UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

Form 10-Q

(Mark One)

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

For the Quarterly Period Ended March 31, 2018

OR

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

For the transition period from to

Commission file number 001-38137

Akcea Therapeutics, Inc.

(Exact name of Registrant as specified in its charter)

Delaware	**47-2608175**
(State or other jurisdiction of incorporation or organization)	(IRS Employer Identification No.)

55 Cambridge Parkway, Suite 100, Cambridge, MA 02142
(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 and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☒ No☐

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

Large accelerated filer ☐	Accelerated filer ☐
Non-accelerated filer ☒ (Do not check if a smaller reporting company)	Smaller reporting company ☐
	Emerging growth company ☒

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

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

The number of shares of common stock outstanding as of April 30, 2018 was 85,593,246.

AKCEA THERAPEUTICS, INC.
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TRADEMARKS

"Akcea," the Akcea logo, and other trademarks or service marks of Akcea Therapeutics, Inc. appearing in this report are the property of Akcea Therapeutics, Inc. This report contains additional trade names, trademarks and service marks of others, which are the property of their respective owners. Solely for convenience, trademarks and trade names referred to in this report may appear without the ® or TM symbols.

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

	March 31, 2018	December 31, 2017 (as revised)
ASSETS		
Current assets:		
Cash and cash equivalents	$ 69,907	$ 58,367
Short-term investments	175,028	201,763
Contracts receivable	-	5,413
Other current assets	5,628	1,302
Total current assets	250,563	266,845
Property, plant and equipment, net	50	77
Licenses, net	1,191	1,221
Deposits and other assets	661	661
Total assets	$ 252,465	$ 268,804
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 2,578	$ 2,381
Payable to Ionis Pharmaceuticals, Inc.	27,737	14,365
Accrued compensation	3,773	4,083
Accrued liabilities	13,413	7,570
Current portion of deferred revenue	48,866	58,192
Other current liabilities	1,929	1,875
Total current liabilities	98,296	88,466
Long-term portion of deferred rent	10	12
Long-term portion of deferred revenue	7,859	12,501
Total liabilities	106,165	100,979
Stockholders' equity:		
Common stock, $0.001 par value; 100,000,000 shares authorized at March 31, 2018 and December 31, 2017; 66,803,803 and 66,541,629 shares issued and outstanding at March 31, 2018 and December 31, 2017, respectively	67	67
Additional paid-in capital	472,549	464,430
Accumulated other comprehensive loss	(468)	(451)
Accumulated deficit	(325,848)	(296,221)
Total stockholders' equity	146,300	167,825
Total liabilities and stockholders' equity	$ 252,465	$ 268,804

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,	
	2018	2017 (as revised)
Revenue:		
Research and development revenue under collaborative agreement	$ 17,108	$ 6,094
Total revenue	17,108	6,094
Expenses:		
Research and development	27,970	64,794
General and administrative	19,465	4,676
Total operating expenses	47,435	69,470
Loss from operations	(30,327)	(63,376)
Other income (expense):		
Investment income	868	61
Interest expense	—	(541)
Other expense	(168)	—
Loss before income tax expense	(29,627)	(63,856)
Income tax expense	—	—
Net loss	$ (29,627)	$ (63,856)
Net loss per share of preferred stock, basic and diluted	$ —	$ (2.21)
Weighted-average shares of preferred stock outstanding, basic and diluted	—	28,884,540
Net loss per share of common stock, basic and diluted	$ (0.44)	$ —
Weighted-average shares of common stock outstanding, basic and diluted	66,616,337	—

See accompanying notes.

AKCEA THERAPEUTICS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF COMPREHENSIVE LOSS
(in thousands)
(Unaudited)

	Three Months Ended March 31,	
	2018	**2017**
		(as revised)
Net loss	$ (29,627)	$ (63,856)
Unrealized gains (losses) on investments, net of tax	(45)	(28)
Currency translation adjustment	28	6
Comprehensive loss	$ (29,644)	$ (63,878)

See accompanying notes.

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

	Three Months Ended March 31,	
	2018	**2017 (as revised)**
Operating activities:		
Net loss	$ (29,627)	$ (63,856)
Adjustments to reconcile net loss to net cash (used in) provided by operating activities:		
Depreciation	27	29
Amortization of licenses	30	30
Amortization of premium on investments, net	149	24
Non-cash interest expense for line of credit with Ionis Pharmaceuticals, Inc.	—	541
Stock-based compensation expense	6,384	3,180
Changes in operating assets and liabilities:		
Contracts receivable	5,413	—
Other current and long-term assets	(4,326)	(1,915)
Prepaid amounts to Ionis Pharmaceuticals, Inc.	—	(3,005)
Accounts payable	197	(459)
Payable to Ionis Pharmaceuticals, Inc.	13,372	(9,355)
Accrued compensation	(310)	(1,658)
Deferred rent	(10)	(9)
Accrued liabilities	5,843	331
Income taxes payable	63	(9)
Deferred revenue	(13,968)	102,301
Net cash (used in) provided by operating activities	(16,763)	26,170
Investing activities:		
Purchases of short-term investments	(9,906)	(49,465)
Proceeds from sale of short-term investments	36,447	2,750
Net cash (used in) provided by investing activities	26,541	(46,715)
Financing activities:		
Proceeds from exercise of common stock options and employee stock purchase plan issuances	1,724	—
Proceeds from line of credit from Ionis Pharmaceuticals, Inc.	—	91,000
Offering costs paid	—	(459)
Net cash provided by financing activities	1,724	90,541
Effect of exchange rates on cash	38	5
Net increase in cash and cash equivalents	11,540	70,001
Cash and cash equivalents at beginning of period	58,367	7,857
Cash and cash equivalents at end of period	$ 69,907	$ 77,858
Supplemental disclosures of non-cash financing activities:		
Unpaid deferred offering costs	$ 450	$ 319

See accompanying notes.

1. Basis of Presentation and Organization

The accompanying condensed consolidated financial statements are unaudited and have been prepared in conformity with accounting principles generally accepted in the United States of America, or U.S. GAAP. Certain amounts in the prior period financial statements have been revised to conform to the presentation of the current period financial statements. See Note 2, *Summary of Significant Accounting Policies*, for a discussion of certain revisions to prior period financial statements made in connection with our adoption of the new revenue recognition guidance retroactive to January 1, 2017.

The condensed consolidated financial statements include the accounts of Akcea Therapeutics, Inc. ("we," "our," and "us") and our wholly owned subsidiaries. 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, 2018 and 2017. 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 on the Annual Report on Form 10-K for the fiscal year ended December 31, 2017.

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, 2018, Ionis owned approximately 68% of our common stock and is our majority shareholder. Prior to our IPO, we were wholly owned by Ionis.

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. As of March 31, 2018, we had an accumulated deficit of $325.8 million. During the three months ended March 31, 2018, we incurred a loss of $29.6 million, and used $16.8 million of cash in operations. We expect to continue to generate operating losses in the foreseeable future. We expect that our cash, cash equivalents and investments of $244.9 million as of March 31, 2018, together with the $200.0 million from the common stock issuance to Ionis in conjunction with the licensing transaction with Ionis discussed in Note 10, *Subsequent Events*, will be sufficient to fund our operating expenses and capital expenditure requirements for at least the next 12 months from issuance of these financial statements.

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 1 to our financial statements included on the Annual Report on Form 10-K for the year ended December 31, 2017 except as noted below with respect to our revenue recognition accounting policy.

Use of Estimates

The preparation of condensed consolidated financial statements in conformity with U.S. GAAP requires our management to make estimates and assumptions that affect the amounts reported in the consolidated financial statements and accompanying notes. 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 loss within the condensed consolidated statements of comprehensive loss.

Revenue Recognition

In May 2014, the Financial Accounting Standards Board, or FASB, issued Accounting Standards Update, or ASU, No. 2014-09, which amends the guidance for accounting for revenue from contracts with customers. This ASU supersedes the revenue recognition requirements in ASC Topic 605, *Revenue Recognition*, or Topic 605, and creates a new Topic 606, *Revenue from Contracts with Customers*, or Topic 606. In 2015 and 2016, the FASB issued additional ASUs related to Topic 606 that delayed the effective date of the guidance and clarified various aspects of the new revenue guidance, including principal versus agent considerations, identifying performance obligations, and licensing, and they include other improvements and practical expedients. 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, and 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 options are material rights that should be treated as additional performance obligations. We typically have not 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 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 their 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 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. We have one revenue stream from our strategic collaboration, option and license agreement, or collaboration agreement, with Novartis Pharma AG, or Novartis, which we entered into in January 2017. For a complete discussion of the accounting for our collaboration revenue, see Note 4, Strategic Collaboration with Novartis.

Effective January 1, 2018, we adopted Topic 606 using the full retrospective transition method. Under this method, we revised our consolidated financial statements for prior period amounts including the interim periods included in this Report on Form 10-Q, as if Topic 606 had been effective for such periods. The references "as revised" used herein refer to revisions of data for the three months ended March 31, 2017 and the year ended December 31, 2017 as a result of our adoption of Topic 606.

Impact of Adoption

As a result of adopting Topic 606 on January 1, 2018, we have revised our comparative financial statements for the prior year as if Topic 606 had been effective for that period. Under Topic 605, we recognized revenue over time. Under Topic 606, we recognize revenue based on the input method based on total costs of performing services over time. As a result, the following financial statement line items for fiscal year 2017 were affected.

Condensed Consolidated Balance Sheets

	December 31, 2017 (in thousands)		
	As revised under Topic 606	As originally reported under Topic 605	Effect of change
Current portion of deferred revenue	$ 58,192	$ 50,579	$ 7,613
Long-term portion of deferred revenue	12,501	8,306	4,195
Accumulated deficit	$ (296,221)	$ (284,413)	$ (11,808)

Condensed Consolidated Statements of Operations and Comprehensive Loss

	Three Months Ended March 31, 2017 (in thousands, except per share data)		
	As revised under Topic 606	As originally reported under Topic 605	Effect of change
Research and development revenue under collaborative agreements	$ 6,094	$ 9,597	$ (3,503)
Loss from operations	(63,376)	(59,873)	(3,503)
Net loss	(63,856)	(60,353)	(3,503)
Net loss per share of preferred stock, basic and diluted	$ (2.21)	$ (2.09)	$ (0.12)

Condensed Consolidated Statement of Cash Flows

	Three Months Ended March 31, 2017 (in thousands)		
	As revised under Topic 606	As originally reported under Topic 605	Effect of change
Net loss	$ (63,856)	$ (60,353)	$ (3,503)
Adjustments to reconcile net loss to net cash provided by operating activities:			
Deferred revenue	102,301	98,798	3,503
Cash and cash equivalents at beginning of period	7,857	7,857	—
Cash and cash equivalents at end of period	$ 77,858	$ 77,858	$ —

New Accounting Pronouncements - Recently Issued

In February 2016, the FASB issued amended accounting guidance related to lease accounting, which requires us to record all leases with a term longer than one year on our balance sheet. When we record leases on our balance sheet under the new guidance, we will record a liability with a value equal to the present value of payments we will make over the life of the lease and an asset representing the underlying leased asset. The new accounting guidance requires us to determine if any lease we have is an operating or financing lease, similar to current accounting guidance. We will record expense for an operating type lease on a straight-line basis as an operating expense and we will record expense for a financing type lease as interest expense. The new lease standard is effective for annual and interim periods beginning after December 15, 2018, with early adoption permitted. We must adopt the new standard on a modified retrospective basis, which requires us to reflect any leases we have on our consolidated balance sheet for the earliest comparative period presented. We are currently assessing the impact that adoption of this guidance will have on our consolidated financial statements and disclosures.

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 that we do not expect to collect. This change will result in us remeasuring 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 are currently assessing the timing of adoption as well as the effects it will have on our consolidated financial statements and disclosures.

In February 2018, the FASB issued updated guidance for reclassification of tax effects from accumulated other comprehensive income (loss). The updated guidance gives entities an option to reclassify the stranded tax effects resulting from changes due to the Tax Act from accumulated other comprehensive income (loss) to accumulated deficit. The updated guidance is effective for all entities for fiscal years beginning after December 31, 2018, and interim periods within those fiscal years. Early adoption is permitted, and adoption is optional. We are currently assessing the effects this updated guidance could have on our consolidated financial statements and the timing of potential adoption.

3. Investments and Fair Value Measurements

Investments

The following is a summary of our investments at March 31, 2018 and December 31, 2017 (in thousands):

		Gross Unrealized		Estimated
March 31, 2018	**Cost**	**Gains**	**Losses**	**Fair Value**
Available-for-sale securities:				
Corporate debt securities	$ 101,180	$ —	$ (220)	$ 100,960
Debt securities issued by U.S. government agencies	68,782	—	(135)	68,647
Total securities with a maturity of one year or less	169,962	—	(355)	169,607
Corporate debt securities	2,919	—	(23)	2,896
Debt securities issued by U.S. government agencies	2,529	—	(4)	2,525
Total securities with a maturity of one to two years	5,448	—	(27)	5,421
Total available-for-sale securities	$ 175,410	$ —	$ (382)	$ 175,028

		Gross Unrealized		Estimated
December 31, 2017	**Cost**	**Gains**	**Losses**	**Fair Value**
Available-for-sale securities:				
Corporate debt securities	$ 132,434	$ —	$ (206)	$ 132,228
Debt securities issued by U.S. government agencies	38,135	—	(59)	38,076
Total securities with a maturity of one year or less	170,569	—	(265)	170,304
Corporate debt securities	8,267	—	(35)	8,232
Debt securities issued by U.S. government agencies	23,264	—	(37)	23,227
Total securities with a maturity of one to two years	31,531	—	(72)	31,459
Total available-for-sale securities	$ 202,100	$ —	$ (337)	$ 201,763

We recorded unrealized losses related to the securities listed above as of March 31, 2018 and December 31, 2017. We believe that the decline in value of these 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 our debt securities' amortized cost basis 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

We use a three-tier fair value hierarchy to prioritize the inputs used in our fair value measurements. These tiers include: Level 1, defined as observable inputs such as quoted prices in active markets for identical assets, which includes our money market funds and treasury securities classified as available-for-sale securities; Level 2, defined as inputs other than quoted prices in active markets that are either directly or indirectly observable, which includes our fixed income securities and commercial paper classified as available-for-sale securities; and Level 3, defined as unobservable inputs in which little or no market data exists, therefore requiring us to develop our own assumptions. We have not historically held any Level 3 investments. We recognize transfers between levels of the fair value hierarchy on the date of the event or change in circumstances that caused the transfer.

The following tables present the major security types we held at March 31, 2018 and December 31, 2017 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, 2018	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents (1)	$ 65,963	$ 65,963	$ —
Corporate debt securities (2)	103,856	—	103,856
Debt securities issued by U.S. government agencies (2)	71,172	—	71,172
Total	$ 240,991	$ 65,963	$ 175,028

	At December 31, 2017	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents (1)	$ 48,430	$ 48,430	$ —
Corporate debt securities (2)	140,460	—	140,460
Debt securities issued by U.S. government agencies (2)	61,303	—	61,303
Total	$ 250,193	$ 48,430	$ 201,763

(1) Included in cash and cash equivalents on our condensed consolidated balance sheets.
(2) Included in short-term investments on our condensed consolidated balance sheets.

We did not have any Level 3 investments at March 31, 2018 and December 31, 2017. During the three months ended March 31, 2018 and the year ended December 31, 2017, there were no transfers between Level 1 and Level 2.

4. Strategic Collaboration with Novartis

In January 2017, we initiated a strategic collaboration with Novartis for the development and commercialization of AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. 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 FDA and providing initial quantities of the active pharmaceutical ingredient, or API, for each drug. If Novartis exercises an 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 license agreement with Ionis. If Novartis exercises its option for a drug, Novartis will pay us a license fee equal to $150.0 million for each drug licensed by Novartis. In addition, for AKCEA-APO(a)-L_{Rx}, we are eligible to receive up to $600.0 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 $285.0 million for the achievement of commercialization milestones. In addition, for AKCEA-APOCIII-L_{Rx}, 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 will earn the next milestone payment of $25.0 million under this collaboration if Novartis advances 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)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. 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. We plan to co-commercialize any licensed drug commercialized by Novartis in selected markets under terms and conditions that we plan to negotiate with Novartis in the future, through the specialized sales force we are building to commercialize inotersen and volanesorsen.

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

- Development activities for AKCEA-APO(a)-L_{Rx};
- Development activities for AKCEA-APOCIII-L_{Rx};
- API for AKCEA-APO(a)-L_{Rx}; and
- API for AKCEA-APOCIII-L_{Rx}.

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 development or regulatory milestone payments have been included in the transaction price, as all milestone 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)-L_{Rx};
- $40.1 million for development services for AKCEA-APOCIII-L_{Rx};
- $1.5 million for the delivery of AKCEA-APO(a)-L_{Rx} API; and
- $2.8 million for the delivery of AKCEA-APOCIII-L_{Rx} 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)-L_{Rx} as the research and development services are performed. We determined that the period of performance of the research and development services was two years, or through December 2018. 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-L_{Rx} as the research and development services are performed. We determined that the period of performance of the research and development services was two and a half years, or through June 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 recognize the amount attributed to the AKCEA-APO(a)-L_{Rx} API supply when we deliver API to Novartis; and
- We recognized the amount attributed to the AKCEA-APOCIII-L_{Rx} API supply when we delivered API to Novartis in 2017.

At March 31, 2018, the aggregate transaction price allocated to our remaining performance obligations was $56.7 million, which we are recognizing over the estimated period of our performance obligation.

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. Our IPO is discussed in Note 9, *Initial Public Offering*.

During the three months ended March 31, 2018, we earned revenue of $17.1 million from our relationship with Novartis, representing 100% of our revenue. In comparison, we earned revenue of $6.1 million for the same period in 2017 (as revised). During the three months ended March 31, 2018, we recognized $17.1 million of revenue from amounts that were in our beginning deferred revenue balance. Our consolidated balance sheet at March 31, 2018 and December 31, 2017 (as revised) included deferred revenue of $56.7 million and $70.7 million, respectively, related to our relationship with Novartis.

5. Development, Commercialization and License Agreement and Services Agreement with Ionis

We entered into a development, commercialization and license agreement and a services agreement in December 2015 with Ionis. The following section summarizes these related party agreements with Ionis.

Development, Commercialization and License Agreement

Our development, commercialization and license agreement, or the license agreement, with Ionis granted exclusive rights to us to develop and commercialize volanesorsen, AKCEA-APO(a)-L_{Rx}, AKCEA-APOCIII-L_{Rx}, and AKCEA-ANGPTL3-L_{Rx}, which are collectively referred to as the Lipid Drugs. Ionis has 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 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. 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, 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 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 4, *Strategic Collaboration with Novartis.*

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 for our own human resources and personnel services, 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 human resources and personnel 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, 2018 and December 31, 2017, we owed Ionis $27.7 million and $14.4 million, respectively.

The following table summarizes the amounts included in our operating expenses that were generated by transactions with Ionis for the following periods (in thousands):

	Three Months Ended March 31,	
	2018	2017
Services performed by Ionis	$ 1,945	$ 2,957
Active pharmaceutical ingredient manufactured by Ionis	5,229	3,083
Sublicensing expenses	—	48,394
Out-of-pocket expenses paid by Ionis	6,236	8,868
Total expenses generated by transactions with Ionis	13,410	63,302
Payable balance to Ionis at the beginning of the period	14,365	24,355
Prepaid amounts to Ionis	—	3,005
Less: total amounts paid to Ionis during the period	(38)	(42,268)
Less: non-cash sublicensing expenses	—	(33,394)
Total amount payable to Ionis at period end	$ 27,737	$ 15,000

6. Stock-Based Compensation

Stock Plans

2015 Equity Incentive Plan

In December 2015, our board of directors and stockholder adopted and approved our 2015 Equity Incentive Plan, or the 2015 Plan. In May 2017 and June 2017, our board of directors and stockholder, respectively, approved an amendment to our 2015 Equity Incentive Plan in order to, among other things, increase the number of shares of common stock reserved for issuance thereunder to 8,500,000 shares of common stock in conjunction with the IPO. In December 2017 and April 2018, our board of directors and our majority stockholder, respectively, approved an additional amendment to our 2015 Equity Incentive Plan to increase the number of shares of common stock reserved for issuance thereunder to 13,500,000 shares of common stock.

As of March 31, 2018, the aggregate number of shares of common stock that may be issued pursuant to stock awards under the 2015 Plan was 8,500,000 shares, not including an additional 5,000,000 shares approved by the Board of Directors in December 2017, which are subject to shareholder approval on June 1, 2018. The 2015 Plan also provides for the grant of non-statutory stock options, or NSOs, incentive stock options, or ISOs, stock appreciation rights, restricted stock awards and restricted stock unit awards. At March 31, 2018, assuming approval of the additional 5,000,000 shares above, a total of 9,298,024 options were outstanding, of which 3,276,937 were exercisable, 32,529 restricted stock unit awards were outstanding, and 4,201,976 shares were available for future grant under the 2015 Plan.

2017 Employee Stock Purchase Plan

In May 2017 and June 2017, our board of directors and stockholder, respectively, approved our 2017 Employee Stock Purchase Plan, or 2017 ESPP, which became effective upon the completion of our IPO, and the reservation for issuance thereunder of 1,165,416 shares of common stock. In addition, the number of shares of common stock that may be issued under the ESPP will automatically increase commencing on January 1, 2018 and ending on (and including) January 1, 2027 in an amount equal to the lesser of (i) 1% of the total number of shares of Common Stock outstanding on December 31st of the preceding calendar year, and (ii) 500,000 shares of Common Stock.

During the three months ended March 31, 2018, 15,732 shares were issued under our 2017 ESPP. As of March 31, 2018, the aggregate number of shares of common stock that may be issued pursuant to the 2017 ESPP was 1,149,684 shares. At March 31, 2018, accrued liabilities included $144,000 of ESPP contributions related to our current enrollment period for which the related shares will be issued on July 2, 2018.

Stock-Based Compensation

The following table summarizes stock-based compensation expense for the three months ended March 31, 2018 and 2017 (in thousands):

	Three Months Ended March 31,	
	2018	2017
Research and development expenses	$ 2,314	$ 1,600
General and administrative expenses	4,070	1,580
Total	$ 6,384	$ 3,180

7. Accumulated Other Comprehensive Loss

The following table summarizes changes in accumulated other comprehensive loss (in thousands):

	2018
Balance, as of December 31, 2017	$ (451)
Unrealized gains (losses) on investments, net of tax (1)	(45)
Currency translation adjustment	28
Net other comprehensive income (loss)	(17)
Balance, as of March 31, 2018	$ (468)

(1) There was no tax benefit for other comprehensive income (loss) for the three months ended March 31, 2018.

8. Basic and Diluted Net Loss Per Share

The following table summarizes the calculation of basic EPS for the three months ended March 31, 2018 and 2017 (in thousands, except share and per share amounts):

	Three Months Ended March 31,	
	2018	2017
Losses allocated to preferred shares	$ —	$ (63,856)
Weighted-average preferred shares outstanding	—	28,884,540
Basic loss per preferred share	$ —	$ (2.21)
Losses allocated to common shares	$ (29,627)	$ —
Weighted-average common shares outstanding	66,616,337	—
Basic loss per common share	$ (0.44)	$ —

For the three months ended March 31, 2018 and 2017, 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, or ESPP.

9. Initial Public Offering

On July 19, 2017, we completed our IPO. Total net proceeds were $182.3 million, including the following:

- $132.3 million from the sale of 17,968,750 shares of our common stock in our IPO of which $25 million was invested by Ionis; and
- $50.0 million from the purchase of 6,250,000 shares by Novartis in a concurrent private placement.

In addition, both of the following occurred in connection with the completion of our IPO on July 19, 2017:

- the conversion of all outstanding shares of Series A convertible preferred stock into 28,884,540 shares of our common stock; and
- the conversion of $106.0 million of outstanding principal plus accrued interest from the line of credit into 13,438,339 shares of common stock.

10. Subsequent Events

Operating Lease

On April 5, 2018, we entered into an operating lease agreement with MEPT Seaport 13 Stillings LLC, or MEPT, for 30,175 square feet of office space located in Boston, Massachusetts for our new corporate headquarters. The anticipated commencement date of the lease is August 15, 2018. The initial term of the lease is 123 months with one five-year renewal option. Future minimum annual lease payments under this lease are $0.8 million in 2018, $2.2 million in 2019, $2.3 million in 2020, $2.3 million in 2021, $2.3 million in 2022, and $14.2 million thereafter. MEPT will provide us with a three-month free rent period and a tenant improvement allowance up to $3.8 million. We provided the Landlord with a letter of credit to secure our 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.

Inotersen 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 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 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 would be April 17, 2018, the date on which such approval was received.

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

- commercialize inotersen following receipt of regulatory approval and perform certain other non-commercial activities with respect to inotersen, in each case, in accordance with a global strategic plan;
- partner on the completion of all pivotal studies, of a follow-on drug to inotersen, AKCEA-TTR-L_{Rx} and perform other non-commercial activities with respect to AKCEA-TTR-L_{Rx};
- commercialize AKCEA-TTR-L_{Rx}, following receipt of regulatory approval in accordance with a global strategic plan;
- share in profits and losses with respect to inotersen and AKCEA-TTR-L_{Rx};
- 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 payment for the grant of rights under the 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 recent trading average. In addition, we will be 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 inotersen approval milestones are met; up to $145.0 million, if all AKCEA-TTR-L_{Rx} milestones are met; and a total of $1.3 billion, in the form of seven milestones, 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. Subsequent to the achievement of the milestone event for aggregate worldwide annual net sales of $750 million for the products, all subsequent milestone payments must be paid in cash.

We and Ionis also agreed to share inotersen and AKCEA-TTR-L_{Rx} profits and losses as follows: for inotersen, beginning on the earlier of (i) the first day of the quarter after receipt of regulatory approval of inotersen in the United States, or (ii) January 1, 2019, the parties will share profits and losses from the development and commercialization of inotersen (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-L_{Rx} occurs, and (B) on a 50/50 basis commencing on the first day of the first quarter thereafter; and for AKCEA-TTR-L_{Rx}, beginning January 1, 2018, the parties will share all profits and losses from the development and commercialization of AKCEA-TTR-L_{Rx} on a 50/50 basis.

The License Agreement will remain in effect until the expiration of all included payment obligations, or unless earlier terminated. The 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 License Agreement will terminate.

To support the commercialization of inotersen and AKCEA-TTR-L_{Rx}, Ionis purchased 10.7 million shares of our common stock for $200 million and received an additional 8 million shares in consideration of the upfront licensing fee, increasing Ionis' ownership percentage to approximately 75%.

The Amended Services Agreement allows for the expansion of general and administrative services provided to us by Ionis to cover the inotersen and AKCEA-TTR-L_{Rx} products, under terms substantially similar to the prior services agreement.

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

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 and our business, and the therapeutic and commercial potential of inotersen, volanesorsen 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. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs. 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 speak only as of the date of this report. 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, 2017, which are contained in our Annual Report on the Form 10-K for the fiscal year ended on December 31, 2017 filed on February 28, 2018 with the SEC.

OVERVIEW

We are a biopharmaceutical company focused on developing and commercializing drugs to treat patients with rare and serious diseases with leading-edge, RNA-targeted medicines. Our priority is to bring 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- and registration-stage drugs covering multiple targets and diseases using advanced RNA-targeted antisense therapeutics. Our immediate focus is to prepare for the approval and commercial launch of inotersen and volanesorsen as we continue to drive our other clinical programs forward through development.

On March 14, 2018, we announced that we had obtained exclusive worldwide licensing rights from Ionis to inotersen and AKCEA-TTR-L_{Rx}. This licensing transaction was approved by our shareholders in April 2018. Inotersen is currently under regulatory review by the U.S. Food and Drug Administration, or FDA, and the European Medicines Agency, or EMA, for the treatment of hereditary transthyretin amyloidosis, or hATTR. This licensing transaction leverages the commercial infrastructure already in place at Akcea in preparation for the commercial launch of volanesorsen upon regulatory approval. The Akcea team is preparing to launch inotersen in the United States, or U.S., and European Union, or EU following planned approvals in 2018. In collaboration with Ionis, we are also developing AKCEA-TTR-L_{Rx} for hereditary and wild-type forms of ATTR. AKCEA-TTR-L_{Rx} is planned to enter clinical development in 2018.

With the licensing agreement, we have expanded our efforts to treat people with serious and under-served rare diseases focusing on transthyretin amyloidosis, or ATTR, and cardiometabolic diseases.

ATTR

Inotersen is an antisense drug designed to reduce the production of transthyretin, or TTR protein, to treat hereditary ATTR, or hATTR, a severe, rare and fatal genetic disease. In patients with hATTR, both the mutant 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.

Inotersen is currently under regulatory review for marketing authorization in the United States, or U.S., EU and Canada. The FDA has granted Orphan Drug Designation and Fast Track Status to inotersen for the treatment of patients with polyneuropathy due to hATTR and has assigned a prescription drug user fee act, or PDUFA, date of October 6, 2018. The EMA has granted accelerated assessment and Orphan Drug Designation to inotersen. In Canada, our New Drug Submission, or NDS, was granted Priority Review by Health Canada.

Inotersen was discovered and previously developed by Ionis Pharmaceuticals, before being in-licensed by us in April 2018. In addition to inotersen, we and Ionis are developing AKCEA-TTR-L_{Rx} for hereditary and wild-type forms of ATTR and are planning to begin clinical development of this program in 2018.

Cardiometabolic

Our lipid/cardiometabolic drugs, volanesorsen, AKCEA-APO(a)-L$_{Rx}$, AKCEA-ANGPTL3-L$_{Rx}$ and AKCEA-APOCIII-L$_{Rx}$, are all based on antisense technology developed by Ionis. Our most advanced drug, volanesorsen, is currently under review by regulatory agencies in the U.S., EU and Canada for the treatment of people with familial chylomicronemia syndrome, or FCS. In the U.S., the FDA assigned a PDUFA date of August 30, 2018 and scheduled an advisory committee meeting for May 10, 2018. In Canada, our New Drug Submission, or NDS, was granted Priority Review by Health Canada. 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 volanesorsen program demonstrate a favorable risk-benefit profile for patients with FCS. We are preparing for approval and launch of volanesorsen in 2018. Volanesorsen is also in Phase 3 clinical development for the treatment of familial partial lipodystrophy, or FPL. Our other three lipid/cardiometabolic drugs are currently in Phase 2 clinical development.

Commercial Preparation

We are continuing to build the infrastructure to commercialize our drugs globally with a focus on lipid specialists who specialize in treating patients with FCS as the primary call point, and on expanding the team Ionis has established to reach amyloidosis specialists including neurologists, cardiologists and hematologists who treat hATTR . We have hired general managers to lead operations in the U.S., United Kingdom, or UK, France, Germany and Canada. We have also hired sales team members and additional field medical personnel to further disease education prior to both product launches. 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, in January 2017 for the development and commercialization of AKCEA-APO(a)-L$_{Rx}$ and AKCEA-APOCIII-L$_{Rx}$. 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 $15.0 million to Ionis as a sublicense fee. Under our agreement with Novartis, after we complete Phase 2 development of each of AKCEA-APO(a)-L$_{Rx}$ (data planned for the second half of 2018) and AKCEA-APOCIII-L$_{Rx}$ (data planned for 2019), and if, on a drug-by-drug basis, Novartis exercises its option to license a drug and pays us the $150.0 million license fee to do so, Novartis would conduct and pay for a Phase 3 cardiovascular outcome study in high-risk patients and, if approved, commercialize each such licensed drug worldwide. Novartis will have 60 days following the end of the applicable end of Phase 2 meeting to exercise its option for each of these drugs. We plan to co-commercialize any licensed drugs commercialized by Novartis in selected markets, under terms and conditions that we plan to negotiate with Novartis in the future, through the specialized sales force we are building to commercialize inotersen and volanesorsen, if approved. Overall, we are eligible to receive license fees, milestone payments and royalties on sales of each drug Novartis licenses 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 $1.0 billion, plus royalties, which we would generally be required to share equally with Ionis. The calculation of potential aggregate transaction value assumes that Novartis licenses, successfully develops and achieves regulatory approval for both AKCEA-APO(a)-L$_{Rx}$ and AKCEA-APOCIII-L$_{Rx}$ in the U.S., EU and Japan, and that Novartis achieves pre-specified sales targets with respect to both drugs. In addition, to the upfront payment that we have received, for AKCEA-APO(a)-L$_{Rx}$ we are eligible to receive up to $600.0 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 $285.0 million for the achievement of commercialization milestones. In addition, for AKCEA-APOCIII-L$_{Rx}$ 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 $265.0 million for the achievement of commercialization milestones. We are also eligible to receive tiered royalties in the mid-teens to low twenty percent range on net sales of AKCEA-APO(a)-L$_{Rx}$ and AKCEA-APOCIII-L$_{Rx}$, 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 4, *Strategic Collaboration with Novartis,* to our consolidated financial statements for additional information.

We began recognizing revenue under the collaboration with Novartis upon its initiation. Our revenue for the first three months of 2018 was $17.1 million. Our net losses for the three months ended March 31, 2018, have resulted from costs incurred in developing volanesorsen and the other drugs in our pipeline, preparing to commercialize inotersen and volanesorsen, and general and administrative activities associated with our operations. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future as we continue to develop inotersen, volanesorsen and our other drugs, and seek regulatory approval for and prepare to commercialize volanesorsen and inotersen. We expect to incur significant expenses to continue to build the infrastructure to support commercialization, including manufacturing, marketing, sales and distribution functions. Further, we expect to incur additional costs associated with operating as a public company and in building our internal resources to become less reliant on Ionis.

As of March 31, 2018, we had cash, cash equivalents and investments of $244.9 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. In July 2017 we completed our IPO and raised $182.3 million in net proceeds from the IPO including the $50 million Novartis concurrent private placement. In April 2018, we completed a licensing transaction with Ionis to commercialize inotersen for hATTR. In conjunction with this transaction, Ionis purchased 10.7 million shares of our common stock for $200 million. See Note 10, *Subsequent Events*, to our condensed consolidated financial statements included in this Form 10-Q for more information about our inotersen licensing agreement with Ionis. We plan to use our cash on hand as of March 31, 2018, together with the proceeds from the common stock issuance to Ionis in connection with the licensing transaction, to further our commercialization efforts of inotersen and volanesorsen and continue the advancement of our pipeline drugs.

We expect that our cash, cash equivalents and investments of $244.9 million as of March 31, 2018, together with the $200.0 million from the common stock issuance in connection with the licensing transaction with Ionis discussed in Note 10, will be sufficient to fund our operating expenses and capital expenditure requirements for at least the next 12 months from issuance of these financial statements. However, we expect to raise additional funding in the future to continue developing the drugs in our pipeline and to commercialize any approved drug, including the inotersen and volanesorsen brands. 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.

Our Relationship with Ionis

Prior to January 2015, the lipid drugs we licensed from Ionis were part of Ionis' broad pipeline of antisense 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 consolidated financial statements. 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 exclusively licensed volanesorsen, AKCEA-APO(a)-L$_{Rx}$, AKCEA-ANGPTL3-L$_{Rx}$ and AKCEA-APOCIII-L$_{Rx}$ from Ionis effective in January 2015, and inotersen and AKCEA-TTR-L$_{Rx}$ in April 2018. Prior to then, Ionis had been advancing these drugs in development and incurring the expenses for those activities. Under our license agreement with Ionis, Ionis continued and is continuing to conduct development, regulatory and manufacturing activities for our drugs and charge us for this work. In this way, we benefit from Ionis' more than 25 years of experience developing and manufacturing antisense drugs. As we are building our development, regulatory and manufacturing capabilities and capacity, we expect to assume increasing responsibility for these functions and Ionis' responsibilities will decrease. We expect that our collaborative approach will allow us to build these capabilities and capacity while still working closely with Ionis as we transition our drug development activities.

We pay Ionis for the research and development expenses it incurs on our behalf, which include both external and internal expenses in accordance with our license agreement with Ionis. 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 development expenses include costs for the work that Ionis' 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 research and development employees who work either directly or indirectly on the development of our drugs. In accordance with the license agreement, we pay Ionis for external research and development expenses and internal research and development expenses. We also pay Ionis for the active pharmaceutical ingredient, or 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 or pre-filled syringes for our clinical studies, Ionis will contract with a third party to perform this work and Ionis will charge us for the resulting cost.

Under the services agreement, Ionis also provides us certain services, including, without limitation, general and administrative support services and development support services. We pay Ionis for our share of the internal and external expenses for each of these functions based on our relative use of each function, plus an allocation of facility-related expenses. As our business grows and we assume increasing responsibility from Ionis, we are assuming direct responsibility for procuring and financing the services we currently receive from Ionis.

We do not pay a mark-up or profit on the external or internal expenses Ionis bills to us or on the cost of the drugs Ionis manufactures for us. Moreover, Ionis only charges us for the portion of its resources that we use. For example, we do not have to pay for a full-time person if we only need the person's skills for 50% of the time. In this way, we can increase our headcount as our requirements grow. We believe that our expenses reasonably reflect the expenses we would have incurred if we had the capabilities and capacity in place to perform this work ourselves. Further, we do not believe that our expenses will increase significantly as a result of assuming development, regulatory, manufacturing and administrative responsibilities from Ionis because we will only assume these functions when we believe we can do so in a cost-efficient manner. See Note 5, *Development, Commercialization and License Agreement and Services Agreement with Ionis*, to our condensed consolidated financial statements included in this Form 10-Q for more information on our agreements with Ionis.

In conjunction with the license of inotersen and AKCEA-TTR-L_{Rx} in April 2018, we and Ionis have agreed to amend the cost share agreement to reflect the change in our needs and relationship with Ionis. The intent of the amendment is to ensure a smooth transition of the TTR franchise and adequate support from Ionis in key functions, while maintaining overall efficiency. These changes will take effect in the second quarter of 2018.

Recent Key Achievements

- Announcement and closing of the partnership with Ionis to commercialize the TTR franchise.
- Addition of Sarah Boyce to Akcea as president and a member of our board of directors.
- Initiation of the volanesorsen global Early Access Program including initiation of the Early Access to Medicines Scheme, or EAMS, in the UK for the treatment FCS.
- Presentation of multiple data sets at the International Symposium on Amyloidosis, or ISA, including the NEURO-TTR and Open Label Extension Studies for TEGSEDI and the preclinical data set for AKCEA-TTR-L_{Rx}.
- Presentation of AKCEA-APOCIII-L_{Rx} Phase 1/2 results at the American College of Cardiology, or ACC, Annual Scientific Session and Expo.
- Convening of the first FCS global connection summit where the patient leaders named the first Friday in November as FCS Awareness Day.

The information found on, or accessible through, the above referenced websites is not a part of, and is not incorporated into, this Quarterly Report on Form 10-Q.

Critical Accounting Policies

The accounting policies 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 1 of our Annual Report on the Form 10-K for the fiscal year ended on December 31, 2017 and updated below as necessary.

Revenue Recognition

In May 2014, the Financial Accounting Standards Board, or FASB, issued Accounting Standards Update, or ASU, No. 2014-09, which amends the guidance for accounting for revenue from contracts with customers. This ASU supersedes the revenue recognition requirements in ASC Topic 605, *Revenue Recognition*, or Topic 605, and creates a new Topic 606, *Revenue from Contracts with Customers*, or Topic 606. In 2015 and 2016, the FASB issued additional ASUs related to Topic 606 that delayed the effective date of the guidance and clarified various aspects of the new revenue guidance, including principal versus agent considerations, identifying performance obligations, and licensing, and they include other improvements and practical expedients. 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, and 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 options are material rights that should be treated as additional performance obligations. We typically have not 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 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 their 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 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. We have one revenue stream from our strategic collaboration, option and license agreement, or collaboration agreement, with Novartis Pharma AG, or Novartis, which we entered into in January 2017. For a complete discussion of the accounting for our collaboration revenue, see Note 4, Strategic Collaboration with Novartis.

Effective January 1, 2018, we adopted Topic 606 using the full retrospective transition method. Under this method, we revised our consolidated financial statements for prior period amounts including the interim periods included in this Report on Form 10-Q, as if Topic 606 had been effective for such periods. The references "as revised" used herein refer to revisions of data for the three months ended March 31, 2017 and the year ended December 31, 2017 as a result of our adoption of Topic 606.

Impact of Adoption

As a result of adopting Topic 606 on January 1, 2018, we have revised our comparative financial statements for the prior year as if Topic 606 had been effective for that period. Under Topic 605, we recognized revenue over time. Under Topic 606, we recognize revenue based on the input method based on total costs of performing services over time. As a result, the following financial statement line items for fiscal year 2017 were affected.

Condensed Consolidated Balance Sheets

	December 31, 2017 (in thousands)		
	As revised under Topic 606	As originally reported under Topic 605	Effect of change
Current portion of deferred revenue	$ 58,192	$ 50,579	$ 7,613
Long-term portion of deferred revenue	12,501	8,306	4,195
Accumulated deficit	$ (296,221)	$ (284,413)	$ (11,808)

Condensed Consolidated Statements of Operations and Comprehensive Loss

	Three Months Ended March 31, 2017 (in thousands, except per share data)		
	As revised under Topic 606	As originally reported under Topic 605	Effect of change
Research and development revenue under collaborative agreements	$ 6,094	$ 9,597	$ (3,503)
Loss from operations	(63,376)	(59,873)	(3,503)
Net loss	(63,856)	(60,353)	(3,503)
Net loss per share of preferred stock, basic and diluted	$ (2.21)	$ (2.09)	$ (0.12)

Condensed Consolidated Statement of Cash Flows

	Three Months Ended March 31, 2017 (in thousands)		
	As revised under Topic 606	As originally reported under Topic 605	Effect of change
Net loss	$ (63,856)	$ (60,353)	$ (3,503)
Adjustments to reconcile net loss to net cash provided by operating activities:			
Deferred revenues	102,301	98,798	3,503
Cash and cash equivalents at beginning of period	7,857	7,857	—
Cash and cash equivalents at end of period	$ 77,858	$ 77,858	$ —

RESULTS OF OPERATIONS

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

Revenue

For the three months ended March 31, 2018, we recognized $17.1 million compared to $6.1 million for the three months ended March 31, 2017 (as revised), in research and development revenue from our collaboration with Novartis. The increase in revenue is consistent with an increase in the pattern of performance related to increased research and development activities of AKCEA-APO(a)-L_{Rx}, for which we completed patient enrollment in our Phase 2b study in the first quarter, and increased research and development activities of AKCEA-APOCIII-L_{Rx}, for which we initiated patient enrollment in our Phase 2b study in the first quarter.

Operating Expenses

Operating expenses for the three months ended March 31, 2018, were $47.4 million compared to $69.5 million for the same period in 2017. Our operating expenses decreased in part due to the one-time sublicensing expense due to Ionis in the first quarter of 2017 of $48.4 million related to our collaboration with Novartis, of which $33.4 million was non-cash. This decrease was offset in part by increases in expenses due to our growth in headcount, pre-commercial launch activities, development activities and expenses related to the licensing transaction.

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 operating 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.

Research and Development Expenses

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

	Three Months Ended March 31,	
	2018	2017
External volanesorsen expenses	$ 6,559	$ 5,603
Other external research and development project expenses	13,126	4,910
Sublicensing expenses	—	48,394
Research and development personnel and overhead expenses	5,971	4,287
Total research and development expenses, excluding non-cash stock-based compensation expense	25,656	63,194
Non-cash stock-based compensation expense	2,314	1,600
Total research and development expenses	$ 27,970	$ 64,794

Research and development expenses were $25.7 million for the three months ended March 31, 2018 compared to $63.2 million for the same period in 2017. Our decrease in research and development expenses was primarily due to sublicensing expenses related to our collaboration with Novartis, which we incurred in the first quarter of 2017, the majority of which were non-cash. This decrease was offset in part by an increase related to development activities during the first three months of 2018 primarily associated with the completion of enrollment in our Phase 2b study for AKCEA-APO(a)-L_{Rx} which enrolled more than the planned 270 patients, and initiation of the Phase 2b study for AKCEA-APOCIII-L_{Rx}, both in the first quarter of 2018. All amounts exclude non-cash compensation expense related to equity awards.

General and Administrative Expenses

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

	Three Months Ended March 31,	
	2018	2017
General and administrative support expenses	$ 5,487	$ 1,578
Pre-commercialization expenses for volanesorsen	9,909	1,518
Total general and administrative expenses, excluding non-cash stock-based compensation expense	15,396	3,096
Non-cash stock-based compensation expense	4,069	1,580
Total general and administrative expenses	$ 19,465	$ 4,676

General and administrative expenses were $15.4 million for the three months ended March 31, 2018 compared to $3.1 million for the same period in 2017. Our general and administrative expenses increased due to the ongoing buildout of our commercial organization and advancement of pre-commercialization activities necessary to launch volanesorsen, if approved for marketing in the US, EU and Canada as well as expenses incurred associated with the in licensing transaction with Ionis. All amounts exclude non-cash compensation expense related to equity awards.

Investment Income

Investment income for the three months ended March 31, 2018 totaled $0.9 million compared to $0.1 million for the same period in 2017. 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 2018 compared to 2017.

Interest Expense

Interest expense is comprised entirely of interest incurred under our line of credit agreement with Ionis. We incurred no interest expense during the three months ended March 31, 2018. Interest expense for the three months ended March 31, 2017 totaled $0.5 million. The outstanding principal and accrued interest under our line of credit converted into 13,438,339 shares of our common stock in connection with the closing of our IPO in July 2017 and we no longer have access to this line of credit following the closing of our IPO.

Net Loss and Net Loss Per Share

Net loss for the three months ended March 31, 2018 was $29.6 million compared to $63.9 million for the same period in 2017 (as revised). We incurred a lower net loss for the three months ended March 31, 2018 compared to the three months ended March 31, 2017 primarily due to a one-time sublicensing expense due to Ionis of $48.4 million related to our collaboration with Novartis, of which $33.4 million was non-cash recognized in 2017. This decrease was offset by the increase in expenses related to pre-commercialization and development activities for our drugs, the ongoing global expansion of our company, and expenses related to the licensing transaction with Ionis. Basic and diluted net loss per preferred share for the three months ended March 31, 2017 (as revised) was $2.21. We had no outstanding preferred shares at March 31, 2018. Basic and diluted net loss per common share for the three months ended March 31, 2018 was $0.44. We had no outstanding common stock at March 31, 2017.

LIQUIDITY AND CAPITAL RESOURCES

At March 31, 2018, we had cash, cash equivalents and investments of $244.9 million and accumulated deficit of $325.8 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 million.

At March 31, 2018, we had working capital of $152.3 million compared to working capital of $178.4 million at December 31, 2017. Working capital decreased in 2018 primarily due to the decrease in our cash and investments from our on-going business activities and increase in the outstanding payable to Ionis. As of March 31, 2018, our outstanding payable to Ionis was $27.7 million.

In April 2018, the stockholders other than Ionis and its affiliates approved the development, commercialization, collaboration and license agreement, or License Agreement, 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 inotersen and AKCEA-TTR-L $_{Rx}$, Ionis purchased 10.7 million shares of our common stock for $200 million to support our commercialization of inotersen and AKCEA-TTR-L$_{Rx}$.

We do not currently have any approved drugs and, therefore, we do not expect to generate significant revenue from drug sales unless and until we or our partners obtain regulatory approval for and commercialize inotersen, volanesorsen or one of our other drugs in development. 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 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.

Future Funding Requirements

We expect to raise additional funding in the future to continue developing the drugs in our pipeline and to commercialize any approved drug, including expanding our commercial efforts for inotersen and volanesorsen. We expect that our cash, cash equivalents and investments of $244.9 million as of March 31, 2018, together with the $200.0 million from the common stock issuance to Ionis in conjunction with the licensing transaction with Ionis discussed in Note 10, will be sufficient to fund our operating expenses and capital expenditure requirements for at least the next 12 months from issuance of these financial statements. 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 design, initiation, progress, size, timing, costs and results of our clinical and nonclinical studies;
- 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;
- the number and characteristics of drugs that we may pursue;
- our need to expand our development activities, including our need and ability to hire additional employees;
- the effect of competing technological and market developments;
- the cost of establishing sales, marketing, manufacturing and distribution capabilities for our drugs;
- our strategic collaborators' success in developing and commercializing our drugs;
- our need to add infrastructure, implement internal systems and hire additional employees to operate as a public company; and
- the revenue, if any, 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.

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

In April 2018, we entered into an operating lease agreement with MEPT Seaport 13 Stillings LLC, or MEPT, for 30,175 square feet of office space located in Boston, Massachusetts for our new corporate headquarters. The anticipated commencement date of the lease is August 15, 2018. The initial term of the lease is 123 months with one five-year renewal option. Future minimum annual lease payments under this lease are $0.8 million in 2018, $2.2 million in 2019, $2.3 million in 2020, $2.3 million in 2021, $2.3 million in 2022, and $14.2 million thereafter. MEPT will provide us with a three-month free rent period and a tenant improvement allowance up to $3.8 million. We are providing the Landlord with a letter of credit to secure our obligations under the lease in the initial amount of $2.4 million, to be reduced on the third anniversary and the fifth anniversary of the rent commencement date if we meet certain conditions set forth in the lease at each such time.

Also in April 2018, the stockholders other than Ionis and its affiliates approved the development, commercialization, collaboration and license agreement, or License Agreement, and a stock purchase agreement, or Ionis SPA, with Ionis, our majority shareholder which we entered into on March 14, 2018. As part of the licensing transaction we will be 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 inotersen approval milestones are met; up to $145.0 million, if all AKCEA-TTR-L_{Rx} milestones are met; and a total of $1.3 billion, in the form of seven milestones, 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. Subsequent to the achievement of the milestone event for aggregate worldwide annual net sales of $750 million for the products, all subsequent milestone payments must be paid in cash.

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, 2017, as filed with the SEC on February 28, 2018.

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

Market risk represents the risk of loss that may impact our financial position due to adverse changes in financial market prices and rates. Our market risk exposure is primarily the result of fluctuations in interest rates and foreign exchange rates as well as, to a lesser extent, inflation.

Interest Rate Risk

We are exposed to changes in interest rates primarily from our investments in certain investments. We place our cash equivalents and 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. As of March 31, 2018, we had cash, cash equivalents and investments of $244.9 million.

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. A hypothetical 10% change in interest rates during any of the periods presented would not have had a material impact on our financial statements.

Foreign Currency Exchange Risk

Our results of operations are subject to foreign currency exchange rate fluctuations as we have foreign subsidiaries with functional currencies other than the U.S. dollar. We translate our 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. A hypothetical 10% change in foreign exchange rates during any of the periods presented would not have had a material impact on our consolidated financial statements. Our business strategy incorporates potentially significant international expansion, particularly in anticipation of approval of volanesorsen and inotersen, 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 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, 2018. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to March 31, 2018.

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 to ensure we adequately evaluated our contracts and properly assessed the impact of the of new revenue recognition accounting guidance we adopted on January 1, 2018 reflected in our financial statements. 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, 2017.

Risks Related to Our Financial Condition and Need for Additional Capital

We have a limited operating history and may never become 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 never obtained regulatory approval for, or commercialized, any product. Our ability to generate substantial revenue and achieve profitability depends on our ability, alone or with strategic partners, to successfully develop our drugs, and obtain the regulatory approvals necessary to commercialize our drugs, including volanesorsen, inotersen, AKCEA-APO(a)-L$_{Rx}$, AKCEA-TTR-L$_{Rx}$ and our other drugs in development. If volanesorsen and/or inotersen is approved in 2018, we anticipate receiving our first revenue from product sales in 2018. Even if we achieve profitability in the future, we may not sustain profitability in subsequent periods. Our ability to generate revenue from product sales depends heavily on our and our current and future strategic partners' success in:

- completing clinical development of volanesorsen and inotersen for additional indications and nonclinical and clinical development of AKCEA-APO(a)-L$_{Rx}$, AKCEA-TTR-L$_{Rx}$, AKCEA-ANGPTL3-L$_{Rx}$ and AKCEA-APOCIII-L$_{Rx}$;
- seeking and obtaining regulatory and marketing authorization for our drugs, including volanesorsen, inotersen, AKCEA-APO(a)-L$_{Rx}$ and our other drugs in development;
- establishing and maintaining supply and manufacturing relationships with third parties that can provide the amount and quality of products and services we need to continue to develop and, if approved, commercialize volanesorsen, inotersen, AKCEA-APO(a)-L$_{Rx}$, AKCEA-TTR-L$_{Rx}$ and our other drugs in development;
- launching and commercializing volanesorsen, inotersen, AKCEA-APO(a)-L$_{Rx}$, AKCEA-TTR-L$_{Rx}$ by establishing a sales, marketing and distribution infrastructure;
- launching and co-commercializing AKCEA-APO(a)-L$_{Rx}$ and AKCEA-APOCIII-L$_{Rx}$ through our collaboration with Novartis Pharma AG, or Novartis, under terms that we plan to negotiate with Novartis in the future;
- educating physicians about our target patient populations, including patients with familial chylomicronemia syndrome, or FCS, and patients with familial partial lipodystrophy, or FPL;
- obtaining market acceptance of volanesorsen, inotersen, AKCEA-APO(a)-L$_{Rx}$, AKCEA-TTR-L$_{Rx}$ and our other drugs in development as viable treatment options;
- obtaining and maintaining adequate coverage and reimbursement from third-party payors for volanesorsen, inotersen, AKCEA-APO(a)-L$_{Rx}$, AKCEA-TTR-L$_{Rx}$ and our other drugs in development;
- addressing any competing technological and market developments;
- implementing additional internal systems and infrastructure, as needed, to ultimately operate without reliance on Ionis;
- 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 volanesorsen, inotersen, AKCEA-APO(a)-L$_{Rx}$, AKCEA-TTR-L$_{Rx}$ and our other drugs in development without infringing others' intellectual property rights; and
- attracting, hiring and retaining qualified personnel.

We may not successfully develop any products, generate product revenue or achieve profitability. 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 incurred losses since our inception.

Because drug development requires substantial lead-time and funding prior to commercialization, we have incurred expenses while generating limited revenue from our operating activities since our formation. Our net losses were $29.6 million and $63.9 million for the three months ended March 31, 2018 and March 31, 2017, respectively. As of March 31, 2018, we had an accumulated deficit of approximately $325.8 million. Most of the losses resulted from costs incurred in connection with our development programs and from general and administrative costs associated with our operations. 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 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, 2018, we had cash, cash equivalents and investments equal to $244.9 million. Our operating expenses were $47.4 million and $69.5 million for the three months ended March 31, 2018 and March 31, 2017, respectively. In April 2018, we received $200.0 million in proceeds from the common stock we issued in connection with the licensing transaction with Ionis discussed in Note 10, *Subsequent Events*, to our condensed consolidated financial statements included in this Form 10-Q.

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 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 Ionis invested in our IPO and the Novartis concurrent private placement of $50 million. Based on our existing cash, cash equivalents and investments and the proceeds from our IPO and the concurrent private placement with Novartis, we expect to raise additional funding to continue developing the drugs in our pipeline and to seek regulatory approval for and to commercialize volanesorsen and other drugs in our pipeline.

Even if we obtain marketing authorizations to sell volanesorsen, inotersen, AKCEA-APO(a)-L$_{Rx}$ or AKCEA-TTR-L$_{Rx}$, we will incur significant costs to commercialize the approved product. Even if we generate revenue from the sale of any approved products, we may not become 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 volanesorsen, inotersen, AKCEA-APO(a)-L$_{Rx}$, AKCEA-TTR-L$_{Rx}$ 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 volanesorsen for the treatment of FPL. 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; 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, volanesorsen and AKCEA-APOCIII-L_{Rx} have the same mechanism of action, inotersen and AKCEA-TTR-L_{Rx}, also have the same mechanism of action and all of our current drugs, including volanesorsen, AKCEA-APO(a)-L_{Rx}, AKCEA-ANGPTL3-L_{Rx} and AKCEA-APOCIII-L_{Rx}, 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. Similarly, we have an ongoing Phase 3 study of volanesorsen in patients with FPL, an ongoing open label extension study of volanesorsen in patients with FCS and an open label extension study of inotersen in patients with hereditary TTR Amyloidosis (hATTR), and an early access program, or EAP, for both volanesorsen and inotersen. Adverse events or results from these studies or the EAPs could negatively impact our planned marketing approval applications for volanesorsen and inotersen in patients with FCS or hATTR or the commercial opportunity for volanesorsen or inotersen.

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 volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} 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 recently completed a Phase 3 clinical program for volanesorsen for the treatment of FCS and have an ongoing Phase 3 study of volanesorsen in patients with FPL. We are also conducting or plan to conduct additional clinical studies for inotersen, AKCEA-TTR-L_{Rx} AKCEA-APO(a)-L_{Rx}, AKCEA-ANGPTL3-L_{Rx} and AKCEA-APOCIII-L_{Rx}.

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, the FDA or foreign regulatory authorities could claim that we have not tested volanesorsen in a sufficient number of patients to demonstrate volanesorsen is safe and effective in patients with FCS or FPL to support an application for marketing authorization, or that we have not tested inotersen in a sufficient number of patients to demonstrate inotersen is safe and effective in patients with hATTR to support an application for marketing authorization. In such a case, we may need to conduct additional clinical studies before obtaining marketing authorization, which would be expensive and delay these development programs. These risks 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 volanesorsen 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 regulatory approval of volanesorsen and our other drugs in development. Any failure to obtain approval for volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} 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 either volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} or our other drugs may not demonstrate safety or efficacy at the level required by the FDA and foreign regulatory authorities for product approval.

The FDA, EMA, and Health Canada are currently reviewing our application for regulatory approval for inotersen and volanesorsen. We and Ionis intend to conduct clinical studies for AKCEA-TTR-L_{Rx} and may conduct further clinical studies for inotersen.

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, the FDA or foreign regulatory authorities could claim that we have not tested volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx} or AKCEA-TTR-L_{Rx} in a sufficient number of patients to demonstrate that the drug is safe and effective in patients with hATTR or 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 approval for volanesorsen or inotersen 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 volanesorsen, inotersen, AKCEA-APO(a)-L$_{Rx}$, AKCEA-TTR-L$_{Rx}$ and our other drugs in development, we or our partners cannot sell them in the applicable markets.

We cannot guarantee that any of our drugs, including volanesorsen, inotersen, AKCEA-APO(a)-L$_{Rx}$, AKCEA-TTR-L$_{Rx}$ and our other drugs in development, will be safe and effective, or will be approved for commercialization. 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 volanesorsen, inotersen, AKCEA-APO(a)-L$_{Rx}$, AKCEA-TTR-L$_{Rx}$ and our other drugs in development, before they can be approved 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 any of our drugs, including volanesorsen, inotersen, AKCEA-APO(a)-L$_{Rx}$, AKCEA-TTR-L$_{Rx}$ 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 volanesorsen, inotersen, AKCEA-APO(a)-L$_{Rx}$, AKCEA-TTR-L$_{Rx}$ 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, since some patients in the Phase 3 program for volanesorsen 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, some of whom discontinued participation in the studies, including patients who discontinued participation in the APPROACH study due to platelet count declines, the FDA or another regulatory authority may require us to conduct additional studies of volanesorsen before considering an application for marketing approval. 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.

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 volanesorsen, inotersen, AKCEA-APO(a)-L$_{Rx}$, AKCEA-TTR-L$_{Rx}$ and our other drugs in development, or to receive marketing authorization for these drugs 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.

The FDA's Division of Metabolism and Endocrinology Products advisory committee will discuss and advise FDA on the risk-benefit profile of volanesorsen for the treatment of FCS tentatively scheduled for May 10, 2018. In advance of this advisory committee meeting, we and the FDA will submit briefing documents for the committee's review, and these briefing documents will be made available to the public and may include information from the volanesorsen development program that have not previously been disclosed. Historically, for some companies, disclosure of information in this manner has led to increased volatility in their stock price. The advisory committee and FDA may interpret nonclinical and clinical data differently than we and our experts have. Press coverage and public scrutiny of the materials that will be discussed at the advisory committee meeting may negatively affect the potential for our volanesorsen NDA to receive approval or the trading price of our securities. Even if we ultimately obtain approval of the volanesorsen NDA, the matters discussed at the advisory committee meeting could limit our ability to successfully commercialize volanesorsen.

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

The FDA and EMA have granted orphan drug designation to volanesorsen for the treatment of patients with FCS. The EMA has granted orphan drug designation to volanesorsen for the treatment of patients with FPL and we are in the process of applying for orphan drug status for FPL in the United States. The FDA has granted inotersen Orphan Drug Designation for the treatment of patients with polyneuropathy due to hereditary TTR amyloidosis (hATTR), and the EMA has granted Orphan Drug Designation to inotersen for the treatment of patients with ATTR. The FDA granted inotersen Orphan Drug Designation and Fast Track Status. The EMA also granted accelerated assessment to inotersen.

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.

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.

Even if we maintain orphan drug exclusivity for volanesorsen or inotersen 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 are dedicating a substantial amount of our resources to develop and seek regulatory approval for volanesorsen to treat patients with FCS and FPL. In addition, we will dedicate a substantial amount of our resources to commercialize, if approved, inotersen and support the continued development of AKCEA-TTR-L_{Rx}. 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 volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} 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, if approved, our drug products, including volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} 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.

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. If the results of such post-marketing studies are not satisfactory, the FDA or a 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:

- restrictions on our ability to conduct clinical studies, including full or partial clinical holds on ongoing or planned clinical studies;
- restrictions on such products' manufacturing processes;
- changes to the product label;
- restrictions on the marketing of a product;
- restrictions on product distribution;
- 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; 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 inotersen and volanesorsen 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 never obtained regulatory approval for, or commercialized, any product. If regulatory approval is obtained, we plan to commercially launch both inotersen and volanesorsen during 2018. The commercial launches of the products will require significant efforts and the devotion of substantial resources, as we will need to finalize regulatory submissions, ensure 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 volanesorsen and inotersen, 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)-L_{Rx}, AKCEA-TTR-L_{Rx}, AKCEA-ANGPTL3-L_{Rx} and AKCEA-APOCIII-L_{Rx}. 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 establish effective 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 plan to commercialize inotersen and volanesorsen, if approved. To successfully commercialize inotersen and volanesorsen, we must successfully 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 volanesorsen and inotersen in the initial indications we plan to pursue, we will need to optimize and maintain specialty sales forces in each global region we expect to market inotersen and volanesorsen, supported by case managers, reimbursement specialists, partnerships with specialty pharmacies, injection training, routine platelet and renal 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 drug products, as a company we have no prior experience marketing, selling or distributing drug products, and there are significant risks involved in building and managing a commercial infrastructure. It will be expensive and time consuming for us to maintain our own sales forces and related compliance protocols to market inotersen and volanesorsen. We may never successfully optimize or manage this capability and any failure could delay or preclude the inotersen and volanesorsen launch. We and our partners, if any, will have to compete with other companies to recruit, hire, train, manage and retain marketing and sales personnel.

We will incur expenses prior to the launch of inotersen and volanesorsen to integrate and manage the marketing and sales infrastructure. If regulatory requirements or other factors cause a delay in the commercial launch of inotersen or volanesorsen, we would incur additional expenses for having invested in these capabilities earlier than required and prior to realizing any revenue from sales of inotersen or volanesorsen. Our sales force and marketing teams may not successfully commercialize inotersen or volanesorsen.

To the extent we decide to rely on third parties to commercialize inotersen or volanesorsen in a particular geographic market, we may receive less revenue than if we commercialized inotersen or volanesorsen by ourselves. Further we would have less control over the sales efforts of any other third parties involved in commercializing inotersen or volanesorsen.

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 commercial launch and sales of inotersen and volanesorsen may be delayed, less successful or precluded. 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.

****We plan to rely on third-party specialty channels to distribute volanesorsen, inotersen and our other drugs to patients. If we cannot effectively establish and manage this distribution process, it could harm or delay the commercial launch and sales of volanesorsen, inotersen and our other drugs in development.***

We and our strategic partners may contract with, and rely on, third-party specialty pharmacies to distribute volanesorsen, inotersen, and our other 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 building and managing this distribution network. If we cannot effectively build and manage this distribution process, the commercial launch and sales of volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx} and AKCEA-TTR-L_{Rx} will be delayed or less successful, which would harm our results of operations.

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 volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} or our other drugs;
- reduce or discontinue their efforts to sell or support volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} or our other drugs;
- not devote the resources necessary to sell volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} 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 volanesorsen, inotersen, AKCEA-TTR-L_{Rx} and our other drugs in development, we are not likely to generate substantial product revenue or become profitable.

Even if we or our strategic partners obtain a marketing authorization for volanesorsen, inotersen, AKCEA-TTR-L_{Rx} 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 commercializing volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} and our other drugs in development economically unviable.

The degree of market acceptance for volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} 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, in the clinical studies with volanesorsen and inotersen, declines in platelet counts were observed in many patients and some patients discontinued the study because of platelet declines. Therefore, we expect volanesorsen's and inotersen's product labels will require periodic platelet monitoring, which could negatively affect our ability to attract and retain patients for volanesorsen and inotersen. 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 volanesorsen and inotersen through our patient-centric commercial approach where we plan to have greater involvement with physicians and patients, if we cannot effectively maintain patients on volanesorsen and inotersen, we may not be able to generate substantial revenue from volanesorsen and inotersen 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 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 volanesorsen 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 high 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 high enough to justify our product development efforts and our sales and marketing and manufacturing expenses.

The patient population suffering from hATTR 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 inotersen or AKCEA-TTR-L_{Rx} 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, our assessment of the market potential for either inotersen or AKCEA-TTR-L_{Rx} 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 high enough to justify our product development efforts and our sales and marketing and manufacturing expenses.

If we or our partners fail to compete effectively, volanesorsen, inotersen 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 volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} 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, if approved, volanesorsen could face competition from drugs like metreleptin. Metreleptin, produced by Novelion Therapeutics, Inc., is currently approved for use in generalized lipodystrophy patients. In September 2016, Arrowhead Pharmaceuticals, Inc. and Amgen Inc. announced a license and collaboration for development of Arrowhead's preclinical program which uses an RNAi conjugated with a GalNAc for the same target as AKCEA-APO(a)-L_{Rx}. AKCEA-APOCIII-L_{Rx} may 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, if approved, inotersen could face competition from drugs like patisiran and ALN-TTRsc02 in development by Alnylam, tafamidis commercialized in Europe and in development by Pfizer and tolcapone in development by SOM Biotech, and the generic drug diflunisal. If volanesorsen, inotersen 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 volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} 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, volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} and our other drugs in development, if approved, 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 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. State health information privacy and security laws in certain circumstances are more stringent than HIPAA and many of the state laws differ from each other in significant ways and may not have the same effect, thus complicating compliance. 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. Once we have a commercialized drug, we will be 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)-L$_{Rx}$ and AKCEA-APOCIII-L$_{Rx}$.

We have granted Novartis an exclusive option to exclusively license each of AKCEA-APO(a)-L$_{Rx}$ and AKCEA-APOCIII-L$_{Rx}$ pursuant to our strategic collaboration, option and license agreement with Novartis. We plan to substantially depend on Novartis to further develop and commercialize these drugs. 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)-L$_{Rx}$ and AKCEA-APOCIII-L$_{Rx}$;
- seek and obtain regulatory approvals for AKCEA-APO(a)-L$_{Rx}$ and AKCEA-APOCIII-L$_{Rx}$; and
- globally commercialize AKCEA-APO(a)-L$_{Rx}$ and AKCEA-APOCIII-L$_{Rx}$.

If Novartis exercises its option to license one or both of these drugs, we would rely on Novartis to further develop, obtain regulatory approvals for, and commercialize the licensed drug. 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 these drugs, 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)-L_{Rx} or AKCEA-APOCIII-L_{Rx}. Novartis could pursue these technologies and develop these other drugs at the same time as it is developing or commercializing AKCEA-APO(a)-L_{Rx} or AKCEA-APOCIII-L_{Rx}, 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 does not exercise its option, or following option exercise stops developing or commercializing a drug, we will have to seek additional sources for funding and may have to delay or reduce our development and commercialization plans for AKCEA-APO(a)-L_{Rx} or AKCEA-APOCIII-L_{Rx}.

In addition, if Novartis exercises its option to license AKCEA-APO(a)-L_{Rx} or AKCEA-APOCIII-L_{Rx}, Novartis would 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)-L_{Rx} or AKCEA-APOCIII-L_{Rx}. If Novartis does not successfully develop, manufacture or commercialize AKCEA-APO(a)-L_{Rx} or AKCEA-APOCIII-L_{Rx}, we may receive limited or no revenues for these drugs.

AKCEA-APOCIII-L_{Rx} and AKCEA-ANGPTL3-L_{Rx} may compete with volanesorsen, which could reduce our expected revenues for volanesorsen.

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

****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 volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} and our other drugs in development, if approved, we will need to establish 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 to produce our oligonucleotide drugs, and our business could be negatively affected if Ionis 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 volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} and our other drugs in development, or result in enforcement action after authorization that could limit the commercial success of our drugs, including volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} 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 volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} 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 volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} and our other drugs in development.

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

Although we intend to develop and commercialize volanesorsen 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 Novartis an exclusive option to exclusively license AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. 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 a strategic partnership or other collaborative arrangement 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 volanesorsen and our other drugs in development do not have the requisite potential to demonstrate safety and efficacy in the target populations. In addition, we will need to mutually agree with Ionis on the terms of any sublicense to a third party for volanesorsen 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 volanesorsen 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 approximately 75% of the economic interest and voting power of our outstanding common stock, 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 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 (volanesorsen and inotersen), may increase the length of time during which Ionis will control us. Among the terms of the licensing transaction are several changes to our Investor Rights Agreement with Ionis in light of Ionis' increased ownership percentage and increased investment in and reliance on us. As a general matter, these changes increase Ionis' control over our affairs. In addition, our inotersen licensing agreement requires Ionis' consent to the budget related to the commercialization of inotersen and AKCEA-TTR-L_{Rx}.

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).

As a controlled company, we utilize some of these exemptions. Currently a majority of our board is not made up of independent directors. 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.

Stanley T. Crooke, Chairman of the Board and Chief Executive 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 inotersen and AKCEA-TTR-L$_{Rx}$.***

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 inotersen and AKCEA-TTR-L$_{Rx}$ 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 inotersen 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 inotersen and AKCEA-TTR-L$_{Rx}$. Such failure or delay could adversely impact our business, results of operations, financial condition and prospects for future growth.

****The terms of our inotersen licensing agreement may limit our ability to achieve the expected benefits of the licensing transaction.***

While we expect that the licensing transaction will, on the whole, bolster our capabilities, certain terms of our inotersen licensing agreement and its other agreements with Ionis may limit our ability to achieve the expected benefits of the transaction, 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 inotersen and AKCEA-TTR-L$_{Rx}$. In the event of a disagreement at the JSC, 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 Ionis' consent prior to granting any sublicense to a third party for inotersen or AKCEA-TTR-LRx. If Ionis does not grant such consent with respect to a sublicense, then we would not be able to enter into such arrangement, which could delay or prevent our ability to develop and commercialize inotersen and AKCEA-TTR-L$_{Rx}$;
- 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;
- we only have the right to lead the prosecution and enforcement of certain of the patent rights licensed to us under our inotersen licensing agreement, so called product-specific patent rights. Ionis will control the prosecution and enforcement of other patent rights licensed to us, and they may do so in a manner that does not advance or is inconsistent with our interests; and
- although our agreements with Ionis prohibit Ionis from developing and commercializing drugs that modulate TTR via the binding of such drug to the RNA that encodes TTR using the technology licensed to us under our inotersen licensing agreement, Ionis is free to pursue other products that treat the same indications that would be treated by inotersen and AKCEA-TTR-L$_{Rx}$.

Each of the foregoing terms and Ionis' other rights under our inotersen licensing agreement, could limit our ability to realize the expected benefits of our inotersen licensing agreement or otherwise limit our ability to pursue transactions or development efforts other stockholders may view as beneficial.

We will incur incremental costs as a standalone company.

Ionis currently performs or supports many important corporate functions for our company. Our 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 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 volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} 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 agreement to bolster our capabilities, certain terms of the license agreement may limit our ability to achieve this expected benefit, including:

- a Joint Steering Committee, or JSC, comprising two senior members from our company and two senior members from 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, it could delay our ability to develop and commercialize volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} and our other drugs in development;
- we will need to mutually agree with Ionis on the terms of any additional sublicense to a third party for volanesorsen 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 or prevent our ability to develop and commercialize volanesorsen and our other drugs in development;
- 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) or ANGPTL3 to pursue the same indications we are pursuing with our drugs.

Each of the foregoing terms and Ionis' other rights under the license agreement, could limit our ability to realize the expected benefits of the license agreement 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 volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} and our other drugs in development, 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 volanesorsen, inotersen, AKCEA-TTR-L_{Rx} and our other drugs in development.

We obtained our rights to volanesorsen, inotersen, 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 volanesorsen, 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)-L_{Rx} or AKCEA-APOCIII-L_{Rx} 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.

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 volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} 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 volanesorsen patent portfolio currently includes:

- issued patent claims to the specific antisense sequence and chemical composition of volanesorsen 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 volanesorsen;
- additional patent applications designed to protect the volanesorsen composition in Canada; and
- additional methods of use in jurisdictions worldwide for volanesorsen.

The natural term of the issued U.S. patent covering the volanesorsen 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 volanesorsen 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 inotersen 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 inotersen, if approved, in the U.S. and any other jurisdictions where such extension is available, based upon the development and regulatory review periods for inotersen 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 volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} 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 volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} 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 recently issued a patent which they have broadly characterized in their most recent annual report on Form 10-K 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 inotersen or AKCEA-TTR-L_{Rx}, 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 volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx}, 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 volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx}, 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 volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx}, 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.

Although we plan on seeking patent term restoration for our 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 commercialize volanesorsen, inotersen, and our other 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 volanesorsen and inotersen, if approved. We currently have limited sales and marketing capability and therefore intend to recruit a specialty sales force in anticipation of volanesorsen's and inotersen's potential approval.

Future growth will impose significant added responsibilities on our management, including the need to identify, recruit, maintain and integrate 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 future 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 our clinical studies and the regulatory process effectively;
- manage the manufacturing of our drugs for clinical and commercial use;
- integrate current and additional management, administrative, financial and sales and marketing personnel;
- develop a marketing and sales infrastructure;
- hire new personnel necessary to effectively commercialize volanesorsen and our other drugs in development;
- 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 volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} 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 volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} 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)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. 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, following approval, marketing our drugs internationally could materially adversely affect our business.

In addition to our U.S. operations, we plan to establish operations and, following approval, commercialize our products in Europe and 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. Once we establish international operations we will be 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 UK's anticipated exit from the European Union 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 U.K.'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.

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. 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.***

Despite the implementation of security measures, our internal computer systems, and those of our CROs, manufacturers and other third parties on which we rely, are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. If issues were to arise and cause interruptions in our operations, it could result in a material disruption of our drug programs. For example, the loss of clinical study data from completed or ongoing or planned clinical studies could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of or damage to our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the further development of volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} and our other drugs in development could be delayed.

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, Ionis owns approximately 75% 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 volanesorsen and our other drugs in development;
- Novartis' failure to exercise its option and/or effectively develop and commercialize AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx} to the extent it exercises its option to license those drugs from us;
- 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 regulatory approval for volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} 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 volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} 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 volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} 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 volanesorsen, inotersen, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} 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. Immediately following our IPO and concurrent private placement we had 66,541,629 shares of common stock outstanding. Of these, only 14,843,750 shares of our common stock sold in our IPO are freely transferable without restriction or additional registration under the Securities Act. Novartis has agreed that it will not sell any of the shares it purchased in the concurrent private placement 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. Up to an additional 64,114,545 shares of common stock held by Ionis are eligible for sale in the public market, all of which will be subject to volume limitations under Rule 144 under the Securities Act. In addition, 9,000,000 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.

The United States recently passed a comprehensive tax reform bill that could adversely affect our financial performance.

On December 22, 2017, the U.S. government enacted comprehensive tax legislation commonly referred to as the Tax Cut and Jobs Act of 2017, or the Tax Act. The Tax Act makes broad and complex changes to the U.S. tax code. The changes include, but are not limited to, reduction of the corporate tax rate from 35% to 21%, limitation of the tax deduction for interest expense, limitation on the utilization of net operating losses to 80% of taxable income and elimination of net operating loss carrybacks, a mandatory one-time transition tax on certain unrepatriated earnings of foreign subsidiaries, introduction of bonus depreciation that allows for full expensing of qualified property, and modifying or repealing many business tax deductions and credits. Notwithstanding the reduction in the corporate income tax rate, the overall impact of the new federal tax law is uncertain, and our financial performance could be adversely affected. In addition, it is uncertain if, and to what extent various states will conform to the new tax law and foreign countries may react by adopting tax legislation or taking other actions that could adversely affect our business.

Uncertainties in the interpretation and application of the 2017 Tax Cuts and Jobs Act could materially affect our tax obligations, effective tax rate and operating results.

The Tax Act was enacted on December 22, 2017 and significantly affected U.S. tax law by changing how the U.S. imposes income tax on multinational corporations. The U.S. Department of Treasury has broad authority to issue regulations and interpretative guidance that may significantly impact our tax obligations, effective tax rate and our results of operations. The Tax Act will likely be subject to ongoing technical guidance and accounting interpretation, which we will continue to monitor and assess. It is not possible to fully measure the potential impact on our business, prospects or results of operations at this time.

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

None.

(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.

The net proceeds to us, after deducting underwriting discounts and commissions of approximately $8.4 million and offering expenses of approximately $3.1 million, were approximately $132.3 million. No offering expenses were paid directly or indirectly to any of our directors or officers (or their associates) or persons owning ten percent or more of any class of our equity securities or to any other affiliates. There has been no material change in the planned use of proceeds from our initial public offering from those disclosed in the final prospectus for our initial public offering dated as of on July 13, 2017 and filed with the SEC pursuant to Rule 424(b)(4).

As of March 31, 2018, all of the 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 Number	Description of Document
3.1	Amended and Restated Certificate of Incorporation of Akcea Therapeutics, Inc., as amended to date.
3.2(1)	Amended and Restated Bylaws of Akcea Therapeutics, Inc.
4.1(2)	Amended and Restated Investor Rights Agreement, dated March 14, 2018, by and between Akcea Therapeutics, Inc. and Ionis Pharmaceuticals, Inc.
10.1(3)	Development, Commercialization, Collaboration and License Agreement, dated March 14, 2018, by and between Akcea Therapeutics, Inc. and Ionis Pharmaceuticals, Inc.
10.2(4)	Stock Purchase Agreement, dated March 14, 2018, by and between Akcea Therapeutics, Inc. and Ionis Pharmaceuticals, Inc.
10.3(5)	Amended and Restated Services Agreement, dated March 14, 2018, by and between Akcea Therapeutics, Inc. and Ionis Pharmaceuticals, Inc.
10.4(6)	Stockholder Voting Agreement, dated March 14, 2018, by and between Akcea Therapeutics, Inc. and Novartis Pharma AG.
10.5	Akcea Therapeutics, Inc. 2015 Equity Incentive Plan, as amended.
31.1	Certification by Chief Executive Officer pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as amended.
31.2	Certification by Chief Financial Officer pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as amended.
32.1*	Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101	The following financial statements from the Akcea Therapeutics, Inc. Quarterly Report on Form 10-Q for the quarter ended March 31, 2018, formatted in Extensive Business Reporting Language (XBRL): (i) condensed consolidated balance sheets, (ii) condensed consolidated statements of operations, (iii) condensed consolidated statements of comprehensive loss, (iv) condensed consolidated statements of cash flows and (v) notes to condensed consolidated financial statements (detail tagged).
*	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.

(1) Previously filed as Exhibit 3.2 to the Registrant's Current Report on Form 8-K (File No. 001-38137), filed with the Securities and Exchange Commission on July 19, 2017, and incorporated herein by reference.

(2) Previously filed as Exhibit 4.1 to the Registrant's Current Report on Form 8-K (File No. 001-38137), filed with the Securities and Exchange Commission on March 15, 2018, and incorporated herein by reference.

(3) Previously filed as Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-38137), filed with the Securities and Exchange Commission on March 15, 2018, and incorporated herein by reference.

(4) Previously filed as Exhibit 10.2 to the Registrant's Current Report on Form 8-K (File No. 001-38137), filed with the Securities and Exchange Commission on March 15, 2018, and incorporated herein by reference.

(5) Previously filed as Exhibit 10.3 to the Registrant's Current Report on Form 8-K (File No. 001-38137), filed with the Securities and Exchange Commission on March 15, 2018, and incorporated herein by reference.

(6) Previously filed as Exhibit 10.4 to the Registrant's Current Report on Form 8-K (File No. 001-38137), filed with the Securities and Exchange Commission on March 15, 2018, and incorporated herein by reference.

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.

Signatures	Title	Date
/s/ PAULA SOTEROPOULOS Paula Soteropoulos	Chief Executive Officer (on behalf of the Registrant and in her capacity as principal executive officer)	May 4, 2018
/s/ MICHAEL MACLEAN Michael MacLean	Chief Financial Officer (on behalf of the Registrant and in his capacity as principal financial and accounting officer)	May 4, 2018

Exhibit 3.1

CERTIFICATE OF AMENDMENT

TO THE

AMENDED AND RESTATED CERTIFICATE OF INCORPORATION

OF

AKCEA THERAPEUTICS, INC.

Akcea Therapeutics, Inc., a corporation organized and existing under the laws of the state of Delaware (the "Corporation") hereby certifies that:

1. The name of the Corporation is Akcea Therapeutics, Inc.

2. The original Certificate of Incorporation of the Corporation was filed with the Secretary of State of the State of Delaware on December 22, 2014. The Certificate of Incorporation of the Corporation was amended and restated on July 19, 2017.

3. The first paragraph of Article IV of the Amended and Restated Certificate of Incorporation of the Corporation is hereby amended in its entirety to read as follows:

> "A. The Company is authorized to issue two classes of stock to be designated, respectively, "***Common Stock***" and "***Preferred Stock***." The total number of shares which the Company is authorized to issue is 135,000,000 shares. 125,000,000 shares shall be Common Stock, each having a par value of $0.001. 10,000,000 shares shall be Preferred Stock, each having a par value of $0.001."

4. This Certificate of Amendment has been duly adopted in accordance with Section 242 of the General Corporation Law of the State of Delaware (the "DGCL").

[Remainder of Page Intentionally Left Blank]

IN WITNESS WHEREOF, the Corporation has caused this Certificate of Amendment to be executed by the officer below, as of April 16, 2018.

By: /s/ Paula Soteropoulos
Name: Paula Soteropoulos
Title: Chief Executive Officer

AMENDED AND RESTATED
CERTIFICATE OF INCORPORATION OF
AKCEA THERAPEUTICS, INC.

Akcea Therapeutics, Inc., a corporation organized and existing under the laws of the State of Delaware, hereby certifies as follows:

FIRST: The name of this corporation is Akcea Therapeutics, Inc.

SECOND: This corporation's Certificate of Incorporation was originally filed with the Secretary of State of the State of Delaware on December 22, 2014 under the name of Akcea Therapeutics, Inc.

THIRD: The Certificate of Incorporation of said corporation shall be amended and restated to read in full as follows:

I.

The name of this corporation is Akcea Therapeutics, Inc. (the "***Company***").

II.

The address of the registered office of the Company in the State of Delaware is 1209 Orange Street, City of Wilmington, County of New Castle, Delaware 19801 and the name of the registered agent of the Company in the State of Delaware at such address is The Corporation Trust Company.

III.

The purpose of the Company is to engage in any lawful act or activity for which a corporation may be organized under the Delaware General Corporation Law (the "***DGCL***").

IV.

A. The Company is authorized to issue two classes of stock to be designated, respectively, "***Common Stock***" and "***Preferred Stock***." The total number of shares which the Company is authorized to issue is 110,000,000 shares. 100,000,000 shares shall be Common Stock, each having a par value of $0.001. 10,000,000 shares shall be Preferred Stock, each having a par value of $0.001.

B. The Preferred Stock may be issued from time to time in one or more series. The Board of Directors of the Company (the " ***Board of Directors*** ") is hereby expressly authorized to provide for the issue of any or all of the unissued and undesignated shares of the Preferred Stock in one or more series, and to fix the number of shares and to determine or alter for each such series, such voting powers, full or limited, or no voting powers, and such designation, preferences, and relative, participating, optional, or other rights and such qualifications, limitations, or restrictions thereof, as shall be stated and expressed in the resolution or resolutions adopted by the Board of Directors providing for the issuance of such shares and as may be permitted by the DGCL. The Board of Directors is also expressly authorized to increase or decrease the number of shares of any series subsequent to the issuance of shares of that series, but not below the number of shares of such series then outstanding. In case the number of shares of any series shall be decreased in accordance with the foregoing sentence, the shares constituting such decrease shall resume the status that they had prior to the adoption of the resolution originally fixing the number of shares of such series. The number of authorized shares of Preferred Stock may be increased or decreased (but not below the number of shares thereof then outstanding) by the affirmative vote of the holders of a majority of the voting power of the stock of the Company entitled to vote thereon, without a separate vote of the holders of the Preferred Stock, or of any series thereof, unless a vote of any such holders is required pursuant to the terms of any certificate of designation filed with respect to any series of Preferred Stock.

C. Each outstanding share of Common Stock shall entitle the holder thereof to one vote on each matter properly submitted to the stockholders of the Company for their vote; *provided, however* , that, except as otherwise required by law, holders of Common Stock shall not be entitled to vote on any amendment to this Amended and Restated Certificate of Incorporation (this " ***Certificate of Incorporation*** ") (including any certificate of designation filed with respect to any series of Preferred Stock) that relates solely to the terms of one or more outstanding series of Preferred Stock if the holders of such affected series of Preferred Stock are entitled, either separately or together as a class with the holders of one or more other series of Preferred Stock, to vote thereon by law or pursuant to this Certificate of Incorporation (including any certificate of designation filed with respect to any series of Preferred Stock).

V.

For the management of the business and for the conduct of the affairs of the Company, and in further definition, limitation and regulation of the powers of the Company, of its directors and of its stockholders or any class thereof, as the case may be, it is further provided that:

A. The management of the business and the conduct of the affairs of the Company shall be vested in its Board of Directors. The number of directors that shall constitute the Board of Directors shall be fixed exclusively by resolutions adopted by a majority of the authorized number of directors constituting the Board of Directors.

B. Subject to the rights of the holders of any series of Preferred Stock to elect additional directors under specified circumstances, directors shall be elected at each annual meeting of stockholders for a term ending at the next annual meeting of stockholders. Each director shall serve until his or her successor is duly elected and qualified or until his earlier death, resignation or removal. No decrease in the number of directors constituting the Board of Directors shall shorten the term of any incumbent director.

C. Subject to the rights of any series of Preferred Stock that may be designated from time to time to elect additional directors under specified circumstances and subject to any limitation imposed by law, any individual director or directors may be removed with or without cause by the affirmative vote of the holders of a majority of the voting power of all then outstanding shares of capital stock of the Company entitled to vote generally at an election of directors, voting together as a single class.

D. Subject to the rights of the holders of any series of Preferred Stock that may be designated from time to time, any vacancies on the Board of Directors resulting from death, resignation, disqualification, removal or other causes and any newly created directorships resulting from any increase in the number of directors, shall, unless the Board of Directors determines by resolution that any such vacancies or newly created directorships shall be filled by the stockholders, except as otherwise provided by law, be filled only by the affirmative vote of a majority of the directors then in office, even though less than a quorum of the Board of Directors, and not by the stockholders. Any director elected in accordance with the preceding sentence shall hold office for the remainder of the full term of the director for which the vacancy was created or occurred and until such director's successor shall have been elected and qualified.

E. Subject to the rights of the holders of any series of Preferred Stock that may be designated from time to time, the Board of Directors is expressly empowered to adopt, amend or repeal the Amended and Restated Bylaws of the Company (the "***Bylaws***"). Any adoption, amendment or repeal of the Bylaws by the Board of Directors shall require the approval of a majority of the authorized number of directors. The stockholders shall also have power to adopt, amend or repeal the Bylaws, subject to any restrictions which may be set forth in this Certificate of Incorporation (including any certificate of designation that may be filed from time to time); *provided, however,* that, in addition to any vote of the holders of any class or series of stock of the Company required by law or by this Certificate of Incorporation, such action by stockholders shall require the affirmative vote of the holders of at least 66 2/3% of the voting power of all of the then-outstanding shares of the capital stock of the Company entitled to vote generally at an election of directors, voting together as a single class.

F. The directors of the Company need not be elected by written ballot unless the Bylaws so provide.

G. From and after the first date on which Ionis Pharmaceuticals, Inc. (***"Ionis"***) no longer beneficially owns (as determined in accordance with Rules 13d-3 and 13d-5 of the Securities Exchange Act of 1934, as amended) a majority of the voting power of all of the then-outstanding shares of the capital stock of the Company entitled to vote generally at an election of directors, (1) no action shall be taken by the stockholders of the Company except at an annual or special meeting of stockholders called in accordance with the Bylaws and (2) no action shall be taken by the stockholders of the Company by written consent or electronic transmission.

H. Advance notice of stockholder nominations for the election of directors and of business to be brought by stockholders before any meeting of the stockholders of the Company shall be given in the manner provided in the Bylaws.

VI.

A. The liability of a director of the Company for monetary damages shall be eliminated to the fullest extent under applicable law. If the DGCL is amended to authorize corporate action further eliminating or limiting the personal liability of directors, then the liability of a director of the Company shall be eliminated to the fullest extent permitted by the DGCL, as so amended.

B. Any repeal or modification of this Article VI shall be prospective and shall not affect the rights under this Article VI in effect at the time of the alleged occurrence of any act or omission to act giving rise to liability or indemnification.

VII.

A. The Company reserves the right to amend, alter, change or repeal any provision contained in this Certificate of Incorporation, in the manner now or hereafter prescribed by statute, except as provided in Section B of this Article VII, and all rights conferred upon the stockholders herein are granted subject to this reservation.

B. Notwithstanding any other provisions of this Certificate of Incorporation or any provision of law which might otherwise permit a lesser vote or no vote, but in addition to any affirmative vote of the holders of any particular class or series of the Company required by law or by this Certificate of Incorporation or any certificate of designation filed with respect to a series of Preferred Stock that may be designated from time to time, subject to the rights of the holders of any series of Preferred Stock, the affirmative vote of the holders of at least 66 2/3% of the voting power of all of the then-outstanding shares of capital stock of the Company entitled to vote generally at an election of directors, voting together as a single class, shall be required to alter, amend or repeal Articles V, VI, VII, VIII or IX of this Certificate of Incorporation.

VIII.

A. Unless the Company consents in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware shall, to the fullest extent permitted by law, be the sole and exclusive forum for (1) any derivative action or proceeding brought on behalf of the Company; (2) any action asserting a claim of breach of a fiduciary duty owed by any director, officer or other employee of the Company to the Company or the Company's stockholders; (3) any action asserting a claim against the Company or any director or officer or other employee of the Company arising pursuant to any provision of the DGCL, the Certificate of Incorporation or the Bylaws; or (4) any action asserting a claim against the Company or any director or officer or other employee of the Company governed by the internal affairs doctrine.

IX.

A. To the fullest extent permitted by Section 122(17) of the DGCL and except as may be otherwise expressly agreed in writing by the Company and Ionis, the Company, on behalf of itself and its subsidiaries, renounces any interest or expectancy of the Company and its subsidiaries in, or in being offered an opportunity to participate in, business opportunities, which are from time to time presented to Ionis or any of its subsidiaries (other than the Company and its subsidiaries) or any of their respective officers, directors, agents or stockholders, even if the opportunity is one that the Company or its subsidiaries might reasonably be deemed to have pursued or had the ability or desire to pursue if granted the opportunity to do so, unless, in the case of any such person who is a director or officer of the Company, such business opportunity is expressly offered to such director or officer in writing solely in his or her capacity as a director or officer of the Company. Neither the alteration, amendment, addition to or repeal of this Article IX, nor the adoption of any provision of this Certificate of Incorporation (including any certificate of designations relating to any series of Preferred Stock) inconsistent with this Article IX, shall eliminate or reduce the effect of this Article IX in respect of any business opportunity first identified or any other matter occurring, or any cause of action, suit or claim that, but for this Article IX, would accrue or arise, prior to such alteration, amendment, addition, repeal or adoption.

* * * *

FOURTH: This Certificate of Incorporation has been duly adopted and approved by the Board of Directors.

FIFTH: This Certificate of Incorporation has been duly adopted and approved by written consent of the stockholders in accordance with sections 228, 242 and 245 of the DGCL and written notice of such action has been given as provided in section 228 of the DGCL.

IN WITNESS WHEREOF, Akcea Therapeutics, Inc. has caused this Amended and Restated Certificate of Incorporation to be signed by its Chief Financial Officer this 19th day of July, 2017.

AKCEA THERAPEUTICS, INC.

By: /s/ Elizabeth L. Hougen
Name: Elizabeth L. Hougen
Title: Chief Financial Officer

Exhibit 10.5

Akcea Therapeutics, Inc.
2015 Equity Incentive Plan

Adopted by the Board of Directors: December 16, 2015
Approved by the Stockholders: December 16, 2015
Amended by the Board of Directors: July 15, 2016
Approved by the Stockholders: July 15, 2016
Amended by the Board of Directors: May 2, 2017
Approved by the Stockholders: June 19, 2017
Amended by the Board of Directors: December 5, 2017
Approved by the Stockholders: April 17, 2018
Termination Date: December 15, 2025

1. General.

(a) Eligible Stock Award Recipients. The persons eligible to receive Stock Awards are Employees, Directors and Consultants.

(b) Available Stock Awards . The Plan provides for the grant of the following Stock Awards: (i) Incentive Stock Options, (ii) Nonstatutory Stock Options, (iii) Restricted Stock Awards, (iv) Restricted Stock Unit Awards, and (v) Stock Appreciation Rights.

(c) Purpose. The Company, by means of the Plan, seeks to secure and retain the services of the group of persons eligible to receive Stock Awards as set forth in Section 1(a), to provide incentives for such persons to exert maximum efforts for the success of the Company and any Affiliate, and to provide a means by which such eligible recipients may be given an opportunity to benefit from increases in value of the Common Stock through the granting of Stock Awards.

2. Administration.

(a) Administration by Board. The Board shall administer the Plan unless and until the Board delegates administration of the Plan to a Committee, as provided in Section 2(c).

(b) Powers of Board. The Board shall have the power, subject to, and within the limitations of, the express provisions of the Plan:

(i) To determine from time to time (A) which of the persons eligible under the Plan shall be granted Stock Awards; (B) when and how each Stock Award shall be granted; (C) what type or combination of types of Stock Award shall be granted; (D) the provisions of each Stock Award granted (which need not be identical), including the time or times when a person shall be permitted to receive cash or Common Stock pursuant to a Stock Award; (E) the number of shares of Common Stock with respect to which a Stock Award shall be granted to each such person; and (F) the Fair Market Value applicable to a Stock Award.

(ii) To construe and interpret the Plan and Stock Awards granted under it, and to establish, amend and revoke rules and regulations for administration of the Plan. The Board, in the exercise of this power, may correct any defect, omission or inconsistency in the Plan or in any Stock Award Agreement, in a manner and to the extent it shall deem necessary or expedient to make the Plan or Stock Award fully effective.

(iii) To settle all controversies regarding the Plan and Stock Awards granted under it.

(iv) To accelerate the time at which a Stock Award may first be exercised or the time during which a Stock Award or any part thereof will vest in accordance with the Plan, notwithstanding the provisions in the Stock Award stating the time at which it may first be exercised or the time during which it will vest.

(v) To suspend or terminate the Plan at any time. Suspension or termination of the Plan shall not impair rights and obligations under any Stock Award granted while the Plan is in effect except with the written consent of the affected Participant.

(vi) To amend the Plan in any respect the Board deems necessary or advisable, including, without limitation, relating to Incentive Stock Options and certain nonqualified deferred compensation under Section 409A of the Code and/or to bring the Plan or Stock Awards granted under the Plan into compliance therewith, subject to the limitations, if any, of applicable law. However, except as provided in Section 9(a) relating to Capitalization Adjustments, to the extent required by applicable law, stockholder approval shall be required for any amendment of the Plan that either (i) materially increases the number of shares of Common Stock available for issuance under the Plan, (ii) materially expands the class of individuals eligible to receive Stock Awards under the Plan, (iii) materially increases the benefits accruing to Participants under the Plan or materially reduces the price at which shares of Common Stock may be issued or purchased under the Plan, (iv) materially extends the term of the Plan, or (v) expands the types of Stock Awards available for issuance under the Plan. Except as provided above, rights under any Stock Award granted before amendment of the Plan shall not be impaired by any amendment of the Plan unless (i) the Company requests the consent of the affected Participant, and (ii) such Participant consents in writing.

(vii) To submit any amendment to the Plan for stockholder approval, including, but not limited to, amendments to the Plan intended to satisfy the requirements of Section 422 of the Code regarding Incentive Stock Options.

(viii) To approve forms of Stock Award Agreements for use under the Plan and to amend the terms of any one or more Stock Awards, including, but not limited to, amendments to provide terms more favorable than previously provided in the Stock Award Agreement, subject to any specified limits in the Plan that are not subject to Board discretion; *provided however*, that, the rights under any Stock Award shall not be impaired by any such amendment unless (i) the Company requests the consent of the affected Participant, and (ii) such Participant consents in writing. Notwithstanding the foregoing, subject to the limitations of applicable law, if any, and without the affected Participant's consent, the Board may amend the terms of any one or more Stock Awards if necessary to maintain the qualified status of the Stock Award as an Incentive Stock Option or to bring the Stock Award into compliance with Section 409A of the Code and the related guidance thereunder.

(ix) Generally, to exercise such powers and to perform such acts as the Board deems necessary or expedient to promote the best interests of the Company and that are not in conflict with the provisions of the Plan or Stock Awards.

(x) To adopt such procedures and sub-plans as are necessary or appropriate to permit participation in the Plan by Employees, Directors or Consultants who are foreign nationals or employed outside the United States.

(xi) To effect, at any time and from time to time, with the consent of any adversely affected Optionholder, (1) the reduction of the exercise price of any outstanding Option under the Plan, (2) the cancellation of any outstanding Option under the Plan and the grant in substitution therefor of (A) a new Option under the Plan or another equity plan of the Company covering the same or a different number of shares of Common Stock, (B) a Restricted Stock Award, (C) a Stock Appreciation Right, (D) Restricted Stock Unit, (E) cash and/or (F) other valuable consideration (as determined by the Board, in its sole discretion), or (3) any other action that is treated as a repricing under generally accepted accounting principles; provided, however, that no such reduction or cancellation may be effected if it is determined, in the Company's sole discretion, that such reduction or cancellation would result in any such outstanding Option becoming subject to the requirements of Section 409A of the Code.

(c) Delegation to Committee. The Board may delegate some or all of the administration of the Plan to a Committee or Committees. If administration of the Plan is delegated to a Committee, the Committee shall have, in connection with the administration of the Plan, the powers theretofore possessed by the Board that have been delegated to the Committee, including the power to delegate to a subcommittee of the Committee any of the administrative powers the Committee is authorized to exercise (and references in this Plan to the Board shall thereafter be to the Committee or subcommittee), subject, however, to such resolutions, not inconsistent with the provisions of the Plan, as may be adopted from time to time by the Board. The Board may retain the authority to concurrently administer the Plan with the Committee and may, at any time, revest in the Board some or all of the powers previously delegated.

(d) Delegation to an Officer. The Board may delegate to one or more Officers of the Company the authority to do one or both of the following: (i) designate Officers (other than Officers of a Vice President level or senior thereto) and Employees of the Company or any of its Subsidiaries to be recipients of Options (and, to the extent permitted by applicable law, other Stock Awards) and the terms thereof, and (ii) determine the number of shares of Common Stock to be subject to such Stock Awards granted to such Officers and Employees; provided, however, that the Board resolutions regarding such delegation shall specify the total number of shares of Common Stock that may be subject to the Stock Awards granted by such Officer and that such Officer may not grant a Stock Award to himself or herself. Notwithstanding the foregoing, the Board may not delegate authority to an Officer to determine the Fair Market Value of the Common Stock pursuant to Section 13(t) below.

(e) Effect of Board's Decision. All determinations, interpretations and constructions made by the Board in good faith shall not be subject to review by any person and shall be final, binding and conclusive on all persons.

(f) Arbitration. Any dispute or claim concerning any Stock Awards granted (or not granted) pursuant to the Plan or any disputes or claims relating to or arising out of the Plan shall be fully, finally and exclusively resolved by binding and confidential arbitration conducted pursuant to the Commercial Arbitration Rules of the American Arbitration Association in San Diego, California. The Company shall pay all arbitration fees. In addition to any other relief, the arbitrator may award to the prevailing party recovery of its attorneys' fees and costs. By accepting a Stock Award, Participants and the Company waive their respective rights to have any such disputes or claims tried by a judge or jury.

3. Shares Subject to the Plan.

(a) Share Reserve. Subject to Section 9(a) relating to Capitalization Adjustments, the aggregate number of shares of Common Stock of the Company that may be issued pursuant to Stock Awards after the Effective Date shall not exceed 13,500,000 [1] shares. For clarity, the limitation in this Section 3(a) is a limitation in the number of shares of Common Stock that may be issued pursuant to the Plan. Accordingly, this Section 3(a) does not limit the granting of Stock Awards except as provided in Section 7(a).

(b) Reversion of Shares to the Share Reserve. If any shares of Common Stock issued pursuant to a Stock Award are forfeited back to the Company because of the failure to meet a contingency or condition required to vest such shares in the Participant, then the shares which are forfeited shall revert to and again become available for issuance under the Plan. Also, any shares reacquired by the Company pursuant to Section 8(g) or as consideration for the exercise of an Option shall again become available for issuance under the Plan. Furthermore, if a Stock Award (i) expires or otherwise terminates without having been exercised in full or (ii) is settled in cash (i.e., the holder of the Stock Award receives cash rather than stock), such expiration, termination or settlement shall not reduce (or otherwise offset) the number of shares of Common Stock that may be issued pursuant to the Plan. Notwithstanding the provisions of this Section 3(b), any such shares shall not be subsequently issued pursuant to the exercise of Incentive Stock Options.

(c) Incentive Stock Option Limit. Notwithstanding anything to the contrary in this Section 3(c), subject to the provisions of Section 9(a) relating to Capitalization Adjustments, the aggregate maximum number of shares of Common Stock that may be issued pursuant to the exercise of Incentive Stock Options shall be twice the number of shares that may be issued pursuant to all Stock Awards as set forth in Section 3(a) above.

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[1] This is the sum of (i) 6,340,508 shares originally approved by the Company's stockholders in December 2015 (adjusted for the reverse stock split in connection with the Company's initial public offering), *plus* (ii) 2,159,492 shares approved by the Company's stockholders in June 2017, *plus* (iii) 5,000,000 new shares.

(d) **Source of Shares**. The stock issuable under the Plan shall be shares of authorized but unissued or reacquired Common Stock, including shares repurchased by the Company on the open market.

4. **Eligibility**.

(a) **Eligibility for Specific Stock Awards**. Incentive Stock Options may be granted only to employees of the Company or a "parent corporation" or "subsidiary corporation" thereof (as such terms are defined in Sections 424(e) and (f) of the Code). Stock Awards other than Incentive Stock Options may be granted to Employees, Directors and Consultants.

(b) **Ten Percent Stockholders**. A Ten Percent Stockholder shall not be granted an Incentive Stock Option unless the exercise price of such Option is at least one hundred ten percent (110%) of the Fair Market Value of the Common Stock on the date of grant and the Option is not exercisable after the expiration of five (5) years from the date of grant.

(c) **Consultants**. A Consultant shall not be eligible for the grant of a Stock Award if, at the time of grant, either the offer or the sale of the Company's securities to such Consultant is not exempt under Rule 701 of the Securities Act ("***Rule 701***") because of the nature of the services that the Consultant is providing to the Company, because the Consultant is not a natural person, or because of any other provision of Rule 701, unless the Company determines that such grant need not comply with the requirements of Rule 701 and will satisfy another exemption under the Securities Act as well as comply with the securities laws of all other relevant jurisdictions.

5. **Option Provisions**.

Each Option shall be in such form and shall contain such terms and conditions as the Board shall deem appropriate. All Options shall be separately designated Incentive Stock Options or Nonstatutory Stock Options at the time of grant, and, if certificates are issued, a separate certificate or certificates shall be issued for shares of Common Stock purchased on exercise of each type of Option. If an Option is not specifically designated as an Incentive Stock Option, then the Option shall be a Nonstatutory Stock Option. The provisions of separate Options need not be identical; *provided*, *however*, that each Option Agreement shall include (through incorporation of provisions hereof by reference in the Option Agreement or otherwise) the substance of each of the following provisions:

(a) **Term**. Subject to the provisions of Section 4(b) regarding Ten Percent Stockholders, no Option shall be exercisable after the expiration of ten (10) years from the date of its grant or such shorter period specified in the Option Agreement.

(b) **Exercise Price**. Subject to the provisions of Section 4(b) regarding Incentive Stock Options granted to Ten Percent Stockholders, the exercise price of each Option shall be not less than one hundred percent (100%) of the Fair Market Value of the Common Stock subject to the Option on the date the Option is granted. Notwithstanding the foregoing, an Option may be granted with an exercise price lower than one hundred percent (100%) of the Fair Market Value of the Common Stock subject to the Option if such Option is granted pursuant to an assumption or substitution for another option in a manner consistent with the provisions of Section 424(a) of the Code (whether or not such options are Incentive Stock Options).

(c) Consideration. The purchase price of Common Stock acquired pursuant to the exercise of an Option shall be paid, to the extent permitted by applicable law and as determined by the Board in its sole discretion, by any combination of the methods of payment set forth below. The Board shall have the authority to grant Options that do not permit all of the following methods of payment (or otherwise restrict the ability to use certain methods) and to grant Options that require the consent of the Company to utilize a particular method of payment. The permitted methods of payment are as follows:

(i) by cash, check, bank draft or money order payable to the Company;

(ii) pursuant to a program developed under Regulation T as promulgated by the Federal Reserve Board that, prior to the issuance of the stock subject to the Option, results in either the receipt of cash (or check) by the Company or the receipt of irrevocable instructions to pay the aggregate exercise price to the Company from the sales proceeds;

(iii) by delivery to the Company (either by actual delivery or attestation) of shares of Common Stock;

(iv) by a "net exercise" arrangement pursuant to which the Company will reduce the number of shares of Common Stock issued upon exercise by the largest whole number of shares with a Fair Market Value that does not exceed the aggregate exercise price; *provided*, *however*, that the Company shall accept a cash or other payment from the Participant to the extent of any remaining balance of the aggregate exercise price not satisfied by such reduction in the number of whole shares to be issued; *provided*, *further*, that shares of Common Stock will no longer be outstanding under an Option and will not be exercisable thereafter to the extent that (A) shares are used to pay the exercise price pursuant to the "net exercise," (B) shares are delivered to the Participant as a result of such exercise, and (C) shares are withheld to satisfy tax withholding obligations;

(v) according to a deferred payment or similar arrangement approved by the Board between the Company and the Optionholder; *provided*, *however*, that interest shall compound at least annually and shall be charged at the minimum rate of interest necessary to avoid (A) the imputation of interest income to the Company and compensation income to the Optionholder under any applicable provisions of the Code, and (B) the classification of the Option as a liability for financial accounting purposes; or

(vi) in any other form of legal consideration that may be acceptable to the Board.

(d) Transferability of Options. The Board may, in its sole discretion, impose such limitations on the transferability of Options as the Board shall determine. In the absence of such a determination by the Board to the contrary, the following restrictions on the transferability of Options shall apply:

(i) Restrictions on Transfer. An Option shall not be transferable except by will or by the laws of descent and distribution and shall be exercisable during the lifetime of the Optionholder only by the Optionholder; *provided*, *however*, that the Board may, in its sole discretion, permit transfer of the Option to such extent as permitted by Rule 701 of the Securities Act at the time of the grant of the Option and in a manner consistent with applicable tax and securities laws upon the Optionholder's request.

(ii) Domestic Relations Orders. Notwithstanding the foregoing, an Option may be transferred pursuant to a domestic relations order, *provided*, *however*, that an Incentive Stock Option may be deemed to be a Nonstatutory Stock Option as a result of such transfer.

(iii) Beneficiary Designation. Notwithstanding the foregoing, the Optionholder may, by delivering written notice to the Company, in a form provided by or otherwise satisfactory to the Company, designate a third party who, in the event of the death of the Optionholder, shall thereafter be the beneficiary of an Option with the right to exercise the Option and receive the Common Stock or other consideration resulting from the Option exercise.

(e) Vesting of Options Generally. The total number of shares of Common Stock subject to an Option may vest and therefore become exercisable in periodic installments that may or may not be equal. The Option may be subject to such other terms and conditions on the time or times when it may or may not be exercised (which may be based on the satisfaction of performance goals or other criteria) as the Board may deem appropriate. The vesting provisions of individual Options may vary. The provisions of this Section 5(e) are subject to any Option provisions governing the minimum number of shares of Common Stock as to which an Option may be exercised.

(f) Termination of Continuous Service. Except as otherwise provided in the applicable Option Agreement or other agreement between the Optionholder and the Company, in the event that an Optionholder's Continuous Service terminates (other than upon the Optionholder's death or Disability), the Optionholder may exercise his or her Option (to the extent that the Optionholder was entitled to exercise such Option as of the date of termination of Continuous Service) but only within such period of time ending on the earlier of (i) the date three (3) months following the termination of the Optionholder's Continuous Service (or such longer or shorter period specified in the Option Agreement, which period shall not be less than thirty (30) days), or (ii) the expiration of the term of the Option as set forth in the Option Agreement. If, after termination of Continuous Service, the Optionholder does not exercise his or her Option within the time specified herein or in the Option Agreement (as applicable), the Option shall terminate.

(g) Extension of Termination Date. Except as otherwise provided in the applicable Option Agreement or other agreement between the Optionholder and the Company, if the exercise of the Option following the termination of the Optionholder's Continuous Service (other than upon the Optionholder's death or Disability) would be prohibited at any time solely because the issuance of shares of Common Stock would violate the registration requirements under the Securities Act, then the Option shall terminate on the earlier of (i) the expiration of a period of three (3) months after the termination of the Optionholder's Continuous Service during which the exercise of the Option would not be in violation of such registration requirements, or (ii) the expiration of the term of the Option as set forth in the Option Agreement.

(h) Disability of Optionholder. Except as otherwise provided in the applicable Option Agreement or other agreement between the Optionholder and the Company, in the event that an Optionholder's Continuous Service terminates as a result of the Optionholder's Disability, the Optionholder may exercise his or her Option (to the extent that the Optionholder was entitled to exercise such Option as of the date of termination of Continuous Service), but only within such period of time ending on the earlier of (i) the date twelve (12) months following such termination of Continuous Service (or such longer or shorter period specified in the Option Agreement, which period shall not be less than six (6) months), or (ii) the expiration of the term of the Option as set forth in the Option Agreement. If, after termination of Continuous Service, the Optionholder does not exercise his or her Option within the time specified herein or in the Option Agreement (as applicable), the Option shall terminate.

(i) Death of Optionholder. Except as otherwise provided in the applicable Option Agreement or other agreement between the Optionholder and the Company, in the event that (i) an Optionholder's Continuous Service terminates as a result of the Optionholder's death, or (ii) the Optionholder dies within the period (if any) specified in the Option Agreement after the termination of the Optionholder's Continuous Service for a reason other than death, then the Option may be exercised (to the extent the Optionholder was entitled to exercise such Option as of the date of death) by the Optionholder's estate, by a person who acquired the right to exercise the Option by bequest or inheritance or by a person designated as the beneficiary of the Option upon the Optionholder's death, but only within the period ending on the earlier of (i) the date eighteen (18) months following the date of death (or such longer or shorter period specified in the Option Agreement, which period shall not be less than six (6) months), or (ii) the expiration of the term of such Option as set forth in the Option Agreement. If, after the Optionholder's death, the Option is not exercised within the time specified herein or in the Option Agreement (as applicable), the Option shall terminate. If the Optionholder designates a third party beneficiary of the Option in accordance with Section 5(d)(iii), then upon the death of the Optionholder such designated beneficiary shall have the sole right to exercise the Option and receive the Common Stock or other consideration resulting from the Option exercise.

(j) Non-Exempt Employees. No Option granted to an Employee that is a non-exempt employee for purposes of the Fair Labor Standards Act of 1938, as amended, shall be first exercisable for any shares of Common Stock until at least six months following the date of grant of the Option. The foregoing provision is intended to operate so that any income derived by a non-exempt employee in connection with the exercise or vesting of an Option will be exempt from his or her regular rate of pay.

(k) Early Exercise. The Option may, but need not, include a provision whereby the Optionholder may elect at any time before the Optionholder's Continuous Service terminates to exercise the Option as to any part or all of the shares of Common Stock subject to the Option prior to the full vesting of the Option. Subject to the "Repurchase Limitation" in Section 8(l), any unvested shares of Common Stock so purchased may be subject to a repurchase option in favor of the Company or to any other restriction the Board determines to be appropriate. Provided that the "Repurchase Limitation" in Section 8(l) is not violated, the Company shall not be required to exercise its repurchase option until at least six (6) months (or such longer or shorter period of time required to avoid classification of the Option as a liability for financial accounting purposes) have elapsed following exercise of the Option unless the Board otherwise specifically provides in the Option Agreement.

(l) Right of Repurchase. Subject to the "***Repurchase Limitation***" in Section 8(l), the Option may include a provision whereby the Company may elect to repurchase all or any part of the vested shares of Common Stock acquired by the Optionholder pursuant to the exercise of the Option.

(m) Right of First Refusal. The Option may include a provision whereby the Company may elect to exercise a right of first refusal following receipt of notice from the Optionholder of the intent to transfer all or any part of the shares of Common Stock received upon the exercise of the Option. Such right of first refusal shall be subject to the "***Repurchase Limitation***" in Section 8(l). Except as expressly provided in this Section 5(n) or in the Option Agreement, such right of first refusal shall otherwise comply with any applicable provisions of the Bylaws of the Company.

6. Provisions of Stock Awards other than Options.

(a) Restricted Stock Awards. Each Restricted Stock Award Agreement shall be in such form and shall contain such terms and conditions as the Board shall deem appropriate. To the extent consistent with the Company's Bylaws, at the Board's election, shares of Common Stock may be (x) held in book entry form subject to the Company's instructions until any restrictions relating to the Restricted Stock Award lapse; or (y) evidenced by a certificate, which certificate shall be held in such form and manner as determined by the Board. The terms and conditions of Restricted Stock Award Agreements may change from time to time, and the terms and conditions of separate Restricted Stock Award Agreements need not be identical; *provided*, *however*, that each Restricted Stock Award Agreement shall include (through incorporation of the provisions hereof by reference in the agreement or otherwise) the substance of each of the following provisions:

(i) Consideration. A Restricted Stock Award may be awarded in consideration for (A) past or future services actually or to be rendered to the Company or an Affiliate, or (B) any other form of legal consideration that may be acceptable to the Board in its sole discretion and permissible under applicable law.

(ii) Vesting. Subject to the "Repurchase Limitation" in Section 8(l), shares of Common Stock awarded under the Restricted Stock Award Agreement may be subject to forfeiture to the Company in accordance with a vesting schedule to be determined by the Board.

(iii) Termination of Participant's Continuous Service. In the event a Participant's Continuous Service terminates, the Company may receive via a forfeiture condition, any or all of the shares of Common Stock held by the Participant which have not vested as of the date of termination of Continuous Service under the terms of the Restricted Stock Award Agreement.

(iv) Transferability. Rights to acquire shares of Common Stock under the Restricted Stock Award Agreement shall be transferable by the Participant only upon such terms and conditions as are set forth in the Restricted Stock Award Agreement, as the Board shall determine in its sole discretion, so long as Common Stock awarded under the Restricted Stock Award Agreement remains subject to the terms of the Restricted Stock Award Agreement.

(b) Restricted Stock Unit Awards. Each Restricted Stock Unit Award Agreement shall be in such form and shall contain such terms and conditions as the Board shall deem appropriate. The terms and conditions of Restricted Stock Unit Award Agreements may change from time to time, and the terms and conditions of separate Restricted Stock Unit Award Agreements need not be identical, *provided*, *however*, that each Restricted Stock Unit Award Agreement shall include (through incorporation of the provisions hereof by reference in the Agreement or otherwise) the substance of each of the following provisions:

(i) Consideration. At the time of grant of a Restricted Stock Unit Award, the Board will determine the consideration, if any, to be paid by the Participant upon delivery of each share of Common Stock subject to the Restricted Stock Unit Award. The consideration to be paid (if any) by the Participant for each share of Common Stock subject to a Restricted Stock Unit Award may be paid in any form of legal consideration that may be acceptable to the Board in its sole discretion and permissible under applicable law.

(ii) Vesting. At the time of the grant of a Restricted Stock Unit Award, the Board may impose such restrictions or conditions to the vesting of the Restricted Stock Unit Award as it, in its sole discretion, deems appropriate.

(iii) Payment. A Restricted Stock Unit Award may be settled by the delivery of shares of Common Stock, their cash equivalent, any combination thereof or in any other form of consideration, as determined by the Board and contained in the Restricted Stock Unit Award Agreement.

(iv) Additional Restrictions. At the time of the grant of a Restricted Stock Unit Award, the Board, as it deems appropriate, may impose such restrictions or conditions that delay the delivery of the shares of Common Stock (or their cash equivalent) subject to a Restricted Stock Unit Award to a time after the vesting of such Restricted Stock Unit Award.

(v) Dividend Equivalents. Dividend equivalents may be credited in respect of shares of Common Stock covered by a Restricted Stock Unit Award, as determined by the Board and contained in the Restricted Stock Unit Award Agreement. At the sole discretion of the Board, such dividend equivalents may be converted into additional shares of Common Stock covered by the Restricted Stock Unit Award in such manner as determined by the Board. Any additional shares covered by the Restricted Stock Unit Award credited by reason of such dividend equivalents will be subject to all the terms and conditions of the underlying Restricted Stock Unit Award Agreement to which they relate.

(vi) Termination of Participant's Continuous Service. Except as otherwise provided in the applicable Restricted Stock Unit Award Agreement, such portion of the Restricted Stock Unit Award that has not vested will be forfeited upon the Participant's termination of Continuous Service.

(vii) Compliance with Section 409A of the Code. Notwithstanding anything to the contrary set forth herein, any Restricted Stock Unit Award granted under the Plan that is not exempt from the requirements of Section 409A of the Code shall contain such provisions so that such Restricted Stock Unit Award will comply with the requirements of Section 409A of the Code. Such restrictions, if any, shall be determined by the Board and contained in the Restricted Stock Unit Award Agreement evidencing such Restricted Stock Unit Award. For example, such restrictions may include, without limitation, a requirement that any Common Stock that is to be issued in a year following the year in which the Restricted Stock Unit Award vests must be issued in accordance with a fixed pre-determined schedule.

(c) Stock Appreciation Rights. Each Stock Appreciation Right Agreement shall be in such form and shall contain such terms and conditions as the Board shall deem appropriate. Stock Appreciation Rights may be granted as stand-alone Stock Awards or in tandem with other Stock Awards. The terms and conditions of Stock Appreciation Right Agreements may change from time to time, and the terms and conditions of separate Stock Appreciation Right Agreements need not be identical; provided, however, that each Stock Appreciation Right Agreement shall include (through incorporation of the provisions hereof by reference in the agreement or otherwise) the substance of each of the following provisions:

(i) Term. No Stock Appreciation Right shall be exercisable after the expiration of ten (10) years from the date of grant or such shorter period specified in the Stock Appreciation Right Agreement.

(ii) Strike Price. Each Stock Appreciation Right will be denominated in shares of Common Stock equivalents. The strike price of each Stock Appreciation Right granted as a stand-alone or tandem Stock Award shall not be less than one hundred percent (100%) of the Fair Market Value of the Common Stock equivalents subject to the Stock Appreciation Right on the date of grant.

(iii) Calculation of Appreciation. The appreciation distribution payable on the exercise of a Stock Appreciation Right will be not greater than an amount equal to the excess of (A) the aggregate Fair Market Value (on the date of the exercise of the Stock Appreciation Right) of a number of shares of Common Stock equal to the number of shares of Common Stock equivalents in which the Participant is vested under such Stock Appreciation Right, and with respect to which the Participant is exercising the Stock Appreciation Right on such date, over (B) the strike price that will be determined by the Board on the date of grant.

(iv) Vesting. At the time of the grant of a Stock Appreciation Right, the Board may impose such restrictions or conditions to the vesting of such Stock Appreciation Right as it, in its sole discretion, deems appropriate.

(v) Exercise. To exercise any outstanding Stock Appreciation Right, the Participant must provide written notice of exercise to the Company in compliance with the provisions of the Stock Appreciation Right Agreement evidencing such Stock Appreciation Right.

(vi) Non-Exempt Employees. No Stock Appreciation Right granted to an Employee that is a non-exempt employee for purposes of the Fair Labor Standards Act of 1938, as amended, shall be first exercisable for any shares of Common Stock until at least six months following the date of grant of the Stock Appreciation Right. The foregoing provision is intended to operate so that any income derived by a non-exempt employee in connection with the exercise of a Stock Appreciation Right will be exempt from his or her regular rate of pay.

(vii) Payment. The appreciation distribution in respect to a Stock Appreciation Right may be paid in Common Stock, in cash, in any combination of the two or in any other form of consideration, as determined by the Board and contained in the Stock Appreciation Right Agreement evidencing such Stock Appreciation Right.

(viii) Termination of Continuous Service. Except as otherwise provided in the applicable Stock Appreciation Right Agreement or other agreement between the Participant and the Company, in the event that a Participant's Continuous Service terminates (other than upon the Participant's death or Disability), the Participant may exercise his or her Stock Appreciation Right (to the extent that the Participant was entitled to exercise such Stock Appreciation Right as of the date of termination of Continuous Service) but only within such period of time ending on the earlier of (A) the date three (3) months following the termination of the Participant's Continuous Service (or such longer or shorter period specified in the Stock Appreciation Right Agreement, which period shall not be less than thirty (30) days), or (B) the expiration of the term of the Stock Appreciation Right as set forth in the Stock Appreciation Right Agreement. If, after termination of Continuous Service, the Participant does not exercise his or her Stock Appreciation Right within the time specified herein or in the Stock Appreciation Right Agreement (as applicable), the Stock Appreciation Right shall terminate.

(ix) Disability of Participant. Except as otherwise provided in the applicable Stock Appreciation Right Agreement or other agreement between the Participant and the Company, in the event that a Participant's Continuous Service terminates as a result of the Participant's Disability, the Participant may exercise his or her Stock Appreciation Right (to the extent that the Participant was entitled to exercise such Stock Appreciation Right as of the date of termination of Continuous Service), but only within such period of time ending on the earlier of (A) the date twelve (12) months following such termination of Continuous Service (or such longer or shorter period specified in the Stock Appreciation Right Agreement, which period shall not be less than six (6) months), or (B) the expiration of the term of the Stock Appreciation Right as set forth in the Stock Appreciation Right Agreement. If, after termination of Continuous Service, the Participant does not exercise his or her Stock Appreciation Right within the time specified herein or in the Stock Appreciation Right Agreement (as applicable), the Stock Appreciation Right shall terminate.

(x) Death of Participant. Except as otherwise provided in the applicable Stock Appreciation Right Agreement or other agreement between the Participant and the Company, in the event that (i) a Participant's Continuous Service terminates as a result of the Participant's death, or (ii) the Participant dies within the period (if any) specified in the Stock Appreciation Right Agreement after the termination of the Participant's Continuous Service for a reason other than death, then the Stock Appreciation Right may be exercised (to the extent the Participant was entitled to exercise such Stock Appreciation Right as of the date of death) by the Participant's estate, by a person who acquired the right to exercise the Stock Appreciation Right by bequest or inheritance or by a person designated as the beneficiary of the Stock Appreciation Right upon the Participant's death, but only within the period ending on the earlier of (i) the date eighteen (18) months following the date of death (or such longer or shorter period specified in the Stock Appreciation Right Agreement, which period shall not be less than six (6) months), or (ii) the expiration of the term of such Stock Appreciation Right as set forth in the Stock Appreciation Right Agreement. If, after the Participant's death, the Stock Appreciation Right is not exercised within the time specified herein or in the Stock Appreciation Right Agreement (as applicable), the Stock Appreciation Right shall terminate.

(xi) Compliance with Section 409A of the Code. Notwithstanding anything to the contrary set forth herein, any Stock Appreciation Rights granted under the Plan that are not exempt from the requirements of Section 409A of the Code shall contain such provisions so that such Stock Appreciation Rights will comply with the requirements of Section 409A of the Code. Such restrictions, if any, shall be determined by the Board and contained in the Stock Appreciation Right Agreement evidencing such Stock Appreciation Right. For example, such restrictions may include, without limitation, a requirement that a Stock Appreciation Right that is to be paid wholly or partly in cash must be exercised and paid in accordance with a fixed pre-determined schedule.

7. Covenants of the Company.

(a) Availability of Shares. During the terms of the Stock Awards, the Company shall keep available at all times the number of shares of Common Stock reasonably required to satisfy such Stock Awards.

(b) Securities Law Compliance. The Company shall seek to obtain from each regulatory commission or agency having jurisdiction over the Plan such authority as may be required to grant Stock Awards and to issue and sell shares of Common Stock upon exercise of the Stock Awards; *provided*, *however*, that this undertaking shall not require the Company to register under the Securities Act the Plan, any Stock Award or any Common Stock issued or issuable pursuant to any such Stock Award. If, after reasonable efforts, the Company is unable to obtain from any such regulatory commission or agency the authority that counsel for the Company deems necessary for the lawful issuance and sale of Common Stock under the Plan, the Company shall be relieved from any liability for failure to issue and sell Common Stock upon exercise of such Stock Awards unless and until such authority is obtained.

(c) No Obligation to Notify. The Company shall have no duty or obligation to any holder of a Stock Award to advise such holder as to the time or manner of exercising such Stock Award. Furthermore, the Company shall have no duty or obligation to warn or otherwise advise such holder of a pending termination or expiration of a Stock Award or a possible period in which the Stock Award may not be exercised. The Company has no duty or obligation to minimize the tax consequences of a Stock Award to the holder of such Stock Award.

8. Miscellaneous.

(a) Use of Proceeds from Sales of Common Stock. Proceeds from the sale of shares of Common Stock pursuant to Stock Awards shall constitute general funds of the Company.

(b) Corporate Action Constituting Grant of Stock Awards . Corporate action constituting a grant by the Company of a Stock Award to any Participant shall be deemed completed as of the date of such corporate action, unless otherwise determined by the Board, regardless of when the instrument, certificate, or letter evidencing the Stock Award is communicated to, or actually received or accepted by, the Participant.

(c) Stockholder Rights. No Participant shall be deemed to be the holder of, or to have any of the rights of a holder with respect to, any shares of Common Stock subject to such Stock Award unless and until such Participant has satisfied all requirements for exercise of the Stock Award pursuant to its terms and the Participant shall not be deemed to be a stockholder of record until the issuance of the Common Stock pursuant to such exercise has been entered into the books and records of the Company.

(d) No Employment or Other Service Rights. Nothing in the Plan, any Stock Award Agreement or any other instrument executed thereunder or in connection with any Stock Award granted pursuant thereto shall confer upon any Participant any right to continue to serve the Company or an Affiliate in the capacity in effect at the time the Stock Award was granted or shall affect the right of the Company or an Affiliate to terminate (i) the employment of an Employee with or without notice and with or without cause, (ii) the service of a Consultant pursuant to the terms of such Consultant's agreement with the Company or an Affiliate, or (iii) the service of a Director pursuant to the Bylaws of the Company or an Affiliate, and any applicable provisions of the corporate law of the state in which the Company or the Affiliate is incorporated, as the case may be.

(e) Incentive Stock Option $100,000 Limitation. To the extent that the aggregate Fair Market Value (determined at the time of grant) of Common Stock with respect to which Incentive Stock Options are exercisable for the first time by any Optionholder during any calendar year (under all plans of the Company and any Affiliates) exceeds one hundred thousand dollars ($100,000), the Options or portions thereof that exceed such limit (according to the order in which they were granted) shall be treated as Nonstatutory Stock Options, notwithstanding any contrary provision of the applicable Option Agreement(s).

(f) Investment Assurances. The Company may require a Participant, as a condition of exercising or acquiring Common Stock under any Stock Award, (i) to give written assurances satisfactory to the Company as to the Participant's knowledge and experience in financial and business matters and/or to employ a purchaser representative reasonably satisfactory to the Company who is knowledgeable and experienced in financial and business matters and that he or she is capable of evaluating, alone or together with the purchaser representative, the merits and risks of exercising the Stock Award; and (ii) to give written assurances satisfactory to the Company stating that the Participant is acquiring Common Stock subject to the Stock Award for the Participant's own account and not with any present intention of selling or otherwise distributing the Common Stock. The foregoing requirements, and any assurances given pursuant to such requirements, shall be inoperative if (x) the issuance of the shares upon the exercise or acquisition of Common Stock under the Stock Award has been registered under a then currently effective registration statement under the Securities Act, or (y) as to any particular requirement, a determination is made by counsel for the Company that such requirement need not be met in the circumstances under the then applicable securities laws. The Company may, upon advice of counsel to the Company, place legends on stock certificates issued under the Plan as such counsel deems necessary or appropriate in order to comply with applicable securities laws, including, but not limited to, legends restricting the transfer of the Common Stock.

(g) Withholding Obligations. To the extent provided by the terms of a Stock Award Agreement, the Company may, in its sole discretion, satisfy any federal, state or local tax withholding obligation relating to a Stock Award by any of the following means (in addition to the Company's right to withhold from any compensation paid to the Participant by the Company) or by a combination of such means: (i) causing the Participant to tender a cash payment; (ii) withholding shares of Common Stock from the shares of Common Stock issued or otherwise issuable to the Participant in connection with the Stock Award; *provided*, *however*, that no shares of Common Stock are withheld with a value exceeding the minimum amount of tax required to be withheld by law (or such lower amount as may be necessary to avoid classification of the Stock Award as a liability for financial accounting purposes); (iii) withholding payment from any amounts otherwise payable to the Participant; (iv) withholding cash from a Stock Award settled in cash; or (v) by such other method as may be set forth in the Stock Award Agreement.

(h) Electronic Delivery. Any reference herein to a "written" agreement or document shall include any agreement or document delivered electronically or posted on the Company's intranet.

(i) Deferrals. To the extent permitted by applicable law, the Board, in its sole discretion, may determine that the delivery of Common Stock or the payment of cash, upon the exercise, vesting or settlement of all or a portion of any Stock Award may be deferred and may establish programs and procedures for deferral elections to be made by Participants. Deferrals by Participants will be made in accordance with Section 409A of the Code. Consistent with Section 409A of the Code, the Board may provide for distributions while a Participant is still an employee. The Board is authorized to make deferrals of Stock Awards and determine when, and in what annual percentages, Participants may receive payments, including lump sum payments, following the Participant's termination of employment or retirement, and implement such other terms and conditions consistent with the provisions of the Plan and in accordance with applicable law.

(j) Compliance with Section 409A. To the extent that the Board determines that any Stock Award granted hereunder is subject to Section 409A of the Code, the Stock Award Agreement evidencing such Stock Award shall incorporate the terms and conditions necessary to avoid the consequences specified in Section 409A(a)(1) of the Code. To the extent applicable, the Plan and Stock Award Agreements shall be interpreted in accordance with Section 409A of the Code and Department of Treasury regulations and other interpretive guidance issued thereunder, including without limitation any such regulations or other guidance that may be issued or amended after the Effective Date. Notwithstanding any provision of the Plan to the contrary, in the event that following the Effective Date the Board determines that any Stock Award may be subject to Section 409A of the Code and related Department of Treasury guidance (including such Department of Treasury guidance as may be issued after the Effective Date), the Board may adopt such amendments to the Plan and the applicable Stock Award Agreement or adopt other policies and procedures (including amendments, policies and procedures with retroactive effect), or take any other actions, that the Board determines are necessary or appropriate to (1) exempt the Stock Award from Section 409A of the Code and/or preserve the intended tax treatment of the benefits provided with respect to the Stock Award, or (2) comply with the requirements of Section 409A of the Code and related Department of Treasury guidance.

(k) Compliance with Exemption Provided by Rule 12h-1(f). If: (i) the aggregate of the number of Optionholders and the number of holders of all other outstanding compensatory employee stock options to purchase shares of Common Stock equals or exceeds five hundred (500), and (ii) the assets of the Company at the end of the Company's most recently completed fiscal year exceed $10 million, then the following restrictions shall apply during any period during which the Company does not have a class of its securities registered under Section 12 of the Exchange Act and is not required to file reports under Section 15(d) of the Exchange Act: (A) the Options and, prior to exercise, the shares of Common Stock acquired upon exercise of the Options may not be transferred until the Company is no longer relying on the exemption provided by Rule 12h-1(f) promulgated under the Exchange Act ("***Rule 12h-1 (f)***"), except: (1) as permitted by Rule 701(c) promulgated under the Securities Act, (2) to a guardian upon the disability of the Optionholder, or (3) to an executor upon the death of the Optionholder (collectively, the "***Permitted Transferees***"); *provided*, *however*, the following transfers are permitted: (i) transfers by the Optionholder to the Company, and (ii) transfers in connection with a change of control or other acquisition involving the Company, if following such transaction, the Options no longer remain outstanding and the Company is no longer relying on the exemption provided by Rule 12h-1(f); *provided further*, that any Permitted Transferees may not further transfer the Options; (B) except as otherwise provided in (A) above, the Options and shares of Common Stock acquired upon exercise of the Options are restricted as to any pledge, hypothecation, or other transfer, including any short position, any "put equivalent position" as defined by Rule 16a-1(h) promulgated under the Exchange Act, or any "call equivalent position" as defined by Rule 16a-1(b) promulgated under the Exchange Act by the Optionholder prior to exercise of an Option until the Company is no longer relying on the exemption provided by Rule 12h-1(f); and (C) at any time that the Company is relying on the exemption provided by Rule 12h-1(f), the Company shall deliver to Optionholders (whether by physical or electronic delivery or written notice of the availability of the information on an internet site) the information required by Rule 701(e)(3), (4), and (5) promulgated under the Securities Act every six (6) months, including financial statements that are not more than one hundred eighty (180) days old; *provided*, *however*, that the Company may condition the delivery of such information upon the Optionholder's agreement to maintain its confidentiality.

(l) Repurchase Limitation. The terms of any repurchase option shall be specified in the Stock Award Agreement. The repurchase price for vested shares of Common Stock shall be the Fair Market Value of the shares of Common Stock on the date of repurchase. The repurchase price for unvested shares of Common Stock shall be the lower of (i) the Fair Market Value of the shares of Common Stock on the date of repurchase or (ii) their original purchase price. However, the Company shall not exercise its repurchase option until at least six (6) months (or such longer or shorter period of time necessary to avoid classification of the Stock Award as a liability for financial accounting purposes) have elapsed following delivery of shares of Common Stock subject to the Stock Award, unless otherwise specifically provided by the Board.

9. Adjustments upon Changes in Common Stock; Other Corporate Events.

(a) Capitalization Adjustments. In the event of a Capitalization Adjustment, the Board shall proportionately and appropriately adjust: (i) the class(es) and maximum number of securities subject to the Plan pursuant to Section 3(a), (ii) the class(es) and maximum number of securities that may be issued pursuant to the exercise of Incentive Stock Options pursuant to Section 3(c), and (iii) the class(es) and number of securities and price per share of stock subject to outstanding Stock Awards. The Board shall make such adjustments, and its determination shall be final, binding and conclusive.

(b) Dissolution or Liquidation. Except as otherwise provided in the Stock Award Agreement, in the event of a dissolution or liquidation of the Company, all outstanding Stock Awards (other than Stock Awards consisting of vested and outstanding shares of Common Stock not subject to the Company's right of repurchase) shall terminate immediately prior to the completion of such dissolution or liquidation, and the shares of Common Stock subject to the Company's repurchase option may be repurchased by the Company notwithstanding the fact that the holder of such Stock Award is providing Continuous Service, *provided*, *however*, that the Board may, in its sole discretion, cause some or all Stock Awards to become fully vested, exercisable and/or no longer subject to repurchase or forfeiture (to the extent such Stock Awards have not previously expired or terminated) before the dissolution or liquidation is completed but contingent on its completion.

(c) Corporate Transaction. The following provisions shall apply to Stock Awards in the event of a Corporate Transaction unless otherwise provided in the instrument evidencing the Stock Award or any other written agreement between the Company or any Affiliate and the holder of the Stock Award or unless otherwise expressly provided by the Board at the time of grant of a Stock Award.

(i) Stock Awards May Be Assumed. Except as otherwise stated in the Stock Award Agreement, in the event of a Corporate Transaction, any surviving corporation or acquiring corporation (or the surviving or acquiring corporation's parent company) may assume or continue any or all Stock Awards outstanding under the Plan or may substitute similar stock awards for Stock Awards outstanding under the Plan (including but not limited to, awards to acquire the same consideration paid to the stockholders of the Company pursuant to the Corporate Transaction), and any reacquisition or repurchase rights held by the Company in respect of Common Stock issued pursuant to Stock Awards may be assigned by the Company to the successor of the Company (or the successor's parent company, if any), in connection with such Corporate Transaction. A surviving corporation or acquiring corporation (or its parent) may choose to assume or continue only a portion of a Stock Award or substitute a similar stock award for only a portion of a Stock Award. The terms of any assumption, continuation or substitution shall be set by the Board in accordance with the provisions of Section 2.

(ii) Stock Awards Held by Current Participants. Except as otherwise stated in the Stock Award Agreement, in the event of a Corporate Transaction in which the surviving corporation or acquiring corporation (or its parent company) does not assume or continue such outstanding Stock Awards or substitute similar stock awards for such outstanding Stock Awards, then with respect to Stock Awards that have not been assumed, continued or substituted and that are held by Participants whose Continuous Service has not terminated prior to the effective time of the Corporate Transaction (referred to as the "***Current Participants***"), the vesting of such Stock Awards (and, if applicable, the time at which such Stock Awards may be exercised) shall (contingent upon the effectiveness of the Corporate Transaction) be accelerated in full to a date prior to the effective time of such Corporate Transaction as the Board shall determine (or, if the Board shall not determine such a date, to the date that is five (5) days prior to the effective time of the Corporate Transaction), and such Stock Awards shall terminate if not exercised (if applicable) at or prior to the effective time of the Corporate Transaction, and any reacquisition or repurchase rights held by the Company with respect to such Stock Awards shall lapse (contingent upon the effectiveness of the Corporate Transaction).

(iii) Stock Awards Held by Persons other than Current Participants. Except as otherwise stated in the Stock Award Agreement, in the event of a Corporate Transaction in which the surviving corporation or acquiring corporation (or its parent company) does not assume or continue such outstanding Stock Awards or substitute similar stock awards for such outstanding Stock Awards, then with respect to Stock Awards that have not been assumed, continued or substituted and that are held by persons other than Current Participants, the vesting of such Stock Awards (and, if applicable, the time at which such Stock Award may be exercised) shall not be accelerated and such Stock Awards (other than a Stock Award consisting of vested and outstanding shares of Common Stock not subject to the Company's right of repurchase) shall terminate if not exercised (if applicable) prior to the effective time of the Corporate Transaction; *provided*, *however*, that any reacquisition or repurchase rights held by the Company with respect to such Stock Awards shall not terminate and may continue to be exercised notwithstanding the Corporate Transaction.

(iv) Payment for Stock Awards in Lieu of Exercise. Notwithstanding the foregoing, in the event a Stock Award will terminate if not exercised prior to the effective time of a Corporate Transaction, the Board may provide, in its sole discretion, that the holder of such Stock Award may not exercise such Stock Award but will receive, in the Board's discretion, such cash consideration (including no consideration) as the Board may consider appropriate, in such form as may be determined by the Board, including a payment equal in value to the excess, if any, of (A) the value of the property the holder of the Stock Award would have received upon the exercise of the Stock Award, over (B) any exercise price payable by such holder in connection with such exercise.

(d) Change in Control. A Stock Award may be subject to additional acceleration of vesting and exercisability upon or after a Change in Control as may be provided in the Stock Award Agreement for such Stock Award or as may be provided in any other written agreement approved by the Board between the Company or any Affiliate and the Participant, but in the absence of such provision, no such acceleration shall occur.

10. Termination or Suspension of the Plan.

(a) Plan Term. The Board may suspend or terminate the Plan at any time. Unless sooner terminated by the Board pursuant to Section 2, the Plan shall automatically terminate on December 15, 2025. No Stock Awards may be granted under the Plan while the Plan is suspended or after it is terminated.

(b) No Impairment of Rights. Suspension or termination of the Plan shall not impair rights and obligations under any Stock Award granted while the Plan is in effect except with the written consent of the affected Participant.

11. Effective Date of Plan.

This Plan shall become effective on the Effective Date.

12. Choice of Law.

The law of the State of Delaware shall govern all questions concerning the construction, validity and interpretation of this Plan, without regard to that state's conflict of laws rules.

13. Definitions. As used in the Plan, the following definitions shall apply to the capitalized terms indicated below:

(a) "***Affiliate***" means, at the time of determination, any "parent" or "majority-owned subsidiary" of the Company, as such terms are defined in Rule 405 of the Securities Act. The Board shall have the authority to determine the time or times at which "parent" or "majority-owned subsidiary" status is determined within the foregoing definition.

(b) "***Board***" means the Board of Directors of the Company.

(c) "***Capitalization Adjustment***" means any change that is made in, or other events that occur with respect to, the Common Stock subject to the Plan or subject to any Stock Award after the Effective Date without the receipt of consideration by the Company (through merger, consolidation, reorganization, recapitalization, reincorporation, stock dividend, dividend in property other than cash, stock split, liquidating dividend, combination of shares, exchange of shares, change in corporate structure or other transaction not involving the receipt of consideration by the Company). Notwithstanding the foregoing, the conversion of any convertible securities of the Company shall not be treated as a transaction "without the receipt of consideration" by the Company.

(d) "***Change in Control***" means the occurrence, in a single transaction or in a series of related transactions, of any one or more of the following events:

(i) any Exchange Act Person becomes the Owner, directly or indirectly, of securities of the Company representing more than fifty percent (50%) of the combined voting power of the Company's then outstanding securities other than by virtue of a merger, consolidation or similar transaction. Notwithstanding the foregoing, a Change in Control shall not be deemed to occur (A) on account of the acquisition of securities of the Company by an investor, any affiliate thereof or any other Exchange Act Person that acquires the Company's securities in a transaction or series of related transactions the primary purpose of which is to obtain financing for the Company through the issuance of equity securities or (B) solely because the level of Ownership held by any Exchange Act Person (the "***Subject Person***") exceeds the designated percentage threshold of the outstanding voting securities as a result of a repurchase or other acquisition of voting securities by the Company reducing the number of shares outstanding, provided that if a Change in Control would occur (but for the operation of this sentence) as a result of the acquisition of voting securities by the Company, and after such share acquisition, the Subject Person becomes the Owner of any additional voting securities that, assuming the repurchase or other acquisition had not occurred, increases the percentage of the then outstanding voting securities Owned by the Subject Person over the designated percentage threshold, then a Change in Control shall be deemed to occur;

(i i) there is consummated a merger, consolidation or similar transaction involving (directly or indirectly) the Company and, immediately after the consummation of such merger, consolidation or similar transaction, the stockholders of the Company immediately prior thereto do not Own, directly or indirectly, either (A) outstanding voting securities representing more than fifty percent (50%) of the combined outstanding voting power of the surviving Entity in such merger, consolidation or similar transaction or (B) more than fifty percent (50%) of the combined outstanding voting power of the parent of the surviving Entity in such merger, consolidation or similar transaction, in each case in substantially the same proportions as their Ownership of the outstanding voting securities of the Company immediately prior to such transaction;

(iii) the stockholders of the Company approve or the Board approves a plan of complete dissolution or liquidation of the Company, or a complete dissolution or liquidation of the Company shall otherwise occur, except for a liquidation into a parent corporation; or

(iv) there is consummated a sale, lease, exclusive license or other disposition of all or substantially all of the consolidated assets of the Company and its Subsidiaries (in each case as determined by the Board in its sole discretion), other than a sale, lease, license or other disposition of all or substantially all of the consolidated assets of the Company and its Subsidiaries to an Entity, more than fifty percent (50%) of the combined voting power of the voting securities of which are Owned by stockholders of the Company in substantially the same proportions as their Ownership of the outstanding voting securities of the Company immediately prior to such sale, lease, license or other disposition.

Notwithstanding the foregoing definition or any other provision of this Plan, (A) the term Change in Control shall not include a sale of assets, merger or other transaction effected exclusively for the purpose of changing the domicile of the Company, and (B) the definition of Change in Control (or any analogous term) in an individual written agreement between the Company or any Affiliate and the Participant shall supersede the foregoing definition with respect to Stock Awards subject to such agreement; provided, however, that if no definition of Change in Control or any analogous term is set forth in such an individual written agreement, the foregoing definition shall apply.

(e) "***Code***" means the Internal Revenue Code of 1986, as amended.

(f) "***Committee***" means a committee of one or more Directors to whom authority has been delegated by the Board in accordance with Section 2(c).

(g) "***Common Stock***" means the common stock of the Company.

(h) "***Company***" means Akcea Therapeutics, Inc., a Delaware corporation.

(i) "***Consultant***" means any person, including an advisor, who is (i) engaged by the Company or an Affiliate to render consulting or advisory services and is compensated for such services, or (ii) serving as a member of the board of directors of an Affiliate and is compensated for such services. However, service solely as a Director, or payment of a fee for such service, shall not cause a Director to be considered a "*Consultant*" for purposes of the Plan.

(j) "***Continuous Service***" means that the Participant's service with the Company or an Affiliate, whether as an Employee, Director or Consultant, is not interrupted or terminated. A change in the capacity in which the Participant renders service to the Company or an Affiliate as an Employee, Director, or Consultant or a change in the Entity for which the Participant renders such service, provided that there is no interruption or termination of the Participant's service with the Company or an Affiliate, shall not terminate a Participant's Continuous Service; provided, however, if the Entity for which a Participant is rendering service ceases to qualify as an Affiliate, as determined by the Board in its sole discretion, such Participant's Continuous Service shall be considered to have terminated on the date such Entity ceases to qualify as an Affiliate. For example, a change in status from an employee of the Company to a consultant of an Affiliate or to a Director shall not constitute an interruption of Continuous Service. To the extent permitted by law, the Board or the chief executive officer of the Company, in that party's sole discretion, may determine whether Continuous Service shall be considered interrupted in the case of any leave of absence approved by that party, including sick leave, military leave or any other personal leave. Notwithstanding the foregoing, a leave of absence shall be treated as Continuous Service for purposes of vesting in a Stock Award only to such extent as may be provided in the Company's leave of absence policy, in the written terms of any leave of absence agreement or policy applicable to the Participant, or as otherwise required by law.

(k) "***Corporate Transaction***" means the occurrence, in a single transaction or in a series of related transactions, of any one or more of the following events:

(i) the consummation of a sale or other disposition of all or substantially all, as determined by the Board in its sole discretion, of the consolidated assets of the Company and its Subsidiaries;

(ii) the consummation of a sale or other disposition of at least ninety percent (90%) of the outstanding securities of the Company (other than a distribution of the shares by Ionis to the Ionis stockholders);

(iii) the consummation of a merger, consolidation or similar transaction following which the Company is not the surviving corporation; or

(iv) the consummation of a merger, consolidation or similar transaction following which the Company is the surviving corporation but the shares of Common Stock outstanding immediately preceding the merger, consolidation or similar transaction are converted or exchanged by virtue of the merger, consolidation or similar transaction into other property, whether in the form of securities, cash or otherwise.

(l) "***Director***" means a member of the Board.

(m) "***Disability***" means the inability of a Participant to engage in any substantially gainful activity by reason of any medically determinable physical or mental impairment which can be expected to result in death or which has lasted or can be expected to last for a continuous period of not less than twelve (12) months, and shall be determined by the Board on the basis of such medical evidence as the Board deems warranted under the circumstances.

(n) "***Effective Date***" means the effective date of this Plan, which is the earlier of (i) the date that this Plan is first approved by the Company's stockholders, or (ii) the date this Plan is adopted by the Board.

(o) "***Employee***" means any person employed by the Company or an Affiliate. However, service solely as a Director, or payment of a fee for such services, shall not cause a Director to be considered an "*Employee*" for purposes of the Plan.

(p) "***Entity***" means a corporation, partnership, limited liability company or other entity.

(q) "***Exchange Act***" means the Securities Exchange Act of 1934, as amended.

(r) "***Exchange Act Person***" means any natural person, Entity or "group" (within the meaning of Section 13(d) or 14(d) of the Exchange Act), except that "*Exchange Act Person*" shall not include (i) the Company or any Subsidiary of the Company, (ii) any employee benefit plan of the Company or any Subsidiary of the Company or any trustee or other fiduciary holding securities under an employee benefit plan of the Company or any Subsidiary of the Company, (iii) an underwriter temporarily holding securities pursuant to an offering of such securities, (iv) an Entity Owned, directly or indirectly, by the stockholders of the Company in substantially the same proportions as their Ownership of stock of the Company; or (v) any natural person, Entity or "group" (within the meaning of Section 13(d) or 14(d) of the Exchange Act) that, as of the Effective Date of the Plan as set forth in Section 11, is the Owner, directly or indirectly, of securities of the Company representing more than fifty percent (50%) of the combined voting power of the Company's then outstanding securities.

(s) "***Fair Market Value***" means, as of any date, the value of the Common Stock determined as follows:

(i) If the Common Stock is listed on any established stock exchange or traded on any established market, the Fair Market Value of a share of Common Stock will be, unless otherwise determined by the Board, the closing sales price for such stock as quoted on such exchange or market (or the exchange or market with the greatest volume of trading in the Common Stock) on the date of determination, as reported in a source the Board deems reliable.

(ii) Unless otherwise provided by the Board, if there is no closing sales price for the Common Stock on the date of determination, then the Fair Market Value will be the closing sales price on the last preceding date for which such quotation exists.

(iii) In the absence of such markets for the Common Stock, the Fair Market Value will be determined by the Board in good faith and in a manner that complies with Sections 409A and 422 of the Code.

(t) "***Incentive Stock Option***" means an Option that qualifies as an "incentive stock option" within the meaning of Section 422 of the Code and the regulations promulgated thereunder.

(u) "***Nonstatutory Stock Option***" means an Option that does not qualify as an Incentive Stock Option.

(v) "***Officer***" means any person designated by the Company as an officer.

(w) "***Option***" means an Incentive Stock Option or a Nonstatutory Stock Option to purchase shares of Common Stock granted pursuant to the Plan.

(x) "***Option Agreement***" means a written agreement between the Company and an Optionholder evidencing the terms and conditions of an Option grant. Each Option Agreement shall be subject to the terms and conditions of the Plan.

(y) "***Optionholder***" means a person to whom an Option is granted pursuant to the Plan or, if applicable, such other person who holds an outstanding Option.

(z) "***Own***," "***Owned***," "***Owner***," "***Ownership***" A person or Entity shall be deemed to "Own," to have "Owned," to be the "Owner" of, or to have acquired "Ownership" of securities if such person or Entity, directly or indirectly, through any contract, arrangement, understanding, relationship or otherwise, has or shares voting power, which includes the power to vote or to direct the voting, with respect to such securities.

(aa) "***Participant***" means a person to whom a Stock Award is granted pursuant to the Plan or, if applicable, such other person who holds an outstanding Stock Award.

(bb) "***Plan***" means this Akcea Therapeutics, Inc. 2015 Equity Incentive Plan.

(cc) "***Restricted Stock Award***" means an award of shares of Common Stock which is granted pursuant to the terms and conditions of Section 6(a).

(dd) "***Restricted Stock Award Agreement***" means a written agreement between the Company and a holder of a Restricted Stock Award evidencing the terms and conditions of a Restricted Stock Award. Each Restricted Stock Award Agreement shall be subject to the terms and conditions of the Plan.

(ee) "***Restricted Stock Unit Award***" means a right to receive shares of Common Stock which is granted pursuant to the terms and conditions of Section 6(b).

(ff) "***Restricted Stock Unit Award Agreement***" means a written agreement between the Company and a holder of a Restricted Stock Unit Award evidencing the terms and conditions of a Restricted Stock Unit Award grant. Each Restricted Stock Unit Award Agreement shall be subject to the terms and conditions of the Plan.

(gg) "***Securities Act***" means the Securities Act of 1933, as amended.

(hh) "***Stock Appreciation Right***" means a right to receive the appreciation on Common Stock that is granted pursuant to the terms and conditions of Section 6(c).

(ii) "***Stock Appreciation Right Agreement***" means a written agreement between the Company and a holder of a Stock Appreciation Right evidencing the terms and conditions of a Stock Appreciation Right grant. Each Stock Appreciation Right Agreement shall be subject to the terms and conditions of the Plan.

(jj) "***Stock Award***" means any right to receive Common Stock granted under the Plan, including an Incentive Stock Option, a Nonstatutory Stock Option, a Restricted Stock Award, a Restricted Stock Unit Award, or a Stock Appreciation Right.

(kk) "***Stock Award Agreement***" means a written agreement between the Company and a Participant evidencing the terms and conditions of a Stock Award grant. Each Stock Award Agreement shall be subject to the terms and conditions of the Plan.

(ll) "***Subsidiary***" means, with respect to the Company, (i) any corporation of which more than fifty percent (50%) of the outstanding capital stock having ordinary voting power to elect a majority of the board of directors of such corporation (irrespective of whether, at the time, stock of any other class or classes of such corporation shall have or might have voting power by reason of the happening of any contingency) is at the time, directly or indirectly, Owned by the Company, and (ii) any partnership, limited liability company or other entity in which the Company has a direct or indirect interest (whether in the form of voting or participation in profits or capital contribution) of more than fifty percent (50%) .

(mm) "***Ten Percent Stockholder***" means a person who Owns (or is deemed to Own pursuant to Section 424(d) of the Code) stock possessing more than ten percent (10%) of the total combined voting power of all classes of stock of the Company or any Affiliate.

EXHIBIT 31.1

CERTIFICATION

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 quarterly 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 quarterly report;

3. Based on my knowledge, the condensed consolidated financial statements, and other financial information included in this quarterly report, fairly present in all material respects the financial condition, condensed consolidated results of operations and condensed consolidated cash flows of the registrant as of, and for, the periods presented in this quarterly report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, 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 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 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 4, 2018

/s/ PAULA SOTEROPOULOS

Paula Soteropoulos
Chief Executive Officer

EXHIBIT 31.2

CERTIFICATION

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 quarterly 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 quarterly report;

3. Based on my knowledge, the condensed consolidated financial statements, and other financial information included in this quarterly report, fairly present in all material respects the financial condition, condensed consolidated results of operations and condensed consolidated cash flows of the registrant as of, and for, the periods presented in this quarterly report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, 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 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 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 4, 2018

/s/ MICHAEL MACLEAN

Michael MacLean
Chief Financial Officer

Exhibit 32.1

CERTIFICATION

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, 2018, 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 of the Company at the end of the period covered by the Periodic Report and the results of operations of the Company for the period covered by the Periodic Report.

Dated: May 4, 2018

/s/ PAULA SOTEROPOULOS
Paula Soteropoulos
Chief Executive Officer

/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.