings to maintain and expand our operations. Accordingly, investors must rely on sales of their common stock after price appreciation, which may never occur, as the only way to realize any return on their investment. As a result, investors seeking cash dividends should not purchase our common stock.

***Changes in tax laws, regulations and treaties could affect our future taxable income.***

A change in tax laws, treaties or regulations, or their interpretation, of any country in which we operate could materially affect us. For Example, on December 22, 2017, the United States enacted H.R.1., known as the Tax Cuts and Jobs Act, which represented a substantial change to tax laws in the United States, but which did not have a material impact on our financial statements because we maintain a valuation allowance on all our net operating losses and other deferred tax assets. However, any future changes in tax laws in any U.S. or non-U.S jurisdictions could have a material effect on our business.

***We could be subject to additional tax liabilities.***

We are subject to U.S. federal, state, local and sales taxes in the United States and foreign income taxes, withholding taxes and transaction taxes in foreign jurisdictions. Significant judgment is required in evaluating our tax positions and our worldwide provision for taxes. During the ordinary course of business, there are many activities and transactions for which the ultimate tax determination is uncertain. In addition, our tax obligations and effective tax rates could be adversely affected by changes in the relevant tax, accounting and other laws, regulations, principles and interpretations, including those relating to income tax nexus, by recognizing tax losses or lower than anticipated earnings in jurisdictions where we have lower statutory rates and higher than anticipated earnings in jurisdictions where we have higher statutory rates, by changes in foreign currency exchange rates, or by changes in the valuation of our deferred tax assets and liabilities. We may be audited in various jurisdictions, and such jurisdictions may assess additional taxes, sales taxes and value-added taxes against us. Although we believe our tax estimates are reasonable, the final determination of any tax audits or litigation could be materially different from our historical tax provisions and accruals, which could have a material adverse effect on our operating results or cash flows in the period for which a determination is made.

***We could be subject to securities class action litigation.***

In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because biotechnology companies have experienced significant stock price volatility in recent years. If we face such litigation, it could result in substantial costs and a diversion of management's attention and resources, which could harm our business.

***Provisions in our amended and restated certificate of incorporation, our amended and restated bylaws and Delaware law may have anti-takeover effects that could discourage an acquisition of us by others, even if an acquisition would be beneficial to our stockholders, and may prevent attempts by our stockholders to replace or remove our current management.***

Our amended and restated certificate of incorporation, amended and restated bylaws and Delaware law contain provisions that may have the effect of delaying or preventing a change in control of us or changes in our management. Our amended and restated certificate of incorporation and bylaws include provisions that:

- authorize "blank check" preferred stock, which could be issued by our board of directors without stockholder approval and may contain voting, liquidation, dividend and other rights superior to our common stock;
- specify that only board of directors or holders of greater than 10% of our common stock can call special meetings of our stockholders;
- prohibit stockholder action by written consent once Ionis no longer holds a majority of our voting power;
- establish an advance notice procedure for stockholder approvals to be brought before an annual meeting of our stockholders, including proposed nominations of persons for election to our board of directors;
- provide that a majority of directors then in office, even though less than a quorum, may fill vacancies on our board of directors;
- specify that no stockholder is permitted to cumulate votes at any election of directors;
- expressly authorize our board of directors to modify, alter or repeal our amended and restated bylaws; and
- require supermajority votes of the holders of our common stock to amend specified provisions of our amended and restated certificate of incorporation and amended and restated bylaws.

These provisions, alone or together, could delay or prevent hostile takeovers and changes in control or changes in our management. Further, Novartis has agreed that until Novartis holds less than 7.5% of our outstanding common stock, Novartis will vote the Novartis Private Placement Shares consistent with the recommendation of our board of directors. Although Novartis has retained the right to vote the Novartis Private Placement Shares in its sole discretion in connection with certain enumerated matters, including any transaction which would result in our change of control, our agreement with Novartis may nevertheless delay or prevent changes in our management or board of directors.

In addition, because we are incorporated in the State of Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which limits the ability of stockholders owning in excess of 15% of our outstanding voting stock to merge or combine with us.

Any provision of our amended and restated certificate of incorporation or amended and restated bylaws or Delaware law that has the effect of delaying or deterring a change in control could limit your opportunity to receive a premium for your shares of our common stock, and could also affect the price that some investors are willing to pay for our common stock.

Our bylaws designate the Court of Chancery of the State of Delaware and federal court within the State of Delaware as the exclusive forum for certain types of actions and proceedings that our stockholders may initiate, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our bylaws provide that, subject to limited exceptions, the Court of Chancery of the State of Delaware and federal court within the State of Delaware will be exclusive forums for any:

- derivative action or proceeding brought on our behalf;
- action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers or other employees to us or our stockholders;
- action asserting a claim against us arising pursuant to any provision of the Delaware General Corporation Law, our amended and restated certificate of incorporation or our amended and restated bylaws; or
- other action asserting a claim against us that is governed by the internal affairs doctrine.

Any person or entity purchasing or otherwise acquiring any interest in shares of our capital stock shall be deemed to have notice of and to have consented to the provisions of our bylaws described above. This choice of forum provision may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage such lawsuits against us and our directors, officers and employees. Alternatively, if a court were to find these provisions of our amended and restated certificate of incorporation inapplicable to, or unenforceable in respect of, one or more of the specified types of actions or proceedings, we may incur additional costs associated with resolving such matters in other jurisdictions, which could adversely affect our business and financial condition.

## **ITEM 2. UNREGISTERED SALES OF EQUITY SECURITIES AND USE OF PROCEEDS**

### **(a) Recent Sales of Unregistered Equity Securities**

On February 22, 2019, Novartis exercised its option to license AKCEA-APO(a)-LRx as part of our strategic collaboration with Novartis discussed in Note 6, *Strategic Collaboration with Novartis*. As a result, we earned a license fee of \$150.0 million. On March 29, 2019, we issued 2,837,373 shares of our common stock to Ionis in a private placement as payment of the \$75.0 million sublicense fee, increasing Ionis' ownership percentage to 76% as of March 31, 2019. The securities were offered and sold in a private placement exempt from the registration requirements of the Securities Act under Section 4(a)(2) of the Securities Act and Rule 506 thereunder.

Other than the above, we did not issue or sell any other unregistered equity securities during the period covered by this Report.

### **(b) Use of Proceeds**

On July 19, 2017, we closed our initial public offering of 17,968,750 shares of common stock at an offering price of \$8.00 per share, resulting in gross proceeds to us of approximately \$143.8 million. All of the shares issued and sold in our initial public offering were registered under the Securities Act pursuant to a registration statement on Form S-1 (File No. 333-216949), which was declared effective by the SEC on July 13, 2017. Cowen and Company, LLC, Stifel, Nicolaus & Company, Incorporated and Wells Fargo Securities, LLC acted as joint book-running managers for our initial public offering and BMO Capital Markets Corp. acted as lead manager for our initial public offering. The offering commenced on June 20, 2017 and did not terminate before all of the securities registered in the registration statement were sold.

As of March 31, 2019, we have applied all of the offering proceeds in accordance with the planned use of proceeds from our offering as described in final prospectus for our IPO dated July 13, 2017 and filed with the SEC pursuant to Rule 424(b)(4). As of March 31, 2019, all expenses incurred in connection with our initial public offering had been paid.(c) Issuer Purchase of Equity Securities

None.

**ITEM 3. DEFAULT UPON SENIOR SECURITIES**

None.

**ITEM 4. MINE SAFETY DISCLOSURES**

Not applicable.

**ITEM 5. OTHER INFORMATION**

Not Applicable.

**ITEM 6. EXHIBITS**

a. Exhibits

Exhibit	Description	Incorporated by Reference			
		Schedule / Form	File Number	Exhibit	File Date
<a href="#">10.1*#</a>	<a href="#">Amendment No. 1 to the Strategic Collaboration, Option and License Agreement between the Registrant and Novartis Pharma AG dated February 22, 2019</a>				
<a href="#">31.1*</a>	<a href="#">Certification of Principal Executive Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002</a>				
31.2*	<a href="#">Certification of Principal Financial Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002</a>				
32.1**	<a href="#">Certification of Principal Executive Officer and Principal Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002</a>				
101	The following financial statements from the Akcea Therapeutics, Inc. Quarterly Report on Form 10-Q for the quarter ended March 31, 2019, formatted in Extensive Business Reporting Language (XBRL): (i) consolidated balance sheets, (ii) consolidated statements of operations, (iii) consolidated statements of comprehensive loss, (iv) consolidated statements of stockholders' equity, (v) consolidated statements of cash flows and (vi) notes to consolidated financial statements (detail tagged).				

\* Filed herewith.

\*\* This certification is deemed not filed for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or otherwise subject to the liability of that section, nor shall it be deemed incorporated by reference into any filing under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended.

# Confidential treatment has been requested with respect to certain portions of this exhibit. Omitted portions have been filed separately with the Securities and Exchange Commission.

## 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.

AKCEA THERAPEUTICS, INC.

<u>Signatures</u>	<u>Title</u>	<u>Date</u>
<u>/s/ PAULA SOTEROPOULOS</u> Paula Soteropoulos	Chief Executive Officer (on behalf of the Registrant and in her capacity as principal executive officer)	May 9, 2019
<u>/s/ MICHAEL MACLEAN</u> Michael MacLean	Chief Financial Officer (on behalf of the Registrant and in his capacity as principal financial and accounting officer)	May 9, 2019

**AMENDMENT No. 1**  
**to the Strategic Collaboration, Option and License Agreement**  
**between Novartis Pharma AG and Akcea Therapeutics, Inc.**

This Amendment No. 1 (“**Amendment**”) is entered into as of February 22, 2019 (“**Amendment Effective Date**”) by and between **Novartis Pharma AG**, a Swiss corporation having its principal place of business at Lichtstrasse 35, CH-4056 Basel, Switzerland (“**Novartis**”), and **Akcea Therapeutics, Inc.**, a Delaware corporation having its principal place of business at 22 Boston Wharf Road, 9th Floor, Boston, MA 02210, USA (“**Akcea**”). Novartis and Akcea are each referred to individually as a “**Party**” and together as the “**Parties**”.

WHEREAS, Novartis and Akcea are parties to a Strategic Collaboration, Option and License Agreement dated as of January 5th, 2017 (the “**Agreement**”) with respect to the Development and Commercialization of the Product in the Territory;

WHEREAS, the Parties mutually desire to amend, modify and restate certain terms and conditions of the Agreement;

NOW THEREFORE, in consideration of the mutual promises contained herein, and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, and intending to be legally bound, the Parties hereto agree as follows:

**1. DEFINITIONS**

Unless otherwise defined herein, capitalized words in this Amendment shall have the meanings attributed to them in the Agreement.

**2. AMENDMENTS**

The Parties agree that, as of the Amendment Effective Date, the Agreement is amended as set forth in this Section 2.

2.1 Section 6.5 of the Agreement is deleted in its entirety and replaced with the following:

**“6.5(A) Akcea’s Right to Co-Commercialize AKCEA-APO(a)-LRx**

On or before the [\*\*\*] calendar day after [\*\*\*] or [\*\*\*] for AKCEA-APO(a)-LRx, whichever is earlier, Novartis shall deliver written notice to Akcea indicating its election, in Novartis’ sole discretion, to either:

(i) Increase the sales milestones in relation to AKCEA-APO(a)-LRx to the amounts stated below, whereupon Table 3 in Section 7.5 of the Agreement shall be deleted in its entirety and replaced with the following:

Table 3	
Sales Milestone Event for AKCEA-APO(a)-LRx	Milestone Payment
US\$[***] in Annual Net Sales	US\$[***]
US\$[***] in Annual Net Sales	US\$[***]
US\$[***] in Annual Net Sales	US\$[***]

For the avoidance of doubt, if Novartis exercises this option (i), Akcea shall have no right, interest or claim in or to the Co-Commercialization of AKCEA-APO(a)-LRx and Novartis shall have no obligation to negotiate any such rights with Akcea; **or**

(ii) Enter into good faith negotiations with Akcea on the terms and conditions upon which Akcea will Co-Commercialize AKCEA-APO(a)-LRx, whereby the scope of such good faith negotiations would be within the following framework:

- (a) The countries within the scope of the good faith negotiations for the Co-Commercialization of AKCEA-APO(a)-LRx shall be the [\*\*\*], [\*\*\*] (or, in lieu of [\*\*\*]), the [\*\*\*] and [\*\*\*] (each a “**Co-Commercialization Territory**”);
- (b) Akcea would have the right to contribute up to [\*\*\*] percent ([\*\*\*]%) of the Novartis FTEs (*i.e.*, [\*\*\*] FTEs only) in each Co-Commercialization Territory (the “**Contributed FTEs**”);
- (c) The Contributed FTEs shall be [\*\*\*] (*i.e.*, [\*\*\*] filling positions under [\*\*\*] that [\*\*\*] and were [\*\*\*] at least [\*\*\*] ([\*\*\*]) [\*\*\*] prior to the [\*\*\*] for AKCEA-APO(a)-LRx in the respective Co-Commercialization Territory) and shall have a comparable level of scientific and/or commercial expertise as the applicable [\*\*\*] and [\*\*\*] in the applicable Co-Commercialization Territory (*e.g.*, a minimum of [\*\*\*] ([\*\*\*]) years’ experience in cardio-metabolic disease and/or the lipid area);

- (d) Akcea shall be fully responsible for all [\*\*\*] of the Contributed FTEs in each Co-Commercialization Territory;
- (e) The Contributed FTEs shall be fully trained in, and comply with, all applicable Novartis policies and guidelines;
- (f) Novartis shall, in its sole discretion, determine in good faith the [\*\*\*] between the [\*\*\*] and [\*\*\*] and the Contributed FTEs, with consideration being given to the existing [\*\*\*] and any existing relationships that may have been developed around them;
- (g) The Contributed FTEs shall meet the performance standards expected of similarly situated Novartis associates; and
- (h) All remaining terms and conditions upon which Akcea will Co-Commercialize AKCEA-APO(a)-LRx will be negotiated in good faith between the Parties at the time of such negotiation.

**6.5 (B) Akcea's Right to Co-Commercialize AKCEA-APOCIII-LRx.**

Akcea has the right to Co-Commercialize AKCEA-APOCIII-LRx with Novartis in selected markets with the terms and conditions of such Co-Commercialization to be mutually agreed between Akcea and Novartis. If, on or before the [\*\*\*] calendar day after [\*\*\*] or [\*\*\*] for AKCEA-APOCIII-LRx, Akcea delivers written notice to Novartis indicating that Akcea intends to Co-Commercialize AKCEA-APOCIII-LRx, then the Parties shall negotiate in good faith on the terms and conditions upon which Akcea will Co-Commercialize AKCEA-APOCIII-LRx.

**3. INTEGRATION**

As specifically amended hereunder, all terms and conditions of the Agreement remain and shall remain in full force and effect. This Amendment shall hereafter be incorporated into and deemed part of the Agreement and any future reference to the Agreement shall include the terms and conditions of this Amendment.

**4. APPLICABLE LAW & JURISDICTION**

This Amendment shall be governed by, and construed in accordance with, the laws which govern the Agreement, and the Parties submit to the jurisdiction and dispute resolution provisions as set forth in the Agreement.

**5. COUNTERPARTS**

This Amendment may be executed in counterparts with the same effect as if both Parties had signed the same document. All such counterparts shall be deemed an original, shall be construed together and shall constitute one and the same instrument. Signature pages of this Amendment may be exchanged by facsimile or other electronic means without affecting the validity thereof.

[Remainder of Page Intentionally Left Blank – Signature Page to Follow]

IN WITNESS WHEREOF, the Parties intending to be bound have caused this Amendment to be executed by their duly authorized representatives.

**NOVARTIS PHARMA AG**

**AKCEA THERAPEUTICS, INC.**

By: /s/ Neil Johnston  
Name: Neil Johnston  
Title: Global Head BD&L Pharma  
Date: \_\_\_\_\_

By: /s/ Paula Soteropoulos  
Name: Paula Soteropoulos  
Title: CEO  
Date: Feb 14, 2019

By: /s/ Martin Berchtold  
Name: Martin Berchtold  
Title: Senior Legal Counsel  
Date: \_\_\_\_\_

**CERTIFICATION PURSUANT TO  
RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934,  
AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002**

I, Paula Soteropoulos, certify that:

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

Dated: May 9, 2019

By: /s/ Paula Soteropoulos  
**Paula Soteropoulos**  
**Chief Executive Officer**

**CERTIFICATION PURSUANT TO  
RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934,  
AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002**

I, Michael MacLean, certify that:

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

Dated: May 9, 2019

By: /s/ Michael MacLean

**Michael MacLean**  
**Chief Financial Officer**

**CERTIFICATION PURSUANT TO  
18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO  
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002**

Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, Paula Soteropoulos, the Chief Executive Officer of Akcea Therapeutics, Inc., (the “Company”), and Michael MacLean, the Chief Financial Officer of the Company, each hereby certifies that, to the best of his or her knowledge:

- (1) The Company’s Quarterly Report on Form 10-Q for the period ended March 31, 2019, to which this Certification is attached as Exhibit 32.1 (the “Periodic Report”), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and
- (2) The information contained in the Periodic Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Dated: May 9, 2019

By: /s/ Paula Soteropoulos  
**Paula Soteropoulos**  
**Chief Executive Officer**

By: /s/ Michael MacLean  
**Michael MacLean**  
**Chief Financial Officer**

A signed original of this written statement required by Section 906 has been provided to Akcea Therapeutics, Inc. and will be retained by Akcea Therapeutics, Inc. and furnished to the Securities and Exchange Commission or its staff upon request.