UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

Form 10-Q

(Mark One)

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

For the Quarterly Period Ended September 30, 2019

OR

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

For the transition period from _____ to _____

Commission file number 000-19125

Ionis Pharmaceuticals, Inc.

(Exact name of Registrant as specified in its charter)

Delaware	**33-0336973**
(State or other jurisdiction of incorporation or organization)	(IRS Employer Identification No.)
2855 Gazelle Court, Carlsbad, California	**92010**
(Address of Principal Executive Offices)	(Zip Code)

760-931-9200

(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Name of each exchange on which registered	Trading symbol
Common Stock, $.001 Par Value	The Nasdaq Stock Market LLC	"IONS"

Securities registered pursuant to Section 12(g) of the Act: **None**

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

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☒ No ☐

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

Large Accelerated Filer ☒	Accelerated Filer ☐
Non-accelerated Filer ☐	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 7(a)(2)(B) of the Securities 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 voting common stock outstanding as of October 31, 2019 was 140,663,254.

IONIS PHARMACEUTICALS, INC.
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TRADEMARKS

"Ionis," the Ionis logo, and other trademarks or service marks of Ionis Pharmaceuticals, Inc. appearing in this report are the property of Ionis Pharmaceuticals, Inc. "Akcea," the Akcea logo, and other trademarks or service marks appearing in this report, including TEGSEDI (inotersen) and WAYLIVRA (volanesorsen), 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.

IONIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED BALANCE SHEETS
(in thousands, except share data)

	September 30, 2019 (Unaudited)	December 31, 2018
ASSETS		
Current assets:		
Cash and cash equivalents	$ 247,939	$ 278,820
Short-term investments	1,972,891	1,805,252
Contracts receivable	49,077	12,759
Inventories	19,375	8,582
Other current assets	118,809	102,473
Total current assets	2,408,091	2,207,886
Property, plant and equipment, net	148,717	132,160
Patents, net	26,985	24,032
Long-term deferred tax assets	284,997	290,796
Deposits and other assets	26,199	12,910
Total assets	$ 2,894,989	$ 2,667,784
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 13,146	$ 28,660
Accrued compensation	24,404	29,268
Accrued liabilities	52,615	47,503
Income taxes payable	1,945	858
Current portion of long-term obligations	2,060	13,749
Current portion of deferred contract revenue	137,607	160,256
Total current liabilities	231,777	280,294
Long-term deferred contract revenue	492,979	567,359
1 percent convertible senior notes	596,355	568,215
Long-term obligations, less current portion	16,016	4,914
Long-term mortgage debt	59,896	59,842
Total liabilities	1,397,023	1,480,624
Stockholders' equity:		
Common stock, $0.001 par value; 300,000,000 shares authorized, 140,636,397 and 137,928,828 shares issued and outstanding at September 30, 2019 (unaudited) and December 31, 2018, respectively	141	138
Additional paid-in capital	2,219,090	2,047,250
Accumulated other comprehensive loss	(25,375)	(32,016)
Accumulated deficit	(857,563)	(967,293)
Total Ionis stockholders' equity	1,336,293	1,048,079
Noncontrolling interest in Akcea Therapeutics, Inc.	161,673	139,081
Total stockholders' equity	1,497,966	1,187,160
Total liabilities and stockholders' equity	$ 2,894,989	$ 2,667,784

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF OPERATIONS
(in thousands, except for per share amounts)
(Unaudited)

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2019	2018	2019	2018
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 81,672	$ 70,010	$ 211,884	$ 167,743
Product sales, net	11,945	—	28,563	—
Licensing and other royalty revenue	2,082	12,746	11,638	14,232
Total commercial revenue	95,699	82,756	252,085	181,975
Research and development revenue under collaborative agreements	72,193	62,639	376,833	225,584
Total revenue	167,892	145,395	628,918	407,559
Expenses:				
Cost of products sold	967	—	3,373	—
Research, development and patent	104,366	95,255	316,948	301,153
Selling, general and administrative	60,036	68,712	203,368	178,563
Total operating expenses	165,369	163,967	523,689	479,716
Income (loss) from operations	2,523	(18,572)	105,229	(72,157)
Other income (expense):				
Investment income	13,136	9,963	39,015	18,711
Interest expense	(12,002)	(11,282)	(35,404)	(33,332)
Other income (expenses)	(140)	(22)	(332)	(145)
Income (loss) before income tax (expense) benefit	3,517	(19,913)	108,508	(86,923)
Income tax (expense) benefit	14,915	(452)	(9,204)	(824)
Net income (loss)	18,432	(20,365)	99,304	(87,747)
Net loss attributable to noncontrolling interest in Akcea Therapeutics, Inc.	7,732	15,806	10,426	41,412
Net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ 26,163	$ (4,559)	$ 109,730	$ (46,335)
Basic net income (loss) per share	$ 0.19	$ (0.03)	$ 0.81	$ (0.33)
Shares used in computing basic net income (loss) per share	140,551	137,346	139,800	130,507
Diluted net income (loss) per share	$ 0.18	$ (0.03)	$ 0.79	$ (0.33)
Shares used in computing diluted net income (loss) per share	143,408	137,346	142,821	130,507

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF COMPREHENSIVE INCOME (LOSS)
(in thousands)
(Unaudited)

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2019	**2018**	**2019**	**2018**
Net income (loss)	$ 18,432	$ (20,365)	$ 99,304	$ (87,747)
Unrealized gains (losses) on debt securities, net of tax	(1,110)	133	6,666	(834)
Currency translation adjustment	(13)	(31)	(25)	61
Comprehensive income (loss)	17,309	(20,263)	105,945	(88,520)
Comprehensive loss attributable to noncontrolling interests	(7,729)	(13,943)	(10,423)	(38,005)
Comprehensive income (loss) attributable to Ionis Pharmaceuticals, Inc. stockholders	$ 25,038	$ (6,320)	$ 116,368	$ (50,515)

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
Three Months Ended September 30, 2018 and 2019
(In thousands)
(Unaudited)

Description	Common Stock Shares	Common Stock Amount	Additional Paid in Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Ionis Stockholders' Equity	Noncontrolling Interest in Akcea Therapeutics, Inc.	Total Stockholders' Equity
Balance at June 30, 2018	137,157	$ 137	$ 2,011,561	$ (32,634)	$ (1,282,810)	$ 696,254	$ 121,181	$ 817,436
Net loss attributable to Ionis Pharmaceuticals, Inc. common stockholders	—	—	—	—	(4,559)	(4,559)	—	(4,559)
Change in unrealized gains (losses), net of tax	—	—	—	133	—	133	—	133
Foreign currency translation	—	—	—	(31)	—	(31)	—	(31)
Issuance of common stock in connection with employee stock plans	350	1	6,225	—	—	6,226	—	6,226
Stock-based compensation expense	—	—	34,883	—	—	34,883	—	34,883
Noncontrolling interest in Akcea Therapeutics, Inc	—	—	(22,356)	—	—	(22,356)	8,413	(13,943)
Balance at September 30, 2018	137,507	$ 138	$ 2,030,313	$ (32,532)	$ (1,287,369)	$ 710,550	$ 129,594	$ 840,144
Balance at June 30, 2019	140,393	$ 140	$ 2,177,222	$ (24,252)	$ (883,726)	$ 1,269,384	$ 187,818	$ 1,457,202
Net income attributable to Ionis Pharmaceuticals, Inc. common stockholders	—	—	—	—	26,163	26,163	—	26,163
Change in unrealized gains (losses), net of tax	—	—	—	(1,110)	—	(1,110)	—	(1,110)
Foreign currency translation	—	—	—	(13)	—	(13)	—	(13)
Issuance of common stock in connection with employee stock plans	255	1	10,130	—	—	10,131	—	10,131
Stock-based compensation expense	—	—	24,126	—	—	24,126	—	24,126
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(11)	—	(10,804)	—	—	(10,804)	—	(10,804)
Noncontrolling interest in Akcea Therapeutics, Inc.	—	—	18,416	—	—	18,416	(26,145)	(7,729)
Balance at September 30, 2019	140,637	$ 141	$ 2,219,090	$ (25,375)	$ (857,563)	$ 1,336,293	$ 161,673	$ 1,497,966

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
Nine Months Ended September 30, 2018 and 2019
(In thousands)
(Unaudited)

Description	Common Stock Shares	Common Stock Amount	Additional Paid in Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Ionis Stockholders' Equity	Noncontrolling Interest in Akcea Therapeutics, Inc.	Total Stockholders' Equity
Balance at December 31, 2017	124,976	$ 125	$ 1,553,681	$ (31,759)	$ (1,241,034)	$ 281,013	$ 84,267	$ 365,280
Net loss attributable to Ionis Pharmaceuticals, Inc. common stockholders	—	—	—	—	(46,335)	(46,335)	—	(46,335)
Change in unrealized gains (losses), net of tax	—	—	—	(834)	—	(834)	—	(834)
Foreign currency translation	—	—	—	61	—	61	—	61
Biogen stock purchase	11,502	11	447,954	—	—	447,965	—	447,965
Issuance of common stock in connection with employee stock plans	1,029	2	14,800	—	—	14,802	—	14,802
Stock-based compensation expense	—	—	97,210	—	—	97,210	—	97,210
Noncontrolling interest in Akcea Therapeutics, Inc	—	—	(83,332)	—	—	(83,332)	45,327	(38,005)
Balance at September 30, 2018	137,507	$ 138	$ 2,030,313	$ (32,532)	$ (1,287,369)	$ 710,550	$ 129,594	$ 840,144
Balance at December 31, 2018	137,929	$ 138	$ 2,047,250	$ (32,016)	$ (967,293)	$ 1,048,079	$ 139,081	$ 1,187,160
Net income attributable to Ionis Pharmaceuticals, Inc. common stockholders	—	—	—	—	109,730	109,730	—	109,730
Change in unrealized gains (losses), net of tax	—	—	—	6,666	—	6,666	—	6,666
Foreign currency translation	—	—	—	(25)	—	(25)	—	(25)
Issuance of common stock in connection with employee stock plans	2,855	3	112,132	—	—	112,135	—	112,135
Stock-based compensation expense	—	—	111,564	—	—	111,564	—	111,564
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(147)	—	(18,841)	—	—	(18,841)	—	(18,841)
Noncontrolling interest in Akcea Therapeutics, Inc.	—	—	(33,015)	—	—	(33,015)	22,592	(10,423)
Balance at September 30, 2019	140,637	$ 141	$ 2,219,090	$ (25,375)	$ (857,563)	$ 1,336,293	$ 161,673	$ 1,497,966

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF CASH FLOWS
(in thousands)
(Unaudited)

	Nine Months Ended September 30,	
	2019	**2018**
Operating activities:		
Net income (loss)	$ 99,304	$ (87,747)
Adjustments to reconcile net loss to net cash provided by operating activities:		
Depreciation	9,345	7,650
Amortization of right-of-use operating lease assets	1,433	—
Amortization of patents	1,139	1,356
Amortization of premium (discount) on investments, net	(7,064)	791
Amortization of debt issuance costs	1,448	1,343
Amortization of convertible senior notes discount	26,747	24,781
Stock-based compensation expense	111,564	97,210
Non-cash losses related to patents, licensing and property, plant and equipment	216	482
Provision for deferred income taxes	4,103	—
Changes in operating assets and liabilities:		
Contracts receivable	(33,716)	48,223
Inventories	(6,606)	1,604
Other current and long-term assets	(23,377)	(26,573)
Accounts payable	(18,764)	(13,606)
Accrued compensation	(4,864)	(892)
Accrued liabilities and deferred rent	3,909	(14,392)
Deferred contract revenue	(97,029)	447,168
Net cash provided by operating activities	67,788	487,398
Investing activities:		
Purchases of short-term investments	(1,617,726)	(1,156,335)
Proceeds from short-term investments	1,465,600	568,517
Purchases of property, plant and equipment	(23,143)	(12,221)
Acquisition of licenses and other assets, net	(4,196)	(3,317)
Net cash used in investing activities	(179,465)	(603,356)
Financing activities:		
Proceeds from equity awards	112,137	18,254
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(18,841)	—
Proceeds from the issuance of common stock to Biogen	—	447,965
Principal payments on debt obligations	(12,500)	—
Net cash provided by financing activities	80,796	466,219
Net increase in cash and cash equivalents	(30,881)	350,261
Cash and cash equivalents at beginning of period	278,820	129,630
Cash and cash equivalents at end of period	$ 247,939	$ 479,891
Supplemental disclosures of cash flow information:		
Interest paid	$ 5,474	$ 5,434
Income taxes paid	$ 9,037	$ —
Supplemental disclosures of non-cash investing and financing activities:		
Right-of-use assets obtained in exchange for lease liabilities	$ 14,178	$ —
Amounts accrued for capital and patent expenditures	$ 3,251	$ 2,296
Purchases of property, plant and equipment included in long-term obligations	$ —	$ 3,596

See accompanying notes.

1. Basis of Presentation

We prepared the unaudited interim condensed consolidated financial statements for the three and nine months ended September 30, 2019 and 2018 on the same basis as the audited financial statements for the year ended December 31, 2018. We included all normal recurring adjustments in the financial statements, which we considered necessary for a fair presentation of our financial position at such dates and our operating results and cash flows for those periods. 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 for the year ended December 31, 2018 included in our Annual Report on Form 10-K filed with the Securities and Exchange Commission, or SEC.

In the condensed consolidated financial statements, we included the accounts of Ionis Pharmaceuticals, Inc. and the consolidated results of our majority owned affiliate, Akcea Therapeutics, Inc. and its wholly owned subsidiaries. We formed Akcea in December 2014. In July 2017, Akcea completed an initial public offering, or IPO, and therefore, beginning in July 2017, we no longer owned 100 percent of Akcea. In the first quarter of 2019, we received 2.8 million shares of Akcea common stock as payment for the sublicense fee Akcea owed us when Novartis licensed AKCEA-APO(a)-L_{Rx}. At September 30, 2019, our ownership was approximately 75 percent. In the fourth quarter of 2019, we expect to receive an additional 6.9 million shares of Akcea common stock as payment for the sublicense fee Akcea owes us for Pfizer's license of AKCEA-ANGPTL3-L_{Rx}. We reflect changes in our ownership of Akcea in our financial statements in the period the change occurs. Refer to the section titled "Noncontrolling Interest in Akcea" in Note 2, *Significant Accounting Policies*, for further information related to our accounting for our investment in Akcea.

Unless the context requires otherwise, "Ionis", "Company," "we," "our," and "us" refers to Ionis Pharmaceuticals, Inc. and its majority owned affiliate, Akcea Therapeutics, Inc. and its wholly owned subsidiaries.

2. Significant Accounting Policies

Revenue Recognition

Our Revenue Sources

We generally recognize revenue when we have satisfied all contractual obligations and are reasonably assured of collecting the resulting receivable. We are often entitled to bill our customers and receive payment from our customers in advance of recognizing the revenue. In the instances in which we have received payment from our customers in advance of recognizing revenue, we include the amounts in deferred revenue on our consolidated balance sheet.

Commercial Revenue: SPINRAZA royalties and Licensing and other royalty revenue

We earn commercial revenue primarily in the form of royalty payments on net sales of SPINRAZA. We will also recognize as commercial revenue future sales milestone payments and royalties we earn under our partnerships.

Commercial Revenue: Product sales, net

We added product sales from TEGSEDI to our commercial revenue in the fourth quarter of 2018 and we added product sales from WAYLIVRA to our commercial revenue in the third quarter of 2019. In the U.S., we distribute TEGSEDI through an exclusive distribution agreement with a third-party logistics company, or 3PL, that takes title to TEGSEDI. The 3PL is our sole customer in the U.S. The 3PL then distributes TEGSEDI to a specialty pharmacy and a specialty distributor, which we collectively refer to as wholesalers, who then distribute TEGSEDI to health care providers and patients. In Europe, prior to the third quarter of 2019 we distributed TEGSEDI through a non-exclusive distribution model with a 3PL that takes title to TEGSEDI. The 3PL was our sole customer in Europe. The 3PL in Europe then distributed TEGSEDI to hospitals and pharmacies. In the third quarter of 2019, we entered into a distribution arrangement with a 3PL and began to sell both TEGSEDI and WAYLIVRA directly to hospitals and pharmacies in Europe.

Research and development revenue under collaborative agreements

We often enter into collaboration agreements to license and sell our technology on an exclusive or non-exclusive basis. Our collaboration agreements typically contain multiple elements, or performance obligations, including technology licenses or options to obtain technology licenses, research and development, or R&D, services, and manufacturing services.

We provide details about our collaboration agreements in Note 7, *Collaborative Arrangements and Licensing Agreements*, in our Annual Report on Form 10-K for the year ended December 31, 2018. Under each collaboration note we discuss our specific revenue recognition conclusions, including our significant performance obligations under each collaboration.

Steps to Recognize Revenue

We use a five-step process to determine the amount of revenue we should recognize and when we should recognize it. The five step process is as follows:

1. Identify the contract

Accounting rules require us to first determine if we have a contract with our partner, including confirming that we have met each of the following criteria:

- We and our partner approved the contract and we are both committed to perform our obligations;
- We have identified our rights, our partner's rights and the payment terms;
- We have concluded that the contract has commercial substance, meaning that the risk, timing, or amount of our future cash flows is expected to change as a result of the contract; and
- We believe collectability is probable.

2. Identify the performance obligations

We next identify the distinct goods and services we are required to provide under the contract. Accounting rules refer to these as our performance obligations. We typically have only one performance obligation at the inception of a contract, which is to perform R&D services.

Often times we enter into a collaboration agreement in which we provide our partner with an option to license a medicine in the future. We may also provide our partner with an option to request that we provide additional goods or services in the future, such as active pharmaceutical ingredient, or API. We evaluate whether these options are material rights at the inception of the agreement. If we determine an option is a material right, we will consider the option a separate performance obligation. Historically, we have concluded that the options we grant to license a medicine in the future or to provide additional goods and services as requested by our partner are not material rights. These items are contingent upon future events that may not occur. When a partner exercises its option to license a medicine or requests additional goods or services, then we identify a new performance obligation for that item.

In some cases, we deliver a license at the start of an agreement. If we determine that our partner has full use of the license and we do not have any additional material performance obligations related to the license after delivery, then we consider the license to be a separate performance obligation.

3. Determine the transaction price

We then determine the transaction price by reviewing the amount of consideration we are eligible to earn under the collaboration agreement, including any variable consideration. Under our collaboration agreements, consideration typically includes fixed consideration in the form of an upfront payment and variable consideration in the form of potential milestone payments, license fees and royalties. At the start of an agreement, our transaction price usually consists of only the upfront payment. We do not typically include any payments we may receive in the future in our initial transaction price because the payments are not probable and are contingent on certain events. We reassess the total transaction price at each reporting period to determine if we should include additional payments in the transaction price.

Milestone payments are our most common type of variable consideration. We recognize milestone payments using the most likely amount method because we will either receive the milestone payment or we will not, which makes the potential milestone payment a binary event. The most likely amount method requires us to determine the likelihood of earning the milestone payment. We include a milestone payment in the transaction price once it is probable we will achieve the milestone event. Most often, we do not consider our milestone payments probable until we or our partner achieve the milestone event because the majority of our milestone payments are contingent upon events that are not within our control and are usually based on scientific progress. For example, in the first quarter of 2019, we earned $35 million in milestone payments from Roche when Roche dosed the first patient in the Phase 3 study of IONIS-HTT_{Rx} (RG6042). We did not consider these milestone payments probable until Roche achieved the milestone event because the dosing of a patient was a contingent event that was not within our control. We recognized the milestone payments in full in the period the milestone event was achieved because we did not have any remaining performance obligations related to the milestone payments.

4. Allocate the transaction price

Next, we allocate the transaction price to each of our performance obligations. When we have to allocate the transaction price to more than one performance obligation, we make estimates of the relative stand-alone selling price of each performance obligation because we do not typically sell our goods or services on a stand-alone basis. We then allocate the transaction price to each performance obligation based on the relative stand-alone selling price.

We may engage a third party, independent valuation specialist to assist us with determining a stand-alone selling price for collaborations in which we deliver a license at the start of an agreement. We estimate the stand-alone selling price of these licenses using valuation methodologies, such as the relief from royalty method. Under this method, we estimate the amount of income, net of taxes, for the license. We then discount the projected income to present value. The significant inputs we use to determine the projected income of a license could include:

- Estimated future product sales;
- Estimated royalties on future product sales;
- Contractual milestone payments;
- Expenses we expect to incur;
- Income taxes; and
- A discount rate.

We typically estimate the selling price of R&D services by using our internal estimates of the cost to perform the specific services. The significant inputs we use to determine the selling price of our R&D services include:

- The number of internal hours we estimate we will spend performing these services;
- The estimated cost of work we will perform;
- The estimated cost of work that we will contract with third parties to perform; and
- The estimated cost of API we will use.

For purposes of determining the stand-alone selling price of the R&D services we perform and the API we will deliver, accounting guidance requires us to include a markup for a reasonable profit margin.

We do not reallocate the transaction price after the start of an agreement to reflect subsequent changes in stand-alone selling prices.

5. Recognize revenue

We recognize revenue in one of two ways, over time or at a point in time. We recognize revenue over time when we are executing on our performance obligation over time and our partner receives benefit over time. For example, we recognize revenue over time when we provide R&D services. We recognize revenue at a point in time when our partner receives full use of an item at a specific point in time. For example, we recognize revenue at a point in time when we deliver a license or API to a partner.

For R&D services that we recognize over time, we measure our progress using an input method. The input methods we use are based on the effort we expend or costs we incur toward the satisfaction of our performance obligation. We estimate the amount of effort we expend, including the time we estimate it will take us to complete the activities, or costs we incur in a given period, relative to the estimated total effort or costs to satisfy the performance obligation. This results in a percentage that we multiply by the transaction price to determine the amount of revenue we recognize each period. This approach requires us to make numerous estimates and use significant judgement. If our estimates or judgements change over the course of the collaboration, they may affect the timing and amount of revenue that we recognize in the current and future periods. For example, in the third quarter of 2019, we updated our estimate of the total effort we expect to expend to satisfy our performance obligation under our 2013 Strategic Neurology collaboration with Biogen. As of September 30, 2019, we have completed a significant portion of the research and development services. We expect to complete the remainder of our services in 2020. As a result of our change in estimate, in the third quarter of 2019, we recorded a cumulative catch up adjustment of $16.5 million to decrease revenue. We expect to complete the remainder of our services in 2020. Refer to Note 7, *Collaborative Arrangements and Licensing Agreements*, for further discussion of the cumulative catch up adjustment we made.

The following are examples of when we typically recognize revenue based on the types of payments we receive.

Commercial Revenue: SPINRAZA royalties and Licensing and other royalty revenue

We recognize royalty revenue in the period in which the counterparty sells the related product, which in certain cases may require us to estimate our royalty revenue. We recognize royalties from SPINRAZA sales in the period in which Biogen records the sale of SPINRAZA.

Commercial Revenue: Product sales, net

We recognize product sales in the period when our customer obtains control of our products, which occurs at a point in time upon transfer of title to the customer. We classify payments to customers or other parties in the distribution channel for services that are distinct and priced at fair value as selling, general and administrative expenses in our condensed consolidated statements of operations. Otherwise, payments to customers or other parties in the distribution channel that do not meet those criteria are classified as a reduction of revenue, as discussed further below. We exclude from revenues taxes collected from customers relating to product sales and remitted to governmental authorities.

Reserves for Product sales

We record product sales at our net sales price, or transaction price. We include in our transaction price estimated reserves for discounts, returns, chargebacks, rebates, co-pay assistance and other allowances that we offer within contracts between us and our customers, wholesalers, health care providers and other indirect customers. We estimate our reserves using the amounts we have earned or what we can claim on the associated sales. We classify our reserves as a reduction of accounts receivable when we are not required to make a payment or as a current liability when we are required to make a payment. In certain cases, our estimates include a range of possible outcomes that are probability-weighted for relevant factors such as our historical experience, current contractual and statutory requirements, specific known market events and trends, industry data and forecasted customer buying and payment patterns. Overall, our reserves reflect our best estimates under the terms of our respective contracts. When calculating our reserves and related product sales, we only recognize amounts to the extent that we consider it probable that we would not have to reverse in a future period a significant amount of the cumulative sales we previously recognized. The actual amounts we receive may ultimately differ from our reserve estimates. If actual amounts in the future vary from our estimates, we will adjust these estimates, which would affect our net product sales in the respective period.

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

Chargebacks: In the U.S., we estimate obligations resulting from contractual commitments with the government and other entities to sell products to qualified healthcare providers at prices lower than the list prices charged to our U.S. customer. Our U.S. customer charges us for the difference between what it pays for the product and the selling price to the qualified healthcare providers. We also estimate the amount of chargebacks related to our estimated product remaining in the distribution channel at the end of the reporting period that we expect our customer to sell to healthcare providers in future periods. We record reserves for these chargebacks related to product sales to our U.S. customer during the reporting period.

Government rebates: We are subject to discount obligations under government programs, including Medicaid and Medicare programs in the U.S. and we record reserves for government rebates based on statutory discount rates and estimated utilization. We estimate Medicaid and Medicare rebates based on a range of possible outcomes that are probability-weighted for the estimated payer mix. We record these reserves as an accrued liability on our condensed consolidated balance sheet with a corresponding offset reducing our product sales in the same period we recognize the related sale. For Medicare, we also estimate the number of patients in the prescription drug coverage gap for whom we will owe an additional liability under the Medicare Part D program. On a quarterly basis, we update our estimates and record any adjustments in the period that we identify the adjustments.

Trade discounts: We provide customary invoice discounts on product sales to our U.S. customer for prompt payment. We record this discount as a reduction of product sales in the period in which we recognize the related product revenue.

Distribution services: We receive and pay for various distribution services from our U.S. and EU customers and wholesalers in the U.S. For services we receive that are either not distinct from the sale of the product or for which we cannot reasonably estimate the fair value, we classify the costs for such services as a reduction of product sales. To the extent that the services we receive are distinct from the sale of the product, we classify the costs for such services as selling, general and administration, or SG&A, expenses.

Product returns: Our U.S. customer has return rights and the wholesalers have limited return rights primarily related to the product's expiration date. We estimate the amount of product sales that our customer may return. We record our return estimate as an accrued refund liability on our condensed consolidated balance sheet with a corresponding offset reducing our product sales in the same period we recognize the related sale. Based on our distribution model for product sales, contractual inventory limits with our customer and wholesalers and the price of the product, we believe we will have minimal returns. Our EU customers only take title to the product after they receive an order from a hospital or pharmacy and therefore they do not maintain excess inventory levels of our products. Accordingly, we have limited return risk in the EU and we do not estimate returns in the EU.

Other incentives: In the U.S., we estimate reserves for other incentives including co-payment assistance we provide to patients with commercial insurance who have coverage and reside in states that allow co-payment assistance. We record a reserve for the amount we estimate we will pay for co-payment assistance. We base our reserve on the number of estimated claims and our estimate of the cost per claim related to product sales that we have recognized as revenue. We record our other incentive reserve estimates as an accrued liability on our condensed consolidated balance sheet with a corresponding offset reducing our product sales in the same period we recognize the related sale.

Research and development revenue under collaboration agreements:

Upfront payments

When we enter into a collaboration agreement with an upfront payment, we typically record the entire upfront payment as deferred revenue if our only performance obligation is for R&D services we will provide in the future. We amortize the upfront payment into revenue as we perform the R&D services. For example, under our collaboration agreement with Roche to develop IONIS-FB-L_{Rx} for the treatment of complement-mediated diseases, we received a $75 million upfront payment in the fourth quarter of 2018. We allocated the upfront payment to our single performance obligation, R&D services. We are amortizing the $75 million upfront payment using an input method over the estimated period of time we are providing R&D services.

Milestone payments

We are required to include additional consideration in the transaction price when it is probable. We typically include milestone payments for R&D services in the transaction price when they are achieved. We include these milestone payments when they are achieved because there is considerable uncertainty in the research and development processes that trigger these payments under our collaboration agreements. Similarly, we include approval milestone payments in the transaction price once the medicine is approved by the applicable regulatory agency. We will recognize sales-based milestone payments in the period in which we achieve the milestone under the sales-based royalty exception allowed under accounting rules.

We recognize milestone payments that relate to an ongoing performance obligation over our period of performance. For example, in the second quarter of 2019, we achieved a $7.5 million milestone payment from Biogen when we advanced a new target for an unidentified neurological disease under our 2018 strategic neurology collaboration. We added this payment to the transaction price and allocated it to our R&D services performance obligation. We are recognizing revenue related to this milestone payment over our estimated period of performance.

Conversely, we recognize in full those milestone payments that we earn based on our partners' activities when our partner achieves the milestone event and we do not have a performance obligation. For example, in the third quarter of 2019, we recognized an $8 million milestone payment when Biogen initiated a Phase 1/2 study of IONIS-$LRRK2_{Rx}$ (BIIB094) for the treatment of people with Parkinson's disease. We concluded that the milestone payment was not related to our R&D services performance obligation. Therefore, we recognized the milestone payment in full in the third quarter of 2019.

License fees

We generally recognize as revenue the total amount we determine to be the stand-alone selling price of a license when we deliver the license to our partner. This is because our partner has full use of the license and we do not have any additional performance obligations related to the license after delivery. For example, in the third quarter of 2019, we earned a $25 million license fee when GSK licensed our HBV program from us.

Sublicense fees

We recognize sublicense fee revenue in the period in which a party, who has already licensed our technology, further licenses the technology to another party because we do not have any performance obligations related to the sublicense. For example, in the second quarter of 2019, we earned a $20 million sublicense fee when Alnylam Pharmaceuticals sublicensed our technology to Regeneron Pharmaceuticals.

Amendments to agreements

From time to time we amend our collaboration agreements. When this occurs, we are required to assess the following items to determine the accounting for the amendment:

1) If the additional goods and/or services are distinct from the other performance obligations in the original agreement; and
2) If the goods and/or services are at a stand-alone selling price.

If we conclude the goods and/or services in the amendment are distinct from the performance obligations in the original agreement and at a stand-alone selling price, we account for the amendment as a separate agreement. If we conclude the goods and/or services are not distinct and at their stand-alone selling price, we then assess whether the remaining goods or services are distinct from those already provided. If the goods and/or services are distinct from what we have already provided, then we allocate the remaining transaction price from the original agreement and the additional transaction price from the amendment to the remaining goods and/or services. If the goods and/or services are not distinct from what we have already provided, we update the transaction price for our single performance obligation and recognize any change in our estimated revenue as a cumulative adjustment.

For example, in May 2015, we entered into an exclusive license agreement with Bayer to develop and commercialize IONIS-FXI$_{Rx}$ for the prevention of thrombosis. As part of the agreement, Bayer paid us a $100 million upfront payment. At the onset of the agreement, we were responsible for completing a Phase 2 study of IONIS-FXI$_{Rx}$ in people with end-stage renal disease on hemodialysis and for providing an initial supply of API. In February 2017, we amended our agreement with Bayer to advance IONIS-FXI$_{Rx}$ and to initiate development of IONIS-FXI-L$_{Rx}$, which Bayer licensed. As part of the 2017 amendment, Bayer paid us $75 million. We are also eligible to receive milestone payments and tiered royalties on gross margins of IONIS-FXI$_{Rx}$ and IONIS-FXI-L$_{Rx}$. Under the 2017 amendment, we concluded we had a new agreement with three performance obligations. These performance obligations were to deliver the license of IONIS-FXI-L$_{Rx}$, to provide R&D services and to deliver API. We allocated the $75 million transaction price to these performance obligations. Refer to Note 7, *Collaborative Arrangements and Licensing Agreements*, for further discussion of our accounting treatment for our Bayer collaboration.

Multiple agreements

From time to time, we may enter into separate agreements at or near the same time with the same partner. We evaluate such agreements to determine whether we should account for them individually as distinct arrangements or whether the separate agreements should be combined and accounted for together. We evaluate the following to determine the accounting for the agreements:

- Whether the agreements were negotiated together with a single objective;
- Whether the amount of consideration in one contract depends on the price or performance of the other agreement; or
- Whether the goods and/or services promised under the agreements are a single performance obligation.

Our evaluation involves significant judgment to determine whether a group of agreements might be so closely related that accounting guidance requires us to account for them as a combined arrangement.

For example, in the second quarter of 2018, we entered into two separate agreements with Biogen at the same time: a new strategic neurology collaboration agreement and a stock purchase agreement, or SPA. We evaluated the Biogen agreements to determine whether we should treat the agreements separately or combine them. We considered that the agreements were negotiated concurrently and in contemplation of one another. Based on these facts and circumstances, we concluded that we should evaluate the provisions of the agreements on a combined basis.

Contracts Receivable

Our contracts receivable balance represents the amounts we have billed our partners or customers and that are due to us unconditionally for goods we have delivered or services we have performed. When we bill our partners or customers with payment terms based on the passage of time, we consider the contract receivable to be unconditional. We typically receive payment within one quarter of billing our partner or customer.

Unbilled SPINRAZA Royalties

Our unbilled SPINRAZA royalties represent our right to receive consideration from Biogen in advance of when we are eligible to bill Biogen for SPINRAZA royalties. We include these unbilled amounts in other current assets on our condensed consolidated balance sheet.

Deferred Revenue

We are often entitled to bill our customers and receive payment from our customers in advance of our obligation to provide services or transfer goods to our partners. In these instances, we include the amounts in deferred revenue on our condensed consolidated balance sheet. During the three months ended September 30, 2019 and 2018, we recognized $30.3 million and $37.2 million of revenue from amounts that were in our beginning deferred revenue balance for each respective period. During the nine months ended September 30, 2019 and 2018, we recognized $103.5 million and $80.4 million of revenue from amounts that were in our beginning deferred revenue balance for each respective period. For further discussion, refer to our revenue recognition policy above.

Cost of Products Sold

Our cost of products sold includes manufacturing costs, transportation and freight costs and indirect overhead costs associated with the manufacturing and distribution of our products. We also may include certain period costs related to manufacturing services and inventory adjustments in cost of products sold. Prior to obtaining regulatory approval of TEGSEDI in July 2018 and WAYLIVRA in May 2019, we expensed a significant portion of the costs we incurred to produce the supply for each medicine we are using in the commercial launch as research and development expense. We previously expensed $0.2 million and $0.5 million of costs to produce our products related to the product sales revenue we recognized in the three and nine months ended September 30, 2019, respectively.

Noncontrolling Interest in Akcea Therapeutics, Inc.

Prior to Akcea's IPO in July 2017, we owned 100 percent of Akcea. From the closing of Akcea's IPO in July 2017 through mid-April 2018, we owned approximately 68 percent of Akcea. In the second, third and fourth quarters of 2018, we received additional shares of Akcea's stock related to our license of TEGSEDI and AKCEA-TTR-L_{Rx} to Akcea, increasing our ownership percentage to approximately 75 percent. In the first quarter of 2019, we received 2.8 million shares of Akcea common stock as payment for the sublicense fee Akcea owed us when Novartis licensed AKCEA-APO(a)-L_{Rx}, increasing our ownership to approximately 76 percent at March 31, 2019. At September 30, 2019, our ownership in Akcea was approximately 75 percent. In the fourth quarter of 2019, we expect to receive an additional 6.9 million shares of Akcea common stock as payment for the sublicense fee Akcea owes us for Pfizer's license of AKCEA-ANGPTL3-L_{Rx}. We reflect changes in our ownership of Akcea in our financial statements as an adjustment to noncontrolling interest in the period the change occurs. The shares third parties own represent an interest in Akcea's equity that is not controlled by us. However, as we continue to maintain overall control of Akcea through our voting interest, we reflect the assets, liabilities and results of operations of Akcea in our condensed consolidated financial statements. We reflect the noncontrolling interest attributable to other owners of Akcea's common stock in a separate line on the statement of operations and a separate line within stockholders' equity in our condensed consolidated balance sheet. In addition, we record a noncontrolling interest adjustment to account for the stock options Akcea grants, which if exercised, will dilute our ownership in Akcea. This adjustment is a reclassification within stockholders' equity from additional paid-in capital to noncontrolling interest in Akcea equal to the amount of stock-based compensation expense Akcea had recognized.

Cash, Cash equivalents and Investments

We consider all liquid investments with maturities of three months or less when we purchase them to be cash equivalents. Our short-term investments have initial maturities of greater than three months from date of purchase. We classify our short-term debt investments as "available-for-sale" and carry them at fair market value based upon prices on the last day of the fiscal period for identical or similar items. We record unrealized gains and losses on debt securities as a separate component of comprehensive income (loss) and include net realized gains and losses in gain (loss) on investments. We use the specific identification method to determine the cost of securities sold.

We also have equity investments of less than 20 percent ownership in publicly and privately held biotechnology companies that we received as part of a technology license or partner agreement. At September 30, 2019, we held equity investments in two publicly held companies, ProQR Therapeutics N.V., or ProQR, and Antisense Therapeutics Limited, or ATL. We also held equity investments in four privately-held companies, Atlantic Pharmaceuticals Limited, Dynacure SAS, Seventh Sense Biosystems and Suzhou Ribo Life Science Co, Ltd.

Inventory Valuation

We reflect our inventory on our condensed consolidated balance sheet at the lower of cost or market value under the first-in, first-out method, or FIFO. We capitalize the costs of raw materials that we purchase for use in producing our medicines because until we use these raw materials they have alternative future uses. We include in inventory raw material costs for medicines that we manufacture for our partners under contractual terms and that we use primarily in our clinical development activities and drug products. We can use each of our raw materials in multiple products and, as a result, each raw material has future economic value independent of the development status of any single medicine. For example, if one of our medicines failed, we could use the raw materials for that medicine to manufacture our other medicines. We expense these costs as R&D expenses when we begin to manufacture API for a particular medicine if the medicine has not been approved for marketing by a regulatory agency.

We obtained the first regulatory approval for TEGSEDI in July 2018 and in May 2019 for WAYLIVRA. At September 30, 2019, our physical inventory for TEGSEDI and WAYLIVRA included API that we produced prior to when we obtained regulatory approval. As such, this API has no cost basis as we had previously expensed the costs as R&D expenses.

We review our inventory periodically and reduce the carrying value of items we consider to be slow moving or obsolete to their estimated net realizable value based on forecasted demand compared to quantities on hand. We consider several factors in estimating the net realizable value, including shelf life of our inventory, alternative uses for our medicines in development and historical write-offs. We did not record any material inventory write-offs for the nine months ended September 30, 2019. Total inventory was $19.4 million and $8.6 million as of September 30, 2019 and December 31, 2018, respectively.

Leases

Topic 842 Adoption

In February 2016, the Financial Accounting Standards Board, or FASB, issued amended accounting guidance related to lease accounting. This guidance supersedes the lease requirements we previously followed in Accounting Standards Codification, or ASC, Topic 840, *Leases*, or Topic 840, and created a new lease accounting standard, Topic 842, *Leases*, or Topic 842. Under Topic 842, an entity will record on its balance sheet all leases with a term longer than one year. Further, an entity will record a liability with a value equal to the present value of payments it will make over the life of the lease (lease liability) and an asset representing the underlying leased asset (right-of-use asset). The new accounting guidance requires entities to determine if its leases are operating or financing leases. Entities will recognize expense for operating leases on a straight-line basis as an operating expense. If an entity determines a lease is a financing lease, it will record both interest and amortization expense and generally the expense will be higher in the earlier periods of the lease. We adopted Topic 842 on January 1, 2019 and adjusted our opening balance sheet on that date for our right-of-use operating lease assets and operating lease liabilities. At adoption, we recorded $13.5 million in right-of-use operating lease assets and $18.5 million in operating lease liabilities, of which we classified $2 million as a current liability. We adopted Topic 842 using the available practical expedients permitted under the transition guidance within the new standard, which among other things, allowed us to carry forward the historical lease classification of those leases we had in place as of January 1, 2019. The adoption did not have an impact on our condensed consolidated statement of operations.

Leases

We determine if an arrangement contains a lease at inception. We currently only have operating leases. We recognize a right-of-use operating lease asset and associated short- and long-term operating lease liability on our condensed consolidated balance sheet for operating leases greater than one year. Our right-of-use assets represent our right to use an underlying asset for the lease term and our lease liabilities represent our obligation to make lease payments arising from the lease arrangement. We recognize our right-of-use operating lease assets and lease liabilities based on the present value of the future minimum lease payments we will pay over the lease term. We determined the lease term at the inception of the lease, and in certain cases our lease term could include renewal options if we concluded we were reasonably certain that we will exercise the renewal option.

As our current leases do not provide an interest rate implicit in the lease, we used our or Akcea's incremental borrowing rate, based on the information available on the date we adopted Topic 842 or as of the lease inception date in determining the present value of future payments. Our right-of-use operating lease asset also includes any lease payments we made and excludes any tenant improvement allowances we received. We recognize rent expense for our minimum lease payments on a straight-line basis over the expected term of our lease. We recognize period expenses, such as common area maintenance expenses, in the period we incur the expense.

Research, Development and Patent Expenses

Our research and development expenses include wages, benefits, facilities, supplies, external services, clinical trial and manufacturing costs and other expenses that are directly related to our research and development operations. We expense research and development costs as we incur them. When we make payments for research and development services prior to the services being rendered, we record those amounts as prepaid assets on our condensed consolidated balance sheet and we expense them as the services are provided.

We capitalize costs consisting principally of outside legal costs and filing fees related to obtaining patents. We amortize patent costs over the useful life of the patent, beginning with the date the United States Patent and Trademark Office, or foreign equivalent, issues the patent. We review our capitalized patent costs regularly to ensure that they include costs for patents and patent applications that have future value. We evaluate patents and patent applications that we are not actively pursuing and write off any associated costs.

Income Taxes

We account for income taxes using the asset and liability method, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been recognized in our financial statements or tax returns. In addition, deferred tax assets are recorded for the future benefit of utilizing net operating losses and research and development credit carryforwards. We record a valuation allowance when necessary to reduce our net deferred tax assets to the amount expected to be realized.

On December 22, 2017, the U.S. government enacted comprehensive tax legislation commonly referred to as the Tax Cuts and Jobs Act of 2017, or the Tax Act. The Tax Act created a new requirement on global intangible low-taxed income, or GILTI, earned by foreign subsidiaries for tax years beginning on or after January 1, 2018. The GILTI provisions require foreign subsidiary earnings in excess of an allowable return on the foreign subsidiary's assets to be included in our U.S. income tax return. Under U.S. GAAP, we are permitted to make an accounting policy election to either treat taxes due on future inclusions in U.S. taxable income related to GILTI as a current-period expense when incurred or to factor such amounts into our measurement of deferred taxes. We have made the election to account for GILTI as a component of current taxes incurred rather than as a component of deferred taxes.

Long-lived Assets

We evaluate long-lived assets, which include property, plant and equipment, right-of-use operating lease assets and patent costs acquired from third parties, for impairment on at least a quarterly basis and whenever events or changes in circumstances indicate that we may not be able to recover the carrying amount of such assets.

Use of Estimates

The preparation of condensed consolidated financial statements in conformity with accounting principles generally accepted in the United States requires us to make estimates and assumptions that affect the amounts reported in our condensed consolidated financial statements and accompanying notes. Actual results could differ from those estimates.

Basic and Diluted Net Income (Loss) Per Share

Basic net income (loss) per share

We compute basic net income (loss) per share by dividing the total net income (loss) attributable to our common stockholders by our weighted-average number of common shares outstanding during the period.

The calculation of total net income (loss) attributable to our common stockholders for the three and nine months ended September 30, 2019 and 2018 considered our net income for Ionis on a stand-alone basis plus our share of Akcea's net loss for the period. To calculate the portion of Akcea's net loss attributable to our ownership, we multiplied Akcea's loss per share by the weighted average shares we owned in Akcea during the period. As a result of this calculation, our total net income (loss) available to Ionis common stockholders for the calculation of net income (loss) per share is different than net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders in the condensed consolidated statements of operations.

Our basic net income per share for the three months ended September 30, 2019, was calculated as follows (in thousands, except per share amounts):

Three months ended September 30, 2019	**Weighted Average Shares Owned in Akcea**	**Akcea's Net Loss Per Share**	**Ionis' Portion of Akcea's Net Loss**
Common shares	70,221	$ (0.34)	$ (23,772)
Akcea's net loss attributable to our ownership			$ (23,772)
Ionis' stand-alone net income			49,930
Net income available to Ionis common stockholders			$ 26,158
Weighted average shares outstanding			140,551
Basic net income per share			$ 0.19

Our basic net income per share for the nine months ended September 30, 2019, was calculated as follows (in thousands, except per share amounts):

Nine months ended September 30, 2019	**Weighted Average Shares Owned in Akcea**	**Akcea's Net Loss Per Share**	**Ionis' Portion of Akcea's Net Loss**
Common shares	69,681	$ (0.40)	$ (28,174)
Akcea's net loss attributable to our ownership			$ (28,174)
Ionis' stand-alone net income			140,938
Net income available to Ionis common stockholders			$ 112,764
Weighted average shares outstanding			139,800
Basic net income per share			$ 0.81

Our basic net loss per share for the three months ended September 30, 2018, was calculated as follows (in thousands, except per share amounts):

Three months ended September 30, 2018	Weighted Average Shares Owned in Akcea	Akcea's Net Loss Per Share	Ionis' Portion of Akcea's Net Loss
Common shares	65,538	$ (0.73)	$ (47,843)
Akcea's net loss attributable to our ownership			$ (47,843)
Ionis' stand-alone net income			43,226
Net loss available to Ionis common stockholders			$ (4,617)
Weighted average shares outstanding			137,346
Basic net loss per share			$ (0.03)

Our basic net loss per share for the nine months ended September 30, 2018, was calculated as follows (in thousands, except per share amounts):

Nine months ended September 30, 2018	Weighted Average Shares Owned in Akcea	Akcea's Net Loss Per Share	Ionis' Portion of Akcea's Net Loss
Common shares	57,347	$ (1.93)	$ (110,680)
Akcea's net loss attributable to our ownership			$ (110,680)
Ionis' stand-alone net income			67,517
Net loss available to Ionis common stockholders			$ (43,163)
Weighted average shares outstanding			130,507
Basic net loss per share			$ (0.33)

Dilutive net income (loss per share)

For the three and nine months ended September 30, 2019, we had net income available to Ionis common stockholders. As a result, we computed diluted net income per share using the weighted-average number of common shares and dilutive common equivalent shares outstanding during the period.

We calculated our diluted net income per share for the three months ended September 30, 2019 as follows (in thousands except per share amounts):

Three months ended September 30, 2019	Income (Numerator)	Shares (Denominator)	Per-Share Amount
Net income available to Ionis common stockholders	$ 26,158	140,551	$ 0.19
Effect of dilutive securities:			
Shares issuable upon exercise of stock options	—	1,993	
Shares issuable upon restricted stock award issuance	—	844	
Shares issuable related to our Employee Stock Purchase Plan	—	20	
Income available to Ionis common stockholders	$ 26,158	143,408	$ 0.18

We calculated our diluted net income per share for the nine months ended September 30, 2019 as follows (in thousands except per share amounts):

Nine months ended September 30, 2019	Income (Numerator)	Shares (Denominator)	Per-Share Amount
Net income available to Ionis common stockholders	$ 112,764	139,800	$ 0.81
Effect of dilutive securities:			
Shares issuable upon exercise of stock options	—	2,208	
Shares issuable upon restricted stock award issuance	—	793	
Shares issuable related to our Employee Stock Purchase Plan	—	20	
Income available to Ionis common stockholders	$ 112,764	142,821	$ 0.79

For the three and nine months ended September 30, 2019, the calculation excluded the 1 percent notes because the effect on diluted earnings per share was anti-dilutive.

For the three and nine months ended September 30, 2018, we incurred a net loss; therefore, we did not include dilutive common equivalent shares in the computation of diluted net loss per share because the effect would have been anti-dilutive. Common stock from the following would have had an anti-dilutive effect on net loss per share:

- 1 percent convertible senior notes;
- Dilutive stock options;
- Unvested restricted stock units; and
- Employee Stock Purchase Plan, or ESPP.

Convertible Debt

We account for convertible debt instruments that may be settled in cash upon conversion (including partial cash settlement) by separating the liability and equity components of the instruments in a manner that reflects our nonconvertible debt borrowing rate. We determine the carrying amount of the liability component by measuring the fair value of similar debt instruments that do not have the conversion feature. If no similar debt instrument exists, we estimate fair value by using assumptions that market participants would use in pricing a debt instrument, including market interest rates, credit standing, yield curves and volatilities. To determine the fair value of the debt component we are required to use accounting estimates and assumptions. These estimates and assumptions are judgmental in nature and could have a significant impact on the determination of the debt component, and the associated non-cash interest expense.

We assigned a value to the debt component of our convertible notes equal to the estimated fair value of similar debt instruments without the conversion feature, which resulted in us recording our debt at a discount. We are amortizing our debt issuance costs and debt discount over the life of the convertible notes as additional non-cash interest expense utilizing the effective interest method.

Segment Information

We have two operating segments, our Ionis Core segment and Akcea Therapeutics, our majority-owned affiliate. Akcea is a biopharmaceutical company focused on developing and commercializing medicines to treat patients with rare and serious diseases. We provide segment financial information and results for our Ionis Core segment and our Akcea Therapeutics segment based on the segregation of revenues and expenses that our chief decision maker reviews to assess operating performance and to make operating decisions. We allocate a portion of Ionis' development, R&D support and general and administrative expenses to Akcea for work Ionis performs on behalf of Akcea.

Stock-based Compensation Expense

We measure stock-based compensation expense for equity-classified awards, principally related to stock options, restricted stock units, or RSUs, and stock purchase rights under our ESPP based on the estimated fair value of the award on the date of grant. We recognize the value of the portion of the award that we ultimately expect to vest as stock-based compensation expense over the requisite service period in our condensed consolidated statements of operations. We reduce stock-based compensation expense for estimated forfeitures at the time of grant and revise in subsequent periods if actual forfeitures differ from those estimates.

We use the Black-Scholes model to estimate the fair value of stock options granted and stock purchase rights under our ESPP. The expected term of stock options granted represents the period of time that we expect them to be outstanding. We estimate the expected term of options granted based on historical exercise patterns. For the nine months ended September 30, 2019 and 2018, we used the following weighted-average assumptions in our Black-Scholes calculations:

Ionis Employee Stock Options:

	Nine Months Ended September 30,	
	2019	**2018**
Risk-free interest rate	2.3%	2.3%
Dividend yield	0.0%	0.0%
Volatility	60.3%	63.1%
Expected life	4.6 years	4.6 years

Ionis Board of Director Stock Options:

	Nine Months Ended September 30,	
	2019	**2018**
Risk-free interest rate	1.9%	2.8%
Dividend yield	0.0%	0.0%
Volatility	60.7%	61.5%
Expected life	6.6 years	6.6 years

Ionis ESPP:

	Nine Months Ended September 30,	
	2019	**2018**
Risk-free interest rate	2.4%	1.8%
Dividend yield	0.0%	0.0%
Volatility	45.6%	47.3%
Expected life	6 months	6 months

Ionis RSU's:

The fair value of RSUs is based on the market price of our common stock on the date of grant. RSUs vest annually over a four-year period. The weighted-average grant date fair value of RSUs granted to employees for the nine months ended September 30, 2019 was $59.79 per share. The weighted-average grant date fair value of RSUs granted to our board of directors for the nine months ended September 30, 2019 was $64.65 per share.

In addition to our stock plans, Akcea has its own stock plan under which it grants stock options and RSUs and under which it derives its stock-based compensation expense. The following are the weighted-average Black-Scholes assumptions Akcea used under its plan for the nine months ended September 30, 2019 and 2018:

Akcea Employee Stock Options:

	Nine Months Ended September 30,	
	2019	**2018**
Risk-free interest rate	2.3%	2.7%
Dividend yield	0.0%	0.0%
Volatility	75.6%	77.1%
Expected life	6.1 years	6.1 years

Akcea Board of Directors Stock Options:

	Nine Months Ended September 30,	
	2019	**2018**
Risk-free interest rate	1.8%	2.9%
Dividend yield	0.0%	0.0%
Volatility	73.8%	78.2%
Expected life	6.3 years	6.4 years

Akcea ESPP:

	Nine Months Ended September 30,	
	2019	**2018**
Risk-free interest rate	2.4%	1.9%
Dividend yield	0.0%	0.0%
Volatility	60.0%	64.2%
Expected life	6 months	6 months

The following table summarizes stock-based compensation expense for the three and nine months ended September 30, 2019 and 2018 (in thousands).

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2019	2018	2019	2018
Cost of products sold	$ 127	$ —	$ 383	$ —
Research, development and patent	23,744	18,780	71,935	57,698
Selling, general and administrative	255	16,103	39,246	39,512
Total non-cash stock-based compensation expense	$ 24,126	$ 34,883	$ 111,564	$ 97,210

In the third quarter of 2019, three Akcea executive officers terminated their employment and entered into separation agreements with Akcea. As a result, in the third quarter of 2019, Akcea reversed $19.1 million of stock-based compensation expense it had previously recognized related to the executive officers' stock options and RSUs that were no longer going to vest.

As of September 30, 2019, total unrecognized estimated non-cash stock-based compensation expense related to non-vested stock options and RSUs was $143.9 million and $71.3 million, respectively. Our actual expenses may differ from these estimates because we will adjust our unrecognized non-cash stock-based compensation expense for future forfeitures. We expect to recognize the cost of non-cash stock-based compensation expense related to non-vested stock options and RSUs over a weighted average amortization period of 1.2 years and 1.6 years, respectively.

Amendment to Equity Plan

In June 2019, after receiving approval from our stockholders, we amended our 2011 Equity Incentive Plan to increase the total number of shares reserved for issuance under the plan from 16 million to 23 million shares.

Share Repurchase Program

In September 2019, our board of directors approved an initial share repurchase program of up to $125 million of our common stock. Our stock repurchase program has no expiration date. To date, we have not repurchased any shares of our common stock.

Impact of Recently Issued Accounting Standards

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

In August 2018, the FASB issued clarifying guidance on how to account for implementation costs related to cloud-servicing arrangements. The guidance states that if these fees qualify to be capitalized and amortized over the service period, they need to be expensed in the same line item as the service expense and recognized in the same balance sheet category. The update can be applied either retrospectively or prospectively to all implementation costs incurred after the date of adoption. The updated guidance is effective for fiscal years beginning after December 15, 2019, and interim periods within those fiscal years. We plan to adopt this guidance on January 1, 2020 on a prospective basis. We do not anticipate this guidance will have a significant impact on our condensed consolidated financial statements and disclosures.

In August 2018, the FASB updated its disclosure requirements related to Level 1, 2 and 3 fair value measurements. The update included deletion and modification of certain disclosure requirements and additional disclosure related to Level 3 measurements. The guidance is effective for fiscal years beginning after December 31, 2019 and early adoption is permitted. We adopted this updated guidance on January 1, 2019 and it did not have a significant impact on our disclosures.

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

1) When a participant is considered a customer in a collaborative arrangement, all of the associated accounting under Topic 606 should be applied
    - *We will apply all of the associated accounting under Topic 606 when we determine a participant in a collaborative arrangement is a customer*
2) Adds "unit of account" concept to collaboration accounting guidance to align with Topic 606. The "unit of account" concept is used to determine if revenue is recognized or if a contra expense is recognized from consideration received under a collaboration
    - *We will use the "unit of account" concept when we receive consideration under a collaborative arrangement to determine when we recognize revenue or a contra expense*
3) The clarifying guidance precludes us from recognizing revenue under Topic 606 when we determine a transaction with a collaborative partner is not a customer and is not directly related to the sales to third parties
    - *When we conclude a collaboration partner is not a customer and is not directly related to the sales to third parties, we will not recognize revenue for the transaction*

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

3. Investments

As of September 30, 2019, we had invested our excess cash primarily in debt instruments of the U.S. Treasury, financial institutions, corporations, and U.S. government agencies with strong credit ratings and an investment grade rating at or above A-1, P-1 or F-1 by Moody's, Standard & Poor's, or S&P, or Fitch, respectively. We have established guidelines relative to diversification and maturities that maintain safety and liquidity. We periodically review and modify these guidelines to maximize trends in yields and interest rates without compromising safety and liquidity.

The following table summarizes the contract maturity of the available-for-sale securities we held as of September 30, 2019:

One year or less	69%
After one year but within two years	22%
After two years but within three years	9%
Total	100%

As illustrated above, at September 30, 2019, 91 percent of our available-for-sale securities had a maturity of less than two years.

All of our available-for-sale securities are available to us for use in our current operations. As a result, we categorize 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.

At September 30, 2019, we had an ownership interest of less than 20 percent in four private companies and two public companies with which we conduct business. The privately-held companies are Atlantic Pharmaceuticals Limited, Dynacure SAS, Seventh Sense Biosystems and Suzhou Ribo Life Science Co, Ltd. The publicly-traded companies are ProQR and ATL.

The following is a summary of our investments (in thousands):

September 30, 2019	Cost (1)	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale securities:				
Corporate debt securities (2)	$ 752,495	$ 1,484	$ (148)	$ 753,831
Debt securities issued by U.S. government agencies	176,589	321	(45)	176,865
Debt securities issued by the U.S. Treasury (2)	331,371	264	(17)	331,618
Debt securities issued by states of the U.S. and political subdivisions of the states	33,986	4	(27)	33,963
Other municipal debt securities	2,948	—	—	2,948
Total securities with a maturity of one year or less	1,297,389	2,073	(237)	1,299,225
Corporate debt securities	539,820	3,108	(161)	542,767
Debt securities issued by U.S. government agencies	106,536	101	(137)	106,500
Debt securities issued by the U.S. Treasury	34,692	—	(38)	34,654
Debt securities issued by states of the U.S. and political subdivisions of the states	9,283	25	(6)	9,302
Total securities with a maturity of more than one year	690,331	3,234	(342)	693,223
Total available-for-sale securities	$ 1,987,720	$ 5,307	$ (579)	$ 1,992,448
Equity securities:				
Total equity securities included in other current assets (3)	$ 1,212	$ —	$ (606)	$ 606
Total available-for-sale and equity securities	$ 1,988,932	$ 5,307	$ (1,185)	$ 1,993,054

December 31, 2018	Cost (1)	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale securities:				
Corporate debt securities	$ 956,879	$ 13	$ (1,858)	$ 955,034
Debt securities issued by U.S. government agencies	168,839	3	(104)	168,738
Debt securities issued by the U.S. Treasury	244,640	15	(77)	244,578
Debt securities issued by states of the U.S. and political subdivisions of the states (2)	63,572	—	(323)	63,249
Total securities with a maturity of one year or less	1,433,930	31	(2,362)	1,431,599
Corporate debt securities	299,018	194	(1,286)	297,926
Debt securities issued by U.S. government agencies	107,789	194	(109)	107,874
Debt securities issued by the U.S. Treasury	15,600	—	(24)	15,576
Debt securities issued by states of the U.S. and political subdivisions of the states	16,980	—	(287)	16,693
Total securities with a maturity of more than one year	439,387	388	(1,706)	438,069
Total available-for-sale securities	$ 1,873,317	$ 419	$ (4,068)	$ 1,869,668
Equity securities:				
Total equity securities included in other current assets (3)	1,212	137	—	1,349
Total available-for-sale and equity securities	$ 1,874,529	$ 556	$ (4,068)	$ 1,871,017

(1) Our available-for-sale securities are held at amortized cost.

(2) Includes investments classified as cash equivalents on our condensed consolidated balance sheet.

(3) We recognize our equity securities at cost minus impairments, plus or minus changes resulting from observable price changes in orderly transactions for the identical or similar investment of the same issuer on our condensed consolidated balance sheet.

The following is a summary of our investments we consider to be temporarily impaired at September 30, 2019. We believe that the decline in value of these securities is temporary and is 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 full recovery of our debt securities' amortized cost basis at maturity.

		Less than 12 Months of Temporary Impairment		More than 12 Months of Temporary Impairment		Total Temporary Impairment	
(In thousands)	Number of Investments	Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses
Corporate debt securities	104	$ 304,705	$ (268)	$ 31,675	$ (41)	$ 336,380	$ (309)
Debt securities issued by U.S. government agencies	28	102,733	(156)	22,974	(26)	125,707	(182)
Debt securities issued by the U.S. Treasury	9	77,918	(55)	—	—	77,918	(55)
Debt securities issued by states of the U.S. and political subdivisions of the states	13	1,498	(1)	15,597	(32)	17,095	(33)
Total temporarily impaired securities	154	$ 486,854	$ (480)	$ 70,246	$ (99)	$ 557,100	$ (579)

4. 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 and our investment in equity securities in publicly-held biotechnology companies; 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 classify the majority of our securities as Level 2. We obtain the fair value of our Level 2 investments from our custodian bank or from a professional pricing service. We validate the fair value of our Level 2 investments by understanding the pricing model used by the custodian banks or professional pricing service provider and comparing that fair value to the fair value based on observable market prices.

The following tables present the major security types we held at September 30, 2019 and December 31, 2018 that we regularly measure and carry at fair value. At September 30, 2019 and December 31, 2018, our ProQR investment was subject to trading restrictions that extend to the fourth quarter of 2019; as a result, we included a lack of marketability discount in valuing this investment, which is a Level 3 input. The amount we owned in ProQR did not change from December 31, 2018 to September 30, 2019. The tables below segregate each security type by the level within the fair value hierarchy of the valuation techniques we utilized to determine the respective securities' fair value (in thousands):

	At September 30, 2019	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 202,904	$ 202,904	$ —	$ —
Corporate debt securities (2)	1,296,598	—	1,296,598	—
Debt securities issued by U.S. government agencies (3)	283,365	—	283,365	—
Debt securities issued by the U.S. Treasury (4)	366,272	366,272	—	—
Debt securities issued by states of the U.S. and political subdivisions of the states (3)	43,265	—	43,265	—
Other municipal debt securities (3)	2,948	—	2,948	—
Investment in ProQR Therapeutics N.V. (5)	606	—	—	606
Total	$ 2,195,958	$ 569,176	$ 1,626,176	$ 606

	At December 31, 2018	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 146,281	$ 146,281	$ —	$ —
Corporate debt securities (6)	1,252,960	—	1,252,960	—
Debt securities issued by U.S. government agencies (3)	276,612	—	276,612	—
Debt securities issued by the U.S. Treasury (7)	260,154	260,154	—	—
Debt securities issued by states of the U.S. and political subdivisions of the states (3)	79,942	—	79,942	—
Investment in ProQR Therapeutics N.V. (5)	1,349	—	—	1,349
Total	$ 2,017,298	$ 406,435	$ 1,609,514	$ 1,349

The following footnotes reference lines on our condensed consolidated balance sheet:

(1) Included in cash and cash equivalents.

(2) $16.6 million was included in cash and cash equivalents, with the difference included in short-term investments.

(3) Included in short-term investments.

(4) $3.0 million was included in cash and cash equivalents, with the difference included in short-term investments.

(5) Included in other current assets.

(6) $50.2 million was included in cash and cash equivalents, with the difference included in short-term investments.

(7) $14.2 million was included in cash and cash equivalents, with the difference included in short-term investments.

Convertible Notes

Our 1 percent notes had a fair value of $783.7 million at September 30, 2019. We determine the fair value of our notes based on quoted market prices for these notes, which are Level 2 measurements because the notes do not trade regularly.

5. Operating Leases

We lease a facility adjacent to our manufacturing facility that has laboratory and office space that we use to support our manufacturing facility. We lease this space under a non-cancelable operating lease with an initial term ending in June 2021 and an option to extend the lease for up to two five-year periods.

We also lease additional office space and we sublease a portion of this space to Akcea. We lease this space under a non-cancelable operating lease with an initial term ending in June 2023 and an option to extend the lease for one five-year period. The sublease with Akcea is eliminated in our condensed consolidated financial statements.

Akcea entered into an operating lease agreement for office space located in Boston, Massachusetts for its new corporate headquarters in the second quarter of 2018. The lease commencement date was in August 2018 and Akcea took occupancy in September 2018. Akcea is leasing this space under a non-cancelable operating lease with an initial term ending after 123 months and an option to extend the lease for an additional five-year term. Under the lease agreement, Akcea received a three-month free rent period, which commenced on August 15, 2018, and a tenant improvement allowance up to $3.8 million. Akcea provided the lessor with a letter of credit to secure its obligations under the lease in the initial amount of $2.4 million, to be reduced to $1.8 million on the third anniversary of the rent commencement date and to $1.2 million on the fifth anniversary of the rent commencement date if Akcea meets certain conditions set forth in the lease at each such time.

When we determined our lease term for our operating lease right-of-use assets and lease liabilities for these leases, we did not include the extension options for these leases.

Amounts related to our operating leases were as follows (dollar amounts in millions):

	At September 30, 2019
Right-of-use operating lease assets (1)	$ 13.0
Operating lease liabilities (2)	$ 17.7
Weighted average remaining lease term	8.3 years
Weighted average discount rate	7.5%

(1) Included in deposits and other assets on our condensed consolidated balance sheet.

(2) Current portion of $2.1 million was included in current portion of long-term obligations on our condensed consolidated balance sheet, with the difference included in long-term obligations.

During the nine months ended September 30, 2019, we paid $2.9 million of rent payments, which was included in operating activities in our condensed consolidated statement of cash flows.

As of September 30, 2019, the payments for our operating lease liabilities are as follows (in thousands):

	Operating Leases
Remainder of 2019	$ 801
Years ending December 31,	
2020	3,282
2021	3,019
2022	2,781
2023	2,520
Thereafter	11,861
Total minimum lease payments	24,264
Less:	
Imputed interest	(6,533)
Total operating lease liabilities	$ 17,731

Rent expense was $0.8 million and $1.0 million for the three months ended September 30, 2019 and 2018, respectively. Rent expense was $2.7 million and $1.8 million for the nine months ended September 30, 2019 and 2018, respectively.

6. Income Taxes

We recorded an income tax benefit of $14.9 million and an income tax expense of $9.2 million for the three and nine months ended September 30, 2019, compared to income tax expense of $0.5 million and $0.8 million for the same periods in 2018, respectively. The tax benefit recorded for the three months ended September 30, 2019 varies from what we would have recorded using the U.S. federal statutory rate primarily due to a state tax benefit resulting from our combined state tax filings with Akcea, estimated R&D and orphan drug credits, excess tax benefits related to share-based compensation and a benefit related to a change in the estimated tax value of Akcea shares we received in 2018. The increase in our income tax expense for the nine months ended September 30, 2019, compared to the same period in 2018, was primarily due to our expectation that we will generate U.S. federal and state taxable income in 2019. We expect to utilize our deferred tax assets to partially offset our U.S. federal taxable income.

7. Collaborative Arrangements and Licensing Agreements

Below, we have included our collaborations with substantive changes during the first nine months of 2019 from those included in Note 6 of our audited financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2018.

Strategic Partnership

Biogen

We have several strategic collaborations with Biogen focused on using antisense technology to advance the treatment of neurological disorders. These collaborations combine our expertise in creating antisense medicines with Biogen's expertise in developing therapies for neurological disorders. We developed and licensed to Biogen SPINRAZA, our approved medicine to treat people with spinal muscular atrophy, or SMA. In December 2017, we entered into a collaboration with Biogen to identify new antisense medicines for the treatment of SMA. We and Biogen are currently developing eight medicines under collaborations, including medicines to treat people with ALS, Alzheimer's disease and Parkinson's disease. In addition to these medicines, our collaborations with Biogen include a substantial research pipeline that addresses a broad range of neurological diseases. From inception through September 2019, we have received $2.3 billion from our Biogen collaborations, including $1 billion we received from Biogen in the second quarter of 2018 for our 2018 strategic neurology collaboration.

During the three and nine months ended September 30, 2019 and 2018, we earned the following revenue from our relationship with Biogen (in millions, except percentage amounts):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2019	2018	2019	2018
SPINRAZA royalties (commercial revenue)	$ 81.7	$ 70.0	$ 211.9	$ 167.7
R&D revenue	25.5	34.8	81.9	66.9
Total revenue from our relationship with Biogen	$ 107.2	$ 104.8	$ 293.8	$ 234.6
Percentage of total revenue	64%	72%	47%	58%

Neurology Collaborations

2018 Strategic Neurology

In the second quarter of 2019, we achieved two $7.5 million milestone payments from Biogen when we advanced two new targets for unidentified neurological diseases under this collaboration. These milestone payments did not create new performance obligations because they are part of our original R&D services performance obligation. Therefore, we included these amounts in our transaction price for our R&D services performance obligation. We are recognizing revenue for our R&D services performance obligation based on the percentage of completion. From inception through September 2019, we have included $582 million in payments in the transaction price for our R&D services performance obligation under this collaboration. We currently estimate we will satisfy our performance obligation in June 2028.

We will achieve the next payment of $7.5 million if Biogen designates another target under this collaboration.

2013 Strategic Neurology

In the third quarter of 2019, we achieved an $8 million milestone payment when Biogen initiated a Phase 1/2 study of ION859 (IONIS-LRRK2$_{Rx}$) for the treatment of people with Parkinson's disease under this collaboration. We concluded that this milestone payment was not related to our R&D services performance obligation. Therefore, we recognized the $8 million milestone payment in full in the third quarter of 2019 because we do not have any performance obligations related to this payment.

From inception through September 2019, we have included $145 million in total payments in the transaction price for our R&D services performance obligation under this collaboration that we are recognizing over our estimated period of performance. We are recognizing revenue as we perform services based on our effort to satisfy our performance obligation relative to the total effort expected to satisfy our performance obligation. In the third quarter of 2019, we updated our estimate of the total effort we expect to expend to satisfy our performance obligation. As of September 30, 2019, we have completed a significant portion of the research and development services. We expect to complete the remainder of our services in 2020. As a result, we recorded a cumulative catch up adjustment of $16.5 million to decrease revenue in the third quarter of 2019. We will recognize this amount over the estimated remaining period we will perform services.

2012 Neurology

In the second quarter of 2019, we achieved a $7.5 million milestone payment from Biogen when we advanced IONIS-MAPT$_{Rx}$ for Alzheimer's disease under this collaboration. This milestone payment did not create a new performance obligation because it is part of our performance obligation to conduct development of IONIS-MAPT$_{Rx}$. Therefore, we included the $7.5 million milestone payment in our transaction price for our IONIS-MAPT$_{Rx}$ development performance obligation. We are recognizing revenue for our IONIS-MAPT$_{Rx}$ development performance obligation based on the percentage of completion. From inception through September 2019, we have included $25.5 million in the transaction price for our IONIS-MAPT$_{Rx}$ development performance obligation. We currently estimate we will satisfy our performance obligation in September 2020.

We also have a separate performance obligation to perform R&D services under this collaboration. We have allocated $40 million in total payments to the transaction price for our R&D services performance obligation. In the third quarter of 2019, we completed our R&D services performance obligation when we designated a development candidate and Biogen accepted the development candidate. Biogen's decision to accept the development candidate was not within our control. We were recognizing revenue as we performed services based on our effort to satisfy our performance obligation relative to the total effort expected to satisfy our performance obligation. Because Biogen accepted the development candidate, we recognized $6.3 million of accelerated revenue in the third quarter of 2019.

We will achieve the next payment of up to $10 million if we advance a program under this collaboration.

During the nine months of 2019, we did not have any changes to our performance obligations or the timing in which we expect to recognize revenue under our Biogen collaborations, except as noted above.

Our condensed consolidated balance sheet at September 30, 2019 and December 31, 2018 included deferred revenue of $532.4 million and $580.9 million, respectively, related to our relationship with Biogen.

Research, Development and Commercialization Partners

Bayer

In May 2015, we entered into an exclusive license agreement with Bayer to develop and commercialize our programs targeting FXI for the treatment of clotting disorders. In October 2019, Bayer decided it would advance IONIS-FXI-L$_{Rx}$ following positive clinical results and we earned a $10 million milestone payment. At September 30, 2019, we determined that it was not probable that we could earn this milestone payment. As such, we did not recognize any revenue associated with it during the third quarter of 2019. Bayer is now responsible for all global development, regulatory and commercialization activities and costs for the FXI program. From inception through September 2019, we have received over $175 million from our Bayer collaboration, not including the $10 million milestone payment we earned in the fourth quarter of 2019. We will achieve the next payment of $20 million when Bayer initiates a Phase 3 study under the FXI program.

GSK

In March 2010, we entered into an alliance with GSK using our antisense drug discovery platform to discover and develop new drugs against targets for rare and serious diseases, including infectious diseases and some conditions causing blindness. Our collaboration with GSK includes two drugs targeting hepatitis B virus, or HBV: IONIS-HBV$_{Rx}$ and IONIS-HBV-L$_{Rx}$, which we designed to reduce the production of viral proteins associated with HBV infection. In the third quarter of 2019, following positive Phase 2 results, GSK licensed our HBV program, for which we earned a $25 million license fee. From inception through September 2019, we have received more than $164 million in payments under our collaboration with GSK, not including the $25 million license fee, which we expect to receive in the fourth quarter of 2019. We will achieve the next payment of $15 million when GSK initiates a Phase 3 study for a drug under this program.

We identified a new performance obligation when we granted GSK the license of the HBV program and assignment of related intellectual property rights in the third quarter of 2019 because the license is distinct from our other performance obligations. We recognized the $25 million license fee for the HBV program as revenue at that time because GSK had full use of the license without any continuing involvement from us. Additionally, we did not have any further performance obligations related to the license after we delivered it to GSK.

During the three and nine months ended September 30, 2019 and 2018, we earned the following revenue from our relationship with GSK (in millions, except percentage amounts):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2019	2018	2019	2018
R&D revenue	$ 25.1	$ 0.1	$ 25.3	$ 1.5
Percentage of total revenue	15%	0%	4%	0%

We did not have any deferred revenue from our relationship with GSK at September 30, 2019 or December 31, 2018.

Roche

We have two collaborations with Roche, one to develop treatments for Huntington's disease, or HD, and one to develop IONIS-FB-L_{Rx} for the treatment of complement-mediated diseases. In December 2017, upon completion of the Phase 1/2 study of IONIS-HTT_{Rx}, Roche exercised its option to license IONIS-HTT_{Rx} and is now responsible for the global development, regulatory and commercialization activities for IONIS-HTT_{Rx}. In October 2018, we entered into a collaboration agreement with Roche to develop IONIS-FB-L_{Rx} for the treatment of complement-mediated diseases. The first indication we plan to pursue is the treatment of patients with geographic atrophy, or GA, the advanced stage of dry age-related macular degeneration, or AMD. We are responsible for conducting a Phase 2 study in patients with dry AMD. In addition, we plan to evaluate the medicine for a severe and rare renal indication. Roche has the option to license IONIS-FB-L_{Rx} at the completion of these studies. Upon licensing, Roche will be responsible for all further global development, regulatory and commercialization activities and costs. From inception through June 2019, we have received over $220 million from our Roche collaborations, including $35 million in milestone payments we earned in the first quarter of 2019 when Roche dosed the first patient in a Phase 3 study for IONIS-HTT_{Rx}. We will achieve the next payment of $15 million if Roche advances IONIS-HTT_{Rx}.

During the three and nine months ended September 30, 2019 and 2018, we earned the following revenue from our relationship with Roche (in millions, except percentage amounts):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2019	2018	2019	2018
R&D revenue	$ 4.7	$ 1.8	$ 52.3	$ 5.4
Percentage of total revenue	3%	1%	8%	1%

Our revenue in the first nine months of 2019 included $35 million of milestone payments we earned when Roche dosed the first patient in the Phase 3 study of IONIS-HTT_{Rx} in the first quarter of 2019. We recognized these milestone payments in full in the first quarter of 2019 because we do not have any performance obligations related to these milestone payments, as Roche is conducting the Phase 3 study of IONIS-HTT_{Rx}.

During the first nine months of 2019, we did not have any changes to our performance obligations or the timing in which we expect to recognize revenue under our Roche collaborations.

Our condensed consolidated balance sheet at September 30, 2019 and December 31, 2018 included deferred revenue of $56.7 million and $72.6 million, respectively, related to our relationship with Roche.

Akcea Collaborations

The following collaboration agreements relate to Akcea, our majority owned affiliate. Our consolidated results include all the revenue earned and cash received under this collaboration agreement. We reflect the noncontrolling interest attributable to other owners of Akcea's common stock in a separate line on the statement of operations and a separate line within stockholders' equity in our condensed consolidated balance sheet.

Novartis

In January 2017, we and Akcea initiated a collaboration with Novartis to develop and commercialize AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. Under the collaboration agreement, Novartis has an exclusive option to further develop and commercialize AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. Akcea is responsible for completing a Phase 2 program, conducting an end-of-Phase 2 meeting with the FDA and providing initial quantities of API for each medicine. If Novartis exercises an option for either of these medicines, Novartis will be responsible for all further global development, regulatory and co-commercialization activities and costs for such medicine. In the first quarter of 2019, Novartis licensed AKCEA-APO(a)-L_{Rx}. Novartis is responsible for conducting and funding all future development, regulatory and commercialization activities for AKCEA-APO(a)-L_{Rx}, including a global pivotal cardiovascular outcomes study, for which planning and initiation activities are underway. From inception through September 2019, we have received over $343 million from our Novartis collaboration, including $150 million we earned from Novartis in the first quarter of 2019 for the license of AKCEA-APO(a)-L_{Rx}. Akcea paid us $75 million as a sublicense fee in 2.8 million shares of Akcea common stock.

We identified a new performance obligation when we granted Novartis the license of AKCEA-APO(a)-L_{Rx} in the first quarter of 2019 because the license is distinct from our other performance obligations. We recognized the $150 million license fee for AKCEA-APO(a)-L_{Rx} as revenue at that time because Novartis had full use of the license without any continuing involvement from us. Additionally, we did not have any further performance obligations related to the license after we delivered it to Novartis.

Novartis has the option to purchase additional API of AKCEA-APO(a)-L_{Rx} in the future at agreed upon terms and conditions under our collaboration agreement. We identified a new performance obligation when we delivered additional AKCEA-APO(a)-L_{Rx} API to Novartis in the third quarter of 2019 because the delivery of the API is distinct from our other performance obligations. We recognized $5.5 million in revenue for the API we sold to Novartis in the third quarter of 2019.

Akcea is responsible for the development activities under this collaboration. As such, Akcea is recognizing the associated revenue in its statement of operations, and we reflect all of Akcea's revenue in our consolidated results. Akcea pays us sublicense fees for payments that it receives under the collaboration and we recognize those fees as revenue in our Ionis Core operating segment results and Akcea recognizes the fees as R&D expense. In our consolidated results, we eliminate this sublicense revenue and expense. Any cash Akcea receives is included in our condensed consolidated balance sheet.

During the three and nine months ended September 30, 2019 and 2018, we earned the following revenue from our relationship with Novartis (in millions, except percentage amounts):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2019	2018	2019	2018
R&D revenue	$ 8.5	$ 7.2	$ 176.3	$ 42.7
Percentage of total revenue	5%	5%	28%	10%

During the first nine months of 2019, we did not have any changes to our performance obligations, except as noted above, or the timing in which we expect to recognize revenue under our Novartis collaboration.

Our condensed consolidated balance sheet at September 30, 2019 and December 31, 2018 included deferred revenue of $10.8 million and $28.8 million, respectively, related to our relationship with Novartis.

Pfizer

In October 2019, Akcea initiated a collaboration with Pfizer for the license of AKCEA-ANGPTL3-L_{Rx} to treat people with cardiovascular and metabolic diseases. Akcea is currently conducting a Phase 2 study of AKCEA-ANGPTL3-L_{Rx} for the treatment of non-alcoholic fatty liver disease, or NAFLD. Pfizer is responsible for all development and regulatory activities and costs beyond those associated with the ongoing Phase 2 study.

Under the terms of the agreement, Akcea will receive a $250 million upfront license fee, upon closing the transaction, including receiving Hart-Scott Rodino clearance. Akcea is also eligible to receive development, regulatory and sales milestone payments of up to $1.3 billion and tiered royalties in the mid-teens to low-20 percent range on annual worldwide net sales. Akcea has retained the rights to co-commercialize AKCEA-ANGPTL3-L_{Rx} in the U.S. and certain additional markets. The license fee, milestone payments and royalties will be split equally between us and Akcea. Upon receipt of the upfront payment from Pfizer, Akcea expects to pay us its $125 million sublicense fee in 6.9 million shares of Akcea common stock.

8. Segment Information

We have two reportable segments, Ionis Core and Akcea Therapeutics. At September 30, 2019 we owned approximately 75 percent of Akcea. Segment income (loss) from operations includes revenue less operating expenses attributable to each segment.

In our Ionis Core segment we are exploiting our antisense technology to generate a broad pipeline of first-in-class and/or best-in-class medicines for us and our partners. Our Ionis Core segment generates revenue from a multifaceted partnering strategy.

Akcea is a biopharmaceutical company focused on developing and commercializing medicines to treat patients with rare and serious diseases. Akcea generates revenue from TEGSEDI and WAYLIVRA product sales and from its collaborations.

The following tables show our segment revenue and income (loss) from operations for the three and nine months ended September 30, 2019 and 2018 (in thousands), respectively.

Three Months Ended September 30, 2019	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 81,672	$ —	$ —	$ 81,672
Product sales, net	—	11,945	—	11,945
Licensing and other royalty revenue	1,946	136	—	2,082
Total commercial revenue	83,618	12,081	—	95,699
R&D revenue under collaborative agreements	69,165	8,543	(5,515)	72,193
Total segment revenue	$ 152,783	$ 20,624	$ (5,515)	$ 167,892
Total operating expenses	$ 119,147	$ 53,215	$ (6,993)	$ 165,369
Income (loss) from operations	$ 33,636	$ (32,591)	$ 1,478	$ 2,523

Three Months Ended September 30, 2018	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 70,010	$ —	$ —	$ 70,010
Licensing and other royalty revenue	7,946	12,000	(7,200)	12,746
Total commercial revenue	77,956	12,000	(7,200)	82,756
R&D revenue under collaborative agreements	100,105	7,241	(44,707)	62,639
Total segment revenue	$ 178,061	$ 19,241	$ (51,907)	$ 145,395
Total operating expenses	$ 87,664	$ 84,249	$ (7,946)	$ 163,967
Income (loss) from operations	$ 90,397	$ (65,008)	$ (43,961)	$ (18,572)

Nine Months Ended September 30, 2019	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 211,884	$ —	$ —	$ 211,884
Product sales, net	—	28,563	—	28,563
Licensing and other royalty revenue	8,466	6,172	(3,000)	11,638
Total commercial revenue	220,350	34,735	(3,000)	252,085
R&D revenue under collaborative agreements	294,512	176,328	(94,007)	376,833
Total segment revenue	$ 514,862	$ 211,063	$ (97,007)	$ 628,918
Total operating expenses	$ 355,437	$ 256,152	$ (87,900)	$ 523,689
Income (loss) from operations	$ 159,425	$ (45,089)	$ (9,107)	$ 105,229

Nine Months Ended September 30, 2018	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 167,743	$ —	$ —	$ 167,743
Licensing and other royalty revenue	9,432	12,000	(7,200)	14,232
Total commercial revenue	177,175	12,000	(7,200)	181,975
R&D revenue under collaborative agreements	232,850	42,670	(49,936)	225,584
Total segment revenue	$ 410,025	$ 54,670	$ (57,136)	$ 407,559
Total operating expenses	$ 279,084	$ 213,428	$ (12,796)	$ 479,716
Income (loss) from operations	$ 130,941	$ (158,758)	$ (44,340)	$ (72,157)

The following table shows our total assets by segment at September 30, 2019 and December 31, 2018 (in thousands), respectively.

Total Assets	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
September 30, 2019	$ 3,233,175	$ 383,167	$ (721,353)	$ 2,894,989
December 31, 2018	$ 2,975,491	$ 365,261	$ (672,968)	$ 2,667,784

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, "Ionis," "Company," "we," "our," and "us," means Ionis Pharmaceuticals, Inc. and its majority owned affiliate, Akcea Therapeutics, Inc.

Forward-Looking Statements

In addition to historical information contained in this Report on Form 10-Q, the Report includes forward-looking statements regarding our business and the therapeutic and commercial potential of SPINRAZA (nusinersen), TEGSEDI (inotersen), WAYLIVRA (volanesorsen) and our technologies and products in development, including the business of Akcea Therapeutics, Inc., our majority-owned affiliate. 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. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in this report and described in additional detail in our annual report on Form 10-K for the year ended December 31, 2018, which is on file with the U.S. Securities and Exchange Commission and is available from us, and those identified within Part II Item 1A. Risk Factors of this Report. 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.

Overview

We are a leader in discovering and developing RNA-targeted therapeutics with sustained and growing revenues. We have created an efficient and broadly applicable drug discovery platform leveraging our expertise in antisense oligonucleotide therapeutics that we believe has fundamentally changed medicine and transformed the lives of people with devastating and often deadly diseases. Our large, diverse and advanced pipeline of over 40 first-in-class and/or best-in-class medicines addresses diseases across a broad range of therapeutic areas, targeting small, medium and large patient populations.

We have three commercial medicines approved in major markets around the world, SPINRAZA, TEGSEDI and WAYLIVRA. We have two medicines in Phase 3 studies, IONIS-HTT_{Rx}, for Huntington's disease, and tofersen, for SOD1-ALS. We also have the potential for two more medicines to begin Phase 3 studies this year and additional medicines to begin Phase 3 studies by the end of 2020. These medicines, along with the more than 30 additional medicines in our pipeline, represent multiple potential drivers of value for years to come. We believe our efficient drug discovery platform, coupled with our innovation-centric business model, provides us with the flexibility to determine the optimal development and commercialization strategy to maximize the commercial opportunity for each of our medicines and ensure that we continue to produce transformative medicines for patients who need them. We believe we are positioned to drive substantial value for patients and shareholders.

As of September 2019, SPINRAZA was approved in over 50 countries around the world, and our partner Biogen, who is responsible for global SPINRAZA commercial activities, reported that more than 9,300 patients were on SPINRAZA therapy. SPINRAZA was the first approved medicine for the treatment of SMA. SPINRAZA is the established foundation-of-care for patients of all ages and all SMA types with this progressive, debilitating and often fatal genetic disease. SPINRAZA has been recognized with several Prix Galien awards. Through September 30, 2019, we have earned more than $560 million in commercial revenues from royalties on sales of SPINRAZA.

TEGSEDI, a once weekly, self-administered subcutaneous medicine, was approved in 2018 in the U.S., EU and Canada for the treatment of polyneuropathy caused by hATTR in adult patients. hATTR is a debilitating, progressive, and fatal disease. Akcea, our majority-owned affiliate focused on developing and commercializing medicines to treat patients with rare and serious diseases, launched TEGSEDI in the U.S. and EU in late 2018. Our aim is to make TEGSEDI available globally. We plan to achieve this in part through Akcea's exclusive license agreement with PTC to commercialize TEGSEDI in Latin America. In October 2019, TEGSEDI was approved in Brazil. PTC announced that it intends to start launching activities for TEGSEDI immediately in Brazil. In conjunction with the approval, we earned $4 million from PTC. We have earned more than $30 million in TEGSEDI product sales since launching late last year.

WAYLIVRA, a self-administered, subcutaneous medicine, received conditional marketing authorization in May 2019 from the European Commission, or EC, as an adjunct to diet in adult patients with genetically confirmed FCS and at high risk for pancreatitis. Akcea launched WAYLIVRA in the EU in the third quarter of 2019 and is also focused on regulatory discussions in the U.S. and Canada. Akcea is leveraging its existing commercial infrastructure in Europe to market WAYLIVRA. Akcea is continuing to conduct open-label extension and early access programs. We and Akcea also conducted a study of WAYLIVRA for the treatment of people with familial partial lipodystrophy, or FPL. This study is called the BROADEN study. People with FPL lack subcutaneous adipose tissue and have abnormal subcutaneous fat distribution causing increased incidence of potentially life-threatening pancreatitis, diabetes, extreme insulin resistance and increased liver fat. In August 2019, we and Akcea announced topline results from the BROADEN study. In the study, WAYLIVRA met its primary endpoint demonstrating a statistically significant reduction in triglyceride levels. WAYLIVRA also met an important secondary endpoint with a statistically significant reduction in liver fat. Additionally, WAYLIVRA demonstrated a good safety and tolerability profile in patients with FPL in the BROADEN study. We and Akcea are continuing to evaluate the data from this study and are assessing next steps.

In addition to commercializing TEGSEDI and WAYLIVRA, Akcea has four other clinical-stage medicines in its pipeline: AKCEA-APO(a)-L_{Rx} (TQJ230), AKCEA-ANGPTL3-L_{Rx}, AKCEA-APOCIII-L_{Rx} and AKCEA-TTR-L_{Rx}, each of which could potentially treat multiple patient populations. Moving these medicines into Akcea ensures our core focus remains on innovation while enabling us to retain substantial value from these medicines. As of September 2019, we owned approximately 75 percent of Akcea.

In October 2019, Akcea initiated a collaboration with Pfizer for the license of AKCEA-ANGPTL3-L_{Rx} to treat people with cardiovascular and metabolic diseases. Under the terms of the agreement, Akcea will receive a $250 million upfront license fee, upon closing the transaction, including receiving Hart-Scott Rodino clearance. Akcea is also eligible to receive development, regulatory and sales milestone payments of up to $1.3 billion and tiered royalties in the mid-teens to low-20 percent range on annual worldwide net sales. Akcea will pay us 50 percent of the license fee, milestone payments and royalties. Pfizer is responsible for all development and regulatory activities and costs beyond those associated with the ongoing Phase 2 study. Upon receipt of the upfront payment from Pfizer, Akcea expects to pay us its $125 million sublicense fee in 6.9 million shares of Akcea common stock.

We are continuously advancing our technology and pipeline to provide the most value to patients. We have a pipeline of over 40 medicines that, like SPINRAZA, TEGSEDI and WAYLIVRA, have the potential to transform the treatment of diseases with no adequate treatment today. These medicines range from treatments for rare diseases with small patient populations to more common diseases afflicting millions of patients. Our pipeline covers a broad spectrum of therapeutic areas, such as cardiometabolic diseases, neurodegenerative diseases, cancer, severe and rare diseases and others. We believe our large and diverse pipeline contains many near-, mid- and longer-term growth drivers for the company.

We have a distinct partnering strategy based on each specific medicine and the expertise and resources we and our potential partners may bring to a collaboration. We may also develop and commercialize some medicines through affiliates. In general, these are medicines, like TEGSEDI and WAYLIVRA, that can benefit from our internal expertise and infrastructure, have manageable development plans and costs, and have the potential for initial rare disease indications. For other medicines, we may establish collaborations to advance the medicine. We have alliances with a cadre of leading global pharmaceutical companies that are working alongside us in developing our medicines, advancing our technology, preparing to commercialize our medicines and selling our medicines. Our partners include the following companies, among others: AstraZeneca, Bayer, Biogen, GSK, Janssen, Novartis, Pfizer and Roche. Our partners bring resources and expertise that augment and build upon our internal capabilities. We have the potential to earn over $20 billion in future milestone payments and licensing fees from our existing partnerships.

Financial Highlights

The following is a summary of our financial results (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2019	**2018**	**2019**	**2018**
Total revenue	$ 167,892	$ 145,395	$ 628,918	$ 407,559
Total operating expenses	$ 165,369	$ 163,967	$ 523,689	$ 479,716
Income (loss) from operations	$ 2,523	$ (18,572)	$ 105,229	$ (72,157)
Net income (loss)	$ 18,432	$ (20,365)	$ 99,304	$ (87,747)
Net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ 26,163	$ (4,559)	$ 109,730	$ (46,335)

Our revenue for the first nine months of 2019 increased more than 50 percent, compared to the same period in 2018, primarily due to a more than 25 percent increase in commercial revenue from SPINRAZA royalties and increasing R&D revenues including the $150 million license fee we earned from Novartis when it licensed AKCEA-APO(a)-L_{Rx}.

Our operating expenses for the first nine months of 2019 increased, compared to the same period in 2018, principally due to our investments in the global launches of TEGSEDI and WAYLIVRA.

During the first nine months of 2019 we received more than $480 million in payments from our partners, including $230 million from Biogen, $156 million from Novartis, $36 million from Roche and $22 million from Alnylam. This is compared to more than $1.3 billion received in the first nine months of 2018, which included $1 billion from Biogen for our 2018 strategic neurology collaboration. Already in the fourth quarter of 2019, we have generated $260 million in payments from Pfizer and Bayer. We believe our strong financial position should enable us to continue to execute on our corporate goals throughout 2019 and beyond.

Recent Business Highlights *(Q3 2019 and subsequent activities)*

- SPINRAZA – global foundation-of-care for the treatment of patients of all ages with spinal muscular atrophy (SMA)
  - Worldwide sales of SPINRAZA in the first nine months of 2019 increased by nearly 25 percent to over $1.5 billion compared to last year.
  - Patients on SPINRAZA treatment increased by approximately 11 percent compared to last quarter to approximately 9,300 patients across global commercial, clinical and expanded access settings.
  - Biogen plans to initiate the Phase 2/3 DEVOTE study evaluating the safety and potential to achieve increased efficacy with a higher dose of SPINRAZA in SMA patients of all ages, including adults.
  - Biogen presented new long-term follow up data from NURTURE and SHINE adding to the body of evidence underscoring SPINRAZA's durable efficacy and established safety profile across a broad range of SMA patients.
    - NURTURE: Data from pre-symptomatic infants treated for up to nearly four years demonstrating consistent safety and unprecedented motor milestone achievement compared to natural history were published online in *Neuromuscular Disorders*
    - SHINE: Data demonstrating continuing improvement or stabilization in one or more measures of motor function in patients with later-onset SMA treated with SPINRAZA for up to nearly six years were presented at the annual Congress of the European Pediatric Neurology Society

- TEGSEDI – launched in multiple markets for the treatment of polyneuropathy of hereditary transthyretin amyloidosis (hATTR) in adult patients
  - Approved in Brazil and preparing to launch through PTC Therapeutics
  - First commercial patients treated in the United Kingdom following acceptance by the National Institute for Health and Care Excellence, or NICE, and the Scottish Medicines Consortium, or SMC
  - Successfully completed pricing negotiations in Germany
  - Launched in Sweden and Austria following successful completion of reimbursement negotiations
  - Preparing to launch in additional EU countries

- WAYLIVRA – launched in the EU for the treatment of adults with genetically confirmed familial chylomicronemia syndrome (FCS) at high risk for pancreatitis
  - First commercial patients treated in Germany, and a reimbursed early access program (ATU) launched in France
  - Preparing to launch in additional EU countries
  - Published results from Phase 3 APPROACH study in patients with FCS in *The New England Journal of Medicine, or NEJM*
  - Reported top-line results from the BROADEN study of WAYLIVRA in patients with FPL, which met the primary endpoint and a key secondary endpoint

- Biogen Collaboration – Developing robust pipeline of medicines for the treatment of neurological diseases
  - Dosed the first patient in a Phase 1/2 study targeting LRRK2 for the treatment of people with Parkinson's disease.
  - Advanced multiple programs, with eight programs now in development.

- We and Akcea generated $250 million when Pfizer licensed AKCEA-ANGPTL3-L_{Rx} to treat patients with certain cardiovascular and metabolic diseases.
  - We are eligible to receive up to $1.3 billion in milestone payments plus tiered double-digit royalties on worldwide net sales.
  - Our 50 percent portion of the $250 million license fee is expected to be settled in Akcea common stock, demonstrating our confidence in the future of Akcea.

- We earned a $25 million license fee from GSK to develop and commercialize our program for the treatment of people with chronic hepatitis B virus infection.
- We generated $10 million from Bayer to advance IONIS-FXI-L_{Rx} for the treatment of people with clotting disorders.
- We and Akcea presented data from the Phase 1/2 study of AKCEA-TTR-L_{Rx} in healthy volunteers demonstrating >90 percent target reduction and a positive safety profile at the European ATTR Amyloidosis meeting and at the Heart Failure Society of America.
- Roche expanded enrollment in the GENERATION HD1 Phase 3 study of IONIS-HTT_{Rx} (RG6042) in patients with Huntington's disease, or HD.
- We initiated a Phase 2 study of IONIS-FB-L_{Rx} in patients with IgA nephropathy, the second disease indication under our collaboration with Roche to develop the medicine for complement-mediated diseases.

Critical Accounting Policies

We prepare our condensed consolidated financial statements in conformity with accounting principles generally accepted in the United States. As such, we make certain estimates, judgments and assumptions that we believe are reasonable, based upon the information available to us. These judgments involve making estimates about the effect of matters that are inherently uncertain and may significantly impact our quarterly or annual results of operations and financial condition. Each quarter, our senior management reviews the development, selection and disclosure of such estimates with our audit committee of our board of directors. In the following paragraphs, we describe the specific risks associated with these critical accounting policies and we caution that future events rarely develop exactly as one may expect, and that best estimates may require adjustment.

The significant accounting policies, which we believe are the most critical to aid in fully understanding and evaluating our reported financial results, require the following:

- Assessing the propriety of revenue recognition and associated deferred revenue;
- Valuing premiums received under our collaborations;
- Determining the appropriate cost estimates for unbilled preclinical studies and clinical development activities; and
- Accounting for income taxes.

There have been no material changes to our critical accounting policies and estimates from the information provided in Item 7, “Management’s Discussion and Analysis of Financial Condition and Results of Operations” included in our Annual Report on Form 10-K for the year ended December 31, 2018.

Results of Operations

Revenue

Our revenue was as follows (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2019	2018	2019	2018
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 81,672	$ 70,010	$ 211,884	$ 167,743
Product sales, net	11,945	—	28,563	—
Licensing and other royalty revenue	2,082	12,746	11,638	14,232
Total commercial revenue	95,699	82,756	252,085	181,975
R&D revenue:				
Amortization from upfront payments	23,918	31,066	99,263	92,185
Milestone payments	11,981	26,194	64,013	44,583
License fees	25,523	1,649	198,212	64,227
Other services	10,771	3,730	15,345	24,589
Total R&D revenue	72,193	62,639	376,833	225,584
Total revenue	$ 167,892	$ 145,395	$ 628,918	$ 407,559

We significantly increased both commercial and R&D revenue in the first nine months of 2019, compared to the same period in 2018. Commercial revenue increased over 35 percent primarily due to increased SPINRAZA royalties and TEGSEDI product sales. We also added WAYLIVRA product sales in the third quarter of 2019.

Our R&D revenue substantially increased in the first nine months of 2019 compared to the same period in 2018 primarily due to the following:

- $150 million we earned from Novartis when Novartis licensed AKCEA-APO(a)-L_{Rx};
- $35 million we earned from Roche when Roche enrolled the first patient in the Phase 3 study of IONIS-HTT_{Rx} in patients with Huntington's disease;
- $25 million we earned from GSK when GSK licensed our HBV program; and
- $20 million we earned from Alnylam when Alnylam licensed our technology to Regeneron.

We expect to recognize revenue related Pfizer’s license of AKCEA-ANGPTL3-L_{Rx} in the fourth quarter of 2019. We will also recognize $10 million of revenue from Bayer for advancing IONIS-FXI-L_{Rx} in our fourth quarter.

Operating Expenses

To analyze and compare our results of operations to other similar companies, we believe it is important to exclude non-cash compensation expense related to equity awards from our operating expenses. We believe non-cash compensation expense related to equity awards is not indicative of our operating results or cash flows from our operations. Further, we internally evaluate the performance of our operations excluding it.

Our operating expenses by segment were as follows (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2019	2018	2019	2018
Ionis Core	$ 82,667	$ 65,512	$ 243,920	$ 213,114
Akcea Therapeutics	65,569	71,518	256,105	182,188
Elimination of intercompany activity	(6,993)	(7,946)	(87,900)	(12,796)
Subtotal	141,243	129,084	412,125	382,506
Non-cash compensation expense related to equity awards	24,126	34,883	111,564	97,210
Total operating expenses	$ 165,369	$ 163,967	$ 523,689	$ 479,716

Our operating expenses, excluding non-cash compensation expense related to equity awards, increased for both the three and nine months ended September 30, 2019, compared to the same periods last year principally due to our investment in the global launches of TEGSEDI and WAYLIVRA. Stock-based compensation expense increased in the first nine months of 2019, compared to the same period last year primarily due to the increase in the grant date fair value of Akcea stock options granted and from stock option grants made to new employees as Akcea continued to build out its organization. This increase was offset by a reversal of $19.1 million of stock-based compensation expense for three terminated executive officers in the third quarter of 2019. The stock-based compensation expense reversal related to amounts we previously recognized related to these executive officers' stock option and RSU grants that were no longer going to vest.

Cost of Products Sold

Our cost of products sold consisted of manufacturing costs, including certain fixed costs, transportation and freight, indirect overhead costs associated with the manufacturing and distribution of TEGSEDI and WAYLIVRA (beginning in the third quarter of 2019) and certain associated period costs. We do not expect our fixed costs will increase in direct correlation to TEGSEDI and WAYLIVRA product sales. Prior to the regulatory approval of TEGSEDI and WAYLIVRA, we expensed as R&D expense a significant portion of the cost of producing TEGSEDI and WAYLIVRA that Akcea is using in the commercial launches. We expect cost of products sold to increase as we deplete these inventories.

Our cost of products sold by segment were as follows (in thousands):

	September 30, 2019	
	Three Months Ended	Nine Months Ended
Ionis Core	$ —	$ —
Akcea Therapeutics	2,275	10,247
Elimination of intercompany activity	(1,435)	(7,256)
Subtotal	840	2,991
Non-cash compensation expense related to equity awards	127	382
Total cost of products sold	$ 967	$ 3,373

We began recognizing cost of products sold in the third quarter of 2018 when TEGSEDI was approved and in the second quarter of 2019 when WAYLIVRA was approved. We previously expensed $0.2 million and $0.5 million of costs to produce the amount of TEGSEDI and WAYLIVRA we sold in the three and nine months ended September 30, 2019, respectively. We recognized these costs in prior periods because we incurred these costs before we obtained regulatory approval. We did not have cost of products sold in the first nine months of 2018. Akcea includes the amortization for milestone payments it made to us related to the U.S. and European approvals of TEGSEDI in its cost of products sold. Akcea is recognizing this amortization over TEGSEDI's remaining estimated patent life. We eliminate this amortization in our consolidated results. All amounts exclude non-cash compensation expense related to equity awards.

Research, Development and Patent Expenses

Our research, development and patent expenses consist of expenses for antisense drug discovery, antisense drug development, manufacturing and operations and R&D support expenses.

The following table sets forth information on research, development and patent expenses (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2019	2018	2019	2018
Research, development and patent expenses, excluding non-cash compensation expense related to equity awards	$ 80,622	$ 76,475	$ 245,013	$ 243,455
Non-cash compensation expense related to equity awards	23,744	18,780	71,935	57,698
Total research, development and patent expenses	$ 104,366	$ 95,255	$ 316,948	$ 301,153

Our research, development and patent expenses by segment were as follows (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2019	2018	2019	2018
Ionis Core	$ 64,197	$ 49,452	$ 190,269	$ 158,860
Akcea Therapeutics	21,983	27,068	135,388	89,940
Elimination of intercompany activity	(5,558)	(45)	(80,644)	(5,345)
Subtotal	80,622	76,475	245,013	243,455
Non-cash compensation expense related to equity awards	23,744	18,780	71,935	57,698
Total research, development and patent expenses	$ 104,366	$ 95,255	$ 316,948	$ 301,153

Antisense Drug Discovery

We use our proprietary antisense technology to generate information about the function of genes and to determine the value of genes as drug discovery targets. We use this information to direct our own antisense drug discovery research, and that of our partners. Antisense drug discovery is also the function that is responsible for advancing our antisense core technology.

As we continue to advance our antisense technology, we are investing in our drug discovery programs to expand our and our partners' drug pipelines.

Our antisense drug discovery expenses are part of our Ionis Core business segment and were as follows (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2019	2018	2019	2018
Antisense drug discovery expenses, excluding non-cash compensation expense related to equity awards	$ 16,072	$ 14,475	$ 46,397	$ 41,970
Non-cash compensation expense related to equity awards	5,015	4,379	15,805	13,204
Total antisense drug discovery expenses	$ 21,087	$ 18,854	$ 62,202	$ 55,174

Antisense drug discovery expenses were slightly higher for the three and nine months ended September 30, 2019, compared to the same periods in 2018, due to expenses we incurred related to advancing our research programs. All amounts exclude non-cash compensation expense related to equity awards.

Antisense Drug Development

The following table sets forth drug development expenses, including the breakdown for medicines in Phase 3 development and/or commercialization for which we have incurred significant costs (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2019	2018	2019	2018
WAYLIVRA	$ 2,324	$ 3,469	$ 7,429	$ 15,919
TEGSEDI	5,044	3,373	13,161	14,404
Other antisense development projects	21,233	21,413	69,121	62,580
Development overhead expenses	17,557	17,648	53,351	55,286
Total antisense drug development, excluding non-cash compensation expense related to equity awards	46,158	45,903	143,062	148,189
Non-cash compensation expense related to equity awards	11,391	8,434	34,743	25,922
Total antisense drug development expenses	$ 57,549	$ 54,337	$ 177,805	$ 174,111

Our development expenses decreased for the nine months ended September 30, 2019 primarily from WAYLIVRA, TEGSEDI and because Akcea has transitioned all further development of AKCEA-APO(a)-L_{Rx} to Novartis. All amounts exclude non-cash compensation expense related to equity awards.

Our antisense drug development expenses by segment were as follows (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2019	2018	2019	2018
Ionis Core	$ 32,970	$ 20,821	$ 96,992	$ 71,767
Akcea Therapeutics	13,188	25,082	121,070	76,422
Elimination of intercompany activity	—	—	(75,000)	—
Subtotal	46,158	45,903	143,062	148,189
Non-cash compensation expense related to equity awards	11,391	8,434	34,743	25,922
Total antisense drug development expenses	$ 57,549	$ 54,337	$ 177,805	$ 174,111

In the first quarter of 2019, we received 2.8 million shares of Akcea common stock as payment for the $75 million sublicense fee Akcea owed us when Novartis licensed AKCEA-APO(a)-L_{Rx}. Akcea recognized the $75 million sublicense fee in its R&D development expenses. We eliminated this expense in our consolidated results. We expect to receive 6.9 million shares of Akcea common stock as payment for the $125 million sublicense fee Akcea will owe us once the Pfizer license of AKCEA-ANGPTL3-L_{Rx} closes. We expect Akcea will recognize the $125 million sublicense fee in its R&D expenses in the fourth quarter of 2019. We will eliminate this expense in our consolidated results.

We may conduct multiple clinical trials on a drug candidate, including multiple clinical trials for the various indications we may be studying. Furthermore, as we obtain results from trials we may elect to discontinue clinical trials for certain drug candidates in certain indications in order to focus our resources on more promising drug candidates or indications. Our Phase 1 and Phase 2 programs are clinical research programs that fuel our Phase 3 pipeline. When our products are in Phase 1 or Phase 2 clinical trials, they are in a dynamic state in which we may adjust the development strategy for each product. Although we may characterize a product as “in Phase 1” or “in Phase 2,” it does not mean that we are conducting a single, well-defined study with dedicated resources. Instead, we allocate our internal resources on a shared basis across numerous products based on each product’s particular needs at that time. This means we are constantly shifting resources among products. Therefore, what we spend on each product during a particular period is usually a function of what is required to keep the products progressing in clinical development, not what products we think are most important. For example, the number of people required to start a new study is large, the number of people required to keep a study going is modest and the number of people required to finish a study is large. However, such fluctuations are not indicative of a shift in our emphasis from one product to another and cannot be used to accurately predict future costs for each product. And, because we always have numerous medicines in preclinical and early stage clinical research, the fluctuations in expenses from medicine to medicine, in large part, offset one another. If we partner a medicine, it may affect the size of a trial, its timing, its total cost and the timing of the related costs.

Manufacturing and Operations

Expenditures in our manufacturing and operations function consist primarily of personnel costs, specialized chemicals for oligonucleotide manufacturing, laboratory supplies and outside services. Our manufacturing and operations function is responsible for providing drug supplies to antisense drug development, Akcea and our collaboration partners. Our manufacturing procedures include testing to satisfy good laboratory and good manufacturing practice requirements.

Our manufacturing and operations expenses were as follows (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2019	2018	2019	2018
Manufacturing and operations expenses, excluding non-cash compensation expense related to equity awards	$ 9,582	$ 8,085	$ 29,064	$ 30,083
Non-cash compensation expense related to equity awards	2,441	2,236	7,022	7,024
Total manufacturing and operations expenses	$ 12,023	$ 10,321	$ 36,086	$ 37,107

Our manufacturing and operations expenses by segment were as follows (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2019	2018	2019	2018
Ionis Core	$ 8,059	$ 6,931	$ 24,919	$ 24,659
Akcea Therapeutics	7,038	1,154	9,659	10,653
Elimination of intercompany activity	(5,515)	—	(5,515)	(5,229)
Subtotal	9,582	8,085	29,064	30,083
Non-cash compensation expense related to equity awards	2,441	2,236	7,022	7,024
Total manufacturing and operations expenses	$ 12,023	$ 10,321	$ 36,086	$ 37,107

R&D Support

In our research, development and patent expenses, we include support costs such as rent, repair and maintenance for buildings and equipment, utilities, depreciation of laboratory equipment and facilities, amortization of our intellectual property, informatics costs, procurement costs and waste disposal costs. We call these costs R&D support expenses.

The following table sets forth information on R&D support expenses (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2019	2018	2019	2018
Personnel costs	$ 3,666	$ 3,259	$ 10,990	$ 9,456
Occupancy	2,463	2,379	6,894	6,281
Patent expenses	600	513	1,796	1,745
Depreciation and amortization	130	115	389	315
Insurance	498	364	1,321	1,230
Other	1,454	1,382	5,101	4,186
Total R&D support expenses, excluding non-cash compensation expense related to equity awards	8,811	8,012	26,491	23,213
Non-cash compensation expense related to equity awards	4,897	3,731	14,364	11,548
Total R&D support expenses	$ 13,708	$ 11,743	$ 40,855	$ 34,761

R&D support expenses were slightly higher for the three and nine months ended September 30, 2019, compared to the same period in 2018, primarily due to costs associated with the growth of our business. All amounts exclude non-cash compensation expense related to equity awards.

Our R&D support expenses by segment were as follows (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2019	2018	2019	2018
Ionis Core	$ 7,097	$ 7,225	$ 21,961	$ 20,464
Akcea Therapeutics	1,757	832	4,659	2,865
Elimination of intercompany activity	(43)	(45)	(129)	(116)
Subtotal	8,811	8,012	26,491	23,213
Non-cash compensation expense related to equity awards	4,897	3,731	14,364	11,548
Total R&D support expenses	$ 13,708	$ 11,743	$ 40,855	$ 34,761

Selling, General and Administrative Expenses

Selling, general and administrative expenses include personnel and outside costs associated with the pre-commercialization and commercialization activities for our medicines and costs to support our company, our employees and our stockholders including, legal, human resources, investor relations, and finance. Additionally, we include in selling, general and administrative expenses such costs as rent, repair and maintenance of buildings and equipment, depreciation and utilities costs that we need to support the corporate functions listed above. We also include fees we owe under our in-licensing agreements related to SPINRAZA.

The following table sets forth information on selling, general and administrative expenses (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2019	2018	2019	2018
Selling, general and administrative expenses, excluding non-cash compensation expense related to equity awards	$ 59,781	$ 52,609	$ 164,122	$ 139,051
Non-cash compensation expense related to equity awards	255	16,103	39,246	39,512
Total selling, general and administrative expenses	$ 60,036	$ 68,712	$ 203,368	$ 178,563

SG&A expenses were higher for the three and nine months ended September 30, 2019, compared to the same periods in 2018, principally due to the cost of commercializing TEGSEDI and WAYLIVRA. All amounts exclude non-cash compensation expense related to equity awards.

Our selling, general and administrative expenses by segment were as follows (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2019	2018	2019	2018
Ionis Core	$ 18,470	$ 16,060	$ 53,651	$ 54,254
Akcea Therapeutics	41,311	44,450	110,470	92,248
Elimination of intercompany activity	—	(7,901)	—	(7,451)
Subtotal	59,781	52,609	164,121	139,051
Non-cash compensation expense related to equity awards	255	16,103	39,247	39,512
Total selling, general and administrative expenses	$ 60,036	$ 68,712	$ 203,368	$ 178,563

Akcea Therapeutics, Inc.

The following table sets forth information on operating expenses (in thousands) for our Akcea Therapeutics business segment:

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2019	2018	2019	2018
Cost of products sold	$ 2,275	$ —	$ 10,246	$ —
Development and patent expenses	21,983	27,068	135,388	89,940
Selling, general and administrative expenses	41,311	44,450	110,470	92,248
Profit (loss) share for TEGSEDI commercialization activities	(8,889)	—	(29,410)	—
Total operating expenses, excluding non-cash compensation expense related to equity awards	56,680	71,518	226,694	182,188
Non-cash compensation expense related to equity awards	(3,465)	12,731	29,458	31,240
Total Akcea Therapeutics operating expenses	$ 53,215	$ 84,249	$ 256,152	$ 213,428

In the third quarter of 2018, Akcea began recognizing cost of products sold expenses after the approval of TEGSEDI.

Akcea's development and patent expenses increased for the nine months ended September 30, 2019, compared to the same period in 2018 as a result of the one-time $75 million sublicense fee it paid to Ionis in Akcea common stock for Ionis' portion of the license fee Akcea received from Novartis in the first quarter of 2019. Excluding this one-time sublicense fee, Akcea's development expenses decreased primarily because Akcea has transitioned all further development of AKCEA-APO(a)-L_{Rx} to Novartis. In the fourth quarter of 2019, we expect Akcea's development expenses to increase as a result of the one-time $125 million sublicense fee Akcea expects to pay to Ionis once the Pfizer license of AKCEA-ANGPTL3-L_{Rx} closes. The sublicense fees Akcea pays Ionis are eliminated in our consolidated results.

Akcea's SG&A expenses increased in the three and nine months ended September 30, 2019 compared to the same periods in 2018, primarily due to Akcea's commercialization of TEGSEDI and WAYLIVRA. For each period presented, we allocated a portion of Ionis' SG&A expenses to Akcea for work we performed on Akcea's behalf. We include these allocated expenses in Akcea's SG&A expenses in the table above. All amounts exclude non-cash compensation expense related to equity awards.

In the first quarter of 2019, we began sharing profits and losses for TEGSEDI with Akcea under our TTR licensing agreement. As Akcea is the principal for all commercial activities related to the TTR License Agreement, Akcea records all activities related to TEGSEDI on a gross basis in its statement of operations based on the nature of the activity, including revenues, cost of products sold and sales and marketing expenses. Ionis' share of the net profit/loss from commercializing TEGSEDI is separately presented on Akcea's statement of operations on the line titled "Profit (loss) share for TEGSEDI commercialization activities". Since TEGSEDI is currently generating a loss, this represents the amount Ionis owes Akcea under the licensing agreement for its share of the net loss of TEGSEDI commercialization activities during the period. For the three and nine months ended September 30, 2019, our share of losses for TEGSEDI commercialization activities was $8.9 million and $29.4 million, respectively. With the launch of WAYLIVRA in the third quarter of 2019, Akcea will now pay Ionis royalties on WAYLIVRA product sales. We eliminate these amounts in our consolidated results.

All amounts exclude non-cash compensation expense related to equity awards.

Investment Income

Investment income for the three and nine months ended September 30, 2019 was $13.1 million and $39.0 million, respectively, compared to $10.0 million and $18.7 million for the same periods in 2018. The increase in investment income was primarily due to our significantly higher average cash balance during the first nine months of 2019 compared to the same period in 2018.

Interest Expense

The following table sets forth information on interest expense (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2019	2018	2019	2018
Convertible notes:				
Non-cash amortization of the debt discount and debt issuance costs	$ 9,558	$ 8,856	$ 28,140	$ 26,072
Interest expense payable in cash	1,714	1,714	5,141	5,141
Interest on mortgage for primary R&D and manufacturing facilities	607	607	1,790	1,802
Other	123	105	333	317
Total interest expense	$ 12,002	$ 11,282	$ 35,404	$ 33,332

Income Tax Benefit (Expense)

We recorded an income tax benefit of $14.9 million and an income tax expense of $9.2 million for the three and nine months ended September 30, 2019, compared to income tax expense of $0.5 million and $0.8 million for the same periods in 2018, respectively. The tax benefit recorded for the three months ended September 30, 2019 varies from what we would have recorded using the U.S. federal statutory rate primarily due to a state tax benefit resulting from our combined state tax filings with Akcea, estimated R&D and orphan drug credits, excess tax benefits related to share-based compensation and a benefit related to a change in the estimated tax value of Akcea shares we received in 2018. The increase in our income tax expense for the nine months ended September 30, 2019, compared to the same period in 2018, was primarily due to our expectation that we will generate U.S. federal and state taxable income in 2019. We expect to utilize our deferred tax assets to partially offset our U.S. federal taxable income.

Net Income (Loss)

We had a net loss of $18.4 million and net income of $99.3 million for the three and nine months ended September 30, 2019, respectively, compared to a net loss of $20.4 million and $87.7 million for the same periods in 2018. Our net income was primarily due to increased revenue year-over-year.

Net Loss Attributable to Noncontrolling Interest in Akcea Therapeutics, Inc.

At September 30, 2019, we owned approximately 75 percent of Akcea. The shares of Akcea that third parties own represent an interest in Akcea's equity that we do not control. However, because we continue to maintain overall control of Akcea through our voting interest, we reflect the assets, liabilities and results of operations of Akcea in our consolidated financial statements. We reflect the noncontrolling interest attributable to other owners of Akcea's common stock in a separate line called “Net loss attributable to noncontrolling interest in Akcea” on our statement of operations. Our noncontrolling interest in Akcea on our statement of operations for the three and nine months ended September 30, 2019, was a loss of $7.7 million and $10.4 million, respectively, compared to $15.8 million and $41.4 million for the same periods in 2018.

Net Income (Loss) Attributable to Ionis Pharmaceuticals, Inc. Common Stockholders and Net Income (Loss) per Share

We had net income attributable to our common stockholders’ of $26.2 million for the three months ended September 30, 2019, compared to a net loss attributable to our common stockholders’ of $4.6 million for the same period in 2018. For the nine months ended September 30, 2019 we reported net income attributable to our common stockholders of $109.7 million, compared to a net loss attributable to our common stockholders of $46.3 million for the same period in 2018. The increase was primarily due to increases in revenue.

For the three months ended September 30, 2019, basic and diluted net loss per share were $0.19 and $0.18, respectively, compared to $0.03 for the same period in 2018. For the nine months ended September 30, 2019, basic and diluted net income per share were $0.81 and $0.79, respectively, compared to $0.33 for the same period in 2018.

Liquidity and Capital Resources

We have financed our operations primarily from research and development collaborative agreements. We also finance our operations from commercial revenue from SPINRAZA royalties and product sales. From our inception through September 30, 2019, we have earned approximately $3.8 billion in revenue. We have also financed our operations through the sale of our equity securities and the issuance of long-term debt. From the time we were founded through September 30, 2019, we have raised net proceeds of approximately $1.8 billion from the sale of our equity securities, not including the $182.4 million Akcea received in net proceeds from its IPO in July 2017. Additionally, we have borrowed approximately $1.4 billion under long-term debt arrangements to finance a portion of our operations over the same time period.

At September 30, 2019, we had cash, cash equivalents and short-term investments of $2.2 billion and stockholders' equity of $1.5 billion. In comparison, we had cash, cash equivalents and short-term investments of $2.1 billion and stockholders' equity of $1.2 billion at December 31, 2018. Our cash, cash equivalents and short-term investments increased in the first nine months of 2019 primarily from payments we received from Biogen, Novartis and Roche. We expect to receive $260 million in payments we generated from Pfizer and Bayer so far in the fourth quarter of 2019.

In September 2019, our board of directors approved an initial share repurchase program of up to $125 million of our common stock. Our stock repurchase program has no expiration date. To date, we have not repurchased any shares of our common stock. We plan to make stock repurchases under this program over time in open market transactions. We may consider additional share repurchases in the future as part of our overall capital allocation strategy.

At September 30, 2019, we had consolidated working capital of $2.2 billion compared to $1.9 billion at December 31, 2018. As of September 30, 2019, our debt and other obligations totaled $763.4 million compared to $763.9 million at December 31, 2018. The increase in our debt and other obligations is from the operating lease liability we added to our balance sheet when we adopted the new accounting guidance for leases on January 1, 2019.

The following table summarizes our contractual obligations as of September 30, 2019. The table provides a breakdown of when obligations become due. We provide a more detailed description of the major components of our debt in the paragraphs following the table:

Contractual Obligations	**Payments Due by Period (in millions)**				
(selected balances described below)	**Total**	**Less than 1 year**	**1-3 years**	**3-5 years**	**After 5 years**
Convertible senior notes (principal and interest payable)	$ 702.6	$ 6.9	$ 695.7	$ —	$ —
Building mortgage payments	$ 78.8	$ 2.4	$ 4.9	$ 6.9	$ 64.6
Other obligations (principal and interest payable)	$ 1.0	$ 0.1	$ 0.1	$ 0.1	$ 0.7
Operating leases	$ 24.3	$ 3.3	$ 5.9	$ 5.0	$ 10.1
Total	$ 806.7	$ 12.7	$ 706.6	$ 12.0	$ 75.4

Our contractual obligations consist primarily of our convertible debt. In addition, we also have facility mortgages, facility leases and other obligations. Due to the uncertainty with respect to the timing of future cash flows associated with our unrecognized tax benefits, we are unable to make reasonably reliable estimates of the period of cash settlement with the respective taxing authorities. Therefore, we have excluded our gross unrecognized tax benefits from our contractual obligations table above.

1 Percent Convertible Senior Notes

In November 2014, we completed a $500 million offering of convertible senior notes, which mature in 2021 and bear interest at 1 percent. We used a substantial portion of the net proceeds from the issuance of the 1 percent convertible senior notes to repurchase $140 million in principal of our 2¾ percent convertible senior notes. As a result, the principal balance of the 2¾ percent notes following the repurchase in November 2014 was $61.2 million.

In December 2016, we issued an additional $185.5 million of 1 percent convertible senior notes in exchange for the redemption of $61.1 million of our 2¾ percent convertible senior notes. At September 30, 2019, we had a nominal amount of our 2¾ percent convertible senior notes outstanding. At September 30, 2019, we had the following 1 percent convertible senior notes outstanding (amounts in millions except price per share data):

	1 Percent Convertible Senior Notes
Outstanding principal balance	$ 685.5
Original issue date ($500 million of principal)	November 2014
Additional issue date ($185.5 million of principal)	December 2016
Maturity date	November 2021
Interest rate	1 percent
Conversion price per share	$ 66.81
Total shares of common stock subject to conversion	10.3

Interest is payable semi-annually. The notes are convertible under certain conditions, at the option of the note holders. We settle conversions of the notes, at our election, in cash, shares of our common stock or a combination of both. We may not redeem the 1 percent notes prior to maturity, and no sinking fund is provided for them. Holders of the 1 percent notes may require us to purchase some or all of their notes upon the occurrence of certain fundamental changes, as set forth in the indenture governing the 1 percent notes, at a purchase price equal to 100 percent of the principal amount of the notes to be purchased, plus accrued and unpaid interest.

Financing Arrangement

In June 2015, we entered into a five-year revolving line of credit agreement with Morgan Stanley Private Bank, National Association, or Morgan Stanley, which we amended in February 2016. Under the amended credit agreement, Morgan Stanley provided a maximum of $30 million of revolving credit for general working capital purposes. During the third quarter of 2019, we paid off our total outstanding borrowings of $12.5 million under the agreement and subsequently terminated the agreement.

Research and Development and Manufacturing Facilities

In July 2017, we purchased the building that houses our primary R&D facility for $79.4 million. We purchased our manufacturing facility in July 2017 for $14.0 million. We financed the purchase of our primary R&D facility and manufacturing facility, with mortgage debt of $51.3 million and $9.1 million, respectively. Our primary R&D facility mortgage has an interest rate of 3.88 percent. Our manufacturing facility mortgage has an interest rate of 4.20 percent. During the first five years of both mortgages, we are only required to make interest payments. Both mortgages mature in August 2027.

Other Obligations

In addition to contractual obligations, we had outstanding purchase orders as of September 30, 2019 for the purchase of services, capital equipment and materials as part of our normal course of business.

We plan to continue to enter into collaborations with partners to provide for additional revenue to us and we may incur additional cash expenditures related to our obligations under any of the new agreements we may enter into. We currently intend to use our cash, cash equivalents and short-term investments to finance our activities. However, we may also pursue other financing alternatives, like issuing additional shares of our common stock, issuing debt instruments, refinancing our existing debt, or securing lines of credit. Whether we use our existing capital resources or choose to obtain financing will depend on various factors, including the future success of our business, the prevailing interest rate environment and the condition of financial markets generally.

ITEM 3. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

We are exposed to changes in interest rates primarily from our long-term debt arrangements and, secondarily, investments in certain short-term investments. We primarily invest our excess cash in highly liquid short-term investments of the U.S. Treasury and reputable financial institutions, corporations, and U.S. government agencies with strong credit ratings. We typically hold our investments for the duration of the term of the respective instrument. We do not utilize derivative financial instruments, derivative commodity instruments or other market risk sensitive instruments, positions or transactions to manage exposure to interest rate changes. Accordingly, we believe that, while the securities we hold are subject to changes in the financial standing of the issuer of such securities, we are not subject to any material risks arising from changes in interest rates, commodity prices, equity prices or other market changes that affect market risk sensitive instruments.

We are also exposed to changes in foreign currency exchange rates as we have foreign subsidiaries with functional currencies other than the U.S. dollar. We translate our subsidiaries' functional currencies into 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 percent 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 related to TEGSEDI and WAYLIVRA, therefore we expect that the impact of foreign currency exchange rate fluctuations may become more substantial in the future.

ITEM 4. 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 September 30, 2019. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to September 30, 2019.

We also performed an evaluation of any changes in our internal controls over financial reporting that occurred during our last fiscal quarter and that have materially affected, or are reasonably likely to materially affect, our internal controls over financial reporting. 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 changes in our internal controls over financial reporting that occurred during our latest fiscal quarter and that have materially affected, or are reasonably likely to materially affect, our internal controls over financial reporting.

PART II — OTHER INFORMATION

ITEM 1. LEGAL PROCEEDINGS

Not applicable.

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. We have marked with an asterisk those risk factors that reflect substantive changes from the risk factors included in our Annual Report on Form 10-K for the year ended December 31, 2018.

Risks Associated with our Ionis Core and Akcea Therapeutics Businesses

If the market does not accept our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, we are not likely to generate revenues or become consistently profitable.

Even if our medicines are authorized for marketing, including SPINRAZA, TEGSEDI and WAYLIVRA, our success will depend upon the medical community, patients and third-party payors accepting our medicines as medically useful, cost-effective and safe. Even when the FDA or foreign regulatory authorities authorize our or our partners' medicines for commercialization, doctors may not prescribe our medicines to treat patients. We and our partners may not successfully commercialize additional medicines.

Additionally, in many of the markets where we may sell our medicines in the future, if we cannot agree with the government regarding the price we can charge for our medicines, then we may not be able to sell our medicines in that market. Similarly, cost control initiatives by governments or third-party payors could decrease the price received for our medicines or increase patient coinsurance to a level that makes our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, unaffordable.

The degree of market acceptance for our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, 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 medicines and their potential advantages over competing products;
- cost and effectiveness of our medicines compared to other available therapies;
- patient convenience of the dosing regimen for our medicines; and
- reimbursement policies of government and third-party payors.

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

For example, the product label for TEGSEDI in the U.S. has a boxed warning for thrombocytopenia and glomerulonephritis, requires periodic blood and urine monitoring, and TEGSEDI has a Risk Evaluation and Mitigation Strategy, or REMS, program. Our main competition in the U.S. market for TEGSEDI is ONPATTRO (patisiran), marketed by Alnylam Pharmaceuticals, Inc. Although ONPATTRO requires intravenous administration and pre-treatment with steroids, it does not have a boxed warning or REMS. Additionally, in the clinical studies with WAYLIVRA, declines in platelet counts were observed in many patients and some patients discontinued the studies because of platelet declines. The product label for WAYLIVRA requires periodic blood monitoring. In each case, these label requirements could negatively affect our ability to attract and retain patients for these medicines. 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 and Akcea can better maintain patients on TEGSEDI and WAYLIVRA through patient-centric commercial approaches where we plan to have greater involvement with physicians and patients, if we cannot effectively maintain patients on TEGSEDI or WAYLIVRA, we may not be able to generate substantial revenue from TEGSEDI or WAYLIVRA sales.

If we or our partners fail to compete effectively, our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, will not contribute significant revenues.*

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

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

These competitive developments could make our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, obsolete or non-competitive.

Certain of our partners are pursuing other technologies or developing other medicines either on their own or in collaboration with others, including our competitors, to treat the same diseases our own collaborative programs target. Competition may negatively impact a partner's focus on and commitment to our medicines and, as a result, could delay or otherwise negatively affect the commercialization of our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA.

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 of new pharmaceutical products, in obtaining FDA and other regulatory authorizations of such products and in commercializing such 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 medicines, and we will primarily rely on our partners and Akcea to provide this capability.

There are several pharmaceutical and biotechnology companies engaged in the development or commercialization of products against targets that are also targets of products in our development pipeline. For example, ZOLGENSMA (approved in the U.S. for the treatment of pediatric patients less than two years of age with SMA), risdiplam (RG7916), reldesemtiv and firdapse could compete with SPINRAZA, and ONPATTRO (approved in the U.S. and Europe for a similar indication as TEGSEDI), VYNDAQEL and VYNDAMAX (approved in the U.S. for patients with both hereditary and wild type ATTR cardiomyopathy and in the EU for stage 1 hATTR amyloidosis with polyneuropathy), AG10, CRX-1008 and vutrisiran could compete with TEGSEDI. Also, metreleptin and gemcabene could compete with WAYLIVRA, while laquinimod, OMS823, selistat, VX15, WVE-120101 and WVE-120102 could compete with IONIS-HTT_{Rx}. Furthermore, arimoclomol could potentially compete with tofersen.

Following approval, our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA could be subject to regulatory limitations. *

Following approval of a medicine, we and our partners must comply with comprehensive government regulations regarding the manufacture, marketing and distribution of drug products. We or our partners may not obtain the labeling claims necessary or desirable to successfully commercialize our drug products, including SPINRAZA, TEGSEDI and WAYLIVRA.

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

- in the U.S., TEGSEDI's label contains a boxed warning for thrombocytopenia and glomerulonephritis;
- TEGSEDI requires periodic blood and urine monitoring;
- in the U.S., TEGSEDI is available only through a Risk Evaluation and Mitigation Strategy, or REMS, program; and
- WAYLIVRA will require periodic blood monitoring.

In addition, when approved, the FDA or a foreign regulatory authority may condition approval on the performance of post-approval clinical studies or patient monitoring, which could be time consuming and expensive. For example, in connection with the conditional marketing approval for WAYLIVRA in the EU, we are required to conduct a post-authorization safety study to evaluate the safety of WAYLIVRA on thrombocytopenia and bleeding in FCS patients taking WAYLIVRA. If the results of such post-marketing studies are not satisfactory, the FDA 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.

If we or others identify side effects after any of our drug products are on the market, or if manufacturing problems occur subsequent to regulatory approval, we or our partners may lose regulatory approval, or we or our partners may need to conduct additional clinical studies and/or change the labeling of our drug products, including SPINRAZA, TEGSEDI and WAYLIVRA.

We depend on our collaboration with Biogen for the development and commercialization of SPINRAZA.

We have entered into a collaborative arrangement with Biogen to develop and commercialize SPINRAZA. We entered into this collaboration primarily to:

- fund our development activities for SPINRAZA;
- seek and obtain regulatory approvals for SPINRAZA; and
- successfully commercialize SPINRAZA.

We are relying on Biogen to obtain additional regulatory approvals for SPINRAZA, and successfully commercialize SPINRAZA. In general, we cannot control the amount and timing of resources that Biogen devotes to our collaboration. If Biogen fails to further develop SPINRAZA, obtain additional regulatory approvals for SPINRAZA, or commercialize SPINRAZA, or if Biogen's efforts are not effective, our business may be negatively affected.

Our collaboration with Biogen may not continue for various reasons. Biogen can terminate our collaboration at any time. If Biogen stops developing or commercializing SPINRAZA, we would have to seek or spend additional funding, and SPINRAZA's commercialization may be harmed or delayed.

Our collaboration with Biogen may not result in the continued successful commercialization of SPINRAZA. If Biogen does not continue to successfully commercialize SPINRAZA, we will receive limited revenues for SPINRAZA.

If Akcea cannot optimize and maintain effective marketing and sales capabilities or enter into agreements with third parties to market and sell TEGSEDI and WAYLIVRA, we may not generate significant product revenue from TEGSEDI or WAYLIVRA.*

To successfully commercialize TEGSEDI and WAYLIVRA, Akcea must effectively manage its marketing, sales and distribution capabilities or make arrangements with third parties to perform these services. Akcea may not be successful in doing so. To commercialize TEGSEDI and WAYLIVRA in the initial indications Akcea is pursuing, Akcea will need to optimize and maintain a specialty sales force in each global region it expects to market TEGSEDI and WAYLIVRA, supported by case managers, reimbursement specialists, partnerships with specialty pharmacies, injection training, routine blood and urine monitoring and a medical affairs team. It will be expensive and time consuming for Akcea to maintain its own sales force and related compliance protocols to market TEGSEDI and WAYLIVRA. Akcea may never successfully optimize or manage this capability and any failure could preclude the successful commercialization of TEGSEDI and/or WAYLIVRA. Additionally, Akcea and its partners, if any, will have to compete with other companies to recruit, hire, train, manage and retain marketing and sales personnel.

Akcea incurred expenses prior to the launch of TEGSEDI and WAYLIVRA to integrate and manage the associated marketing and sales infrastructure. If regulatory requirements or other factors cause the commercial launch of TEGSEDI or WAYLIVRA to be less successful than expected, Akcea will have incurred expenses for having invested in these capabilities prior to realizing any significant revenue from sales of TEGSEDI or WAYLIVRA. Akcea's sales force and marketing teams may not successfully commercialize TEGSEDI or WAYLIVRA.

Akcea may seek to further penetrate markets by expanding its sales force or through strategic partnerships with other pharmaceutical or biotechnology companies or third-party sales organizations. To the extent we and Akcea decide to rely on third parties to commercialize TEGSEDI or WAYLIVRA in a particular geographic market, such as the collaboration Akcea has with PTC Therapeutics to commercialize TEGSEDI and WAYLIVRA in Latin America, we may receive less revenue than if Akcea commercialized TEGSEDI or WAYLIVRA by itself. Further we would have less control over the sales efforts of any other third parties involved in commercializing TEGSEDI or WAYLIVRA.

Even though certain members of Akcea's management team and other employees have experience commercializing drug products, Akcea has no prior experience marketing, selling or distributing drug products, and there are significant risks involved in building and managing a commercial infrastructure. If Akcea cannot effectively build and manage its 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 TEGSEDI and WAYLIVRA 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. In September 2019, Akcea announced several changes to its senior leadership team, including the departure of its Chief Executive Officer, President, and Chief Operating Officer and the appointment of two new Board members and an interim Chief Executive Officer. These transitions could impair Akcea's ability to manage its business.

If government or other third-party payors fail to provide adequate coverage and payment rates for our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, our revenue will be limited.

In both domestic and foreign markets, sales of our current and future products will depend in part upon the availability of coverage and reimbursement from third-party payors. The majority of people in the U.S. who would fit within our target patient populations for our medicines 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 medicines affordable.

Third-party payors, whether foreign or domestic, or governmental or commercial, are developing increasingly sophisticated methods of controlling healthcare costs. In addition, in the U.S., 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 U.S. and in international markets. For example, in the U.S., recent health reform measures have resulted in reductions in Medicare and other healthcare funding, and there have been several 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 medicines may not be available or adequate in either the U.S. or international markets, which would negatively affect the potential commercial success of our products, our revenue and our profits.

If Biogen cannot manufacture finished drug product for SPINRAZA or the post-launch supply of the active drug substance for SPINRAZA, SPINRAZA may not maintain commercial success.

Biogen is responsible for the long-term supply of both SPINRAZA drug substance and finished drug product. Biogen may not be able to reliably manufacture SPINRAZA drug substance and drug product to support the long-term commercialization of SPINRAZA. If Biogen cannot reliably manufacture SPINRAZA drug substance and drug product, SPINRAZA may not maintain commercial success, which will harm our ability to generate revenue.

If we or our partners fail to obtain regulatory approval for our medicines and additional approvals for SPINRAZA, TEGSEDI and WAYLIVRA, we or our partners cannot sell them in the applicable markets.*

We cannot guarantee that any of our medicines will be considered safe and effective, or will be approved for commercialization. In addition, we cannot guarantee that SPINRAZA, TEGSEDI and WAYLIVRA will be approved in additional markets or for additional indications. We and our partners must conduct time-consuming, extensive and costly clinical studies to show the safety and efficacy of each of our medicines before they can be approved for sale. We must conduct these studies in compliance with FDA regulations and with comparable regulations in other countries.

We and our partners may not obtain necessary regulatory approvals on a timely basis, if at all, for our medicines. It is possible that regulatory agencies will not approve our medicines for marketing or additional marketing authorizations for SPINRAZA, TEGSEDI or WAYLIVRA. If the FDA or another regulatory agency believes that we or our partners have not sufficiently demonstrated the safety or efficacy of any of our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, the agency will not approve the specific medicine or will require additional studies, which can be time consuming and expensive and which will delay or harm commercialization of the medicine. For example, Akcea received a CRL from the FDA and a preliminary notice of noncompliance withdrawal letter from Health Canada for WAYLIVRA. As result, Akcea may need to submit additional data to the FDA and Health Canada or conduct additional clinical studies before obtaining marketing authorization, which would be expensive and cause delays.

Failure to receive marketing authorization for our medicines, or failure to receive additional marketing authorizations for SPINRAZA, TEGSEDI or WAYLIVRA, or delays in these authorizations could prevent or delay commercial introduction of the medicine, and, as a result, could negatively impact our ability to generate revenue from product sales.

If the results of clinical testing indicate that any of our medicines 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 medicines are a relatively new approach to therapeutics. If we cannot demonstrate that our medicines are safe and effective for human use, we may need to abandon one or more of our drug development programs.

In the past, we have invested in clinical studies of medicines that have not met the primary clinical end points in their Phase 3 studies. Similar results could occur in clinical studies for our medicines, including the study of WAYLIVRA in patients with FPL, the study of IONIS-HTT_{Rx} in patients with Huntington's disease and the study of tofersen in adults with SOD1-ALS. If any of our medicines in clinical studies, including WAYLIVRA, IONIS-HTT_{Rx} and tofersen do not show sufficient efficacy in patients with the targeted indication, it could negatively impact our development and commercialization goals for these medicines and our stock price could decline.

Even if our medicines are successful in preclinical and human clinical studies, the medicines may not be successful in late-stage clinical studies.*

Successful results in preclinical or initial human clinical studies, including the Phase 2 results for some of our medicines in development, may not predict the results of subsequent clinical studies, including the study of WAYLIVRA in patients with FPL, the study of IONIS-HTT_{Rx} in patients with Huntington's disease and the study of tofersen in adults with SOD1-ALS. 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 medicine on subjects in the trial;
- we may decide, or regulators may require us, to conduct additional preclinical testing or clinical studies;
- enrollment in our clinical studies may be slower than we anticipate;
- people 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;
- the cost of our clinical studies may be greater than we anticipate; and
- the supply or quality of our medicines or other materials necessary to conduct our clinical studies may be insufficient, inadequate or delayed.

In addition, our current medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, are chemically similar to each other. As a result, a safety observation we encounter with one of our medicines could have, or be perceived by a regulatory authority to have, an impact on a different medicine 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 medicines 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 medicines: 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 recently completed a study of WAYLIVRA in patients with FPL and we have an ongoing open-label extension study of WAYLIVRA in patients with FCS, an ongoing open-label extension study of TEGSEDI and expanded access programs for each medicine. Adverse events or results from these studies could negatively impact our current or planned marketing approval applications for WAYLIVRA or the commercial opportunity for each product.

Any failure or delay in the clinical studies, including the study of IONIS-HTT_{Rx} in patients with Huntington's disease and the study of tofersen in adults with SOD1-ALS, could reduce the commercial potential or viability of our medicines.

If we cannot manufacture our medicines or contract with a third party to manufacture our medicines at costs that allow us to charge competitive prices to buyers, we cannot market our products profitably.

To successfully commercialize any of our medicines, we or our partner would need to establish large-scale commercial manufacturing capabilities either on our own or through a third-party manufacturer. We and Akcea will rely on third-party manufacturers to supply the drug substance and drug product for TEGSEDI and WAYLIVRA. In addition, as our drug development pipeline increases and matures, we will have a greater need for clinical trial and commercial manufacturing capacity. We have limited experience manufacturing pharmaceutical products of the chemical class represented by our medicines, called oligonucleotides, on a commercial scale for the systemic administration of a medicine. There are a small number of suppliers for certain capital equipment and raw materials that we use to manufacture our medicines, and some of these suppliers will need to increase their scale of production to meet our projected needs for commercial manufacturing. Further, we must continue to improve our manufacturing processes to allow us to reduce our drug costs. We may not be able to manufacture our medicines at a cost or in quantities necessary to make commercially successful products.

Also, manufacturers, including us, 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. We and 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 medicines, including authorizations for SPINRAZA, TEGSEDI and WAYLIVRA, or result in enforcement action after authorization that could limit the commercial success of our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA.

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

We depend on independent clinical investigators, contract research organizations and other third-party service providers to conduct our clinical studies for our medicines and expect to continue to do so in the future. For example, we use clinical research organizations, such as Icon Clinical Research Limited, INC Research Toronto, Inc. and Medpace for the clinical studies for our medicines, including TEGSEDI and WAYLIVRA. 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 and approved protocols for the study. 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 third 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 medicines or additional authorizations for SPINRAZA, TEGSEDI and WAYLIVRA.

Risks Associated with our Businesses as a Whole

We have incurred losses, and our business will suffer if we fail to consistently achieve profitability in the future.*

Because drug discovery and development requires substantial lead-time and money prior to commercialization, our expenses have generally exceeded our revenue since we were founded in January 1989. As of September 30, 2019, we had an accumulated deficit of approximately $0.9 billion and stockholders' equity of approximately $1.5 billion. Most of our historical losses resulted from costs incurred in connection with our research and development programs and from selling, general and administrative costs associated with our operations. Most of our income has come from collaborative arrangements, including commercial revenue from royalties and R&D revenue, with additional income from research grants and the sale or licensing of our patents, as well as interest income. If we do not continue to earn substantial revenue, we may incur additional operating losses in the future. We may not successfully develop any additional products or achieve or sustain future profitability.

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

Under the Internal Revenue Code of 1986, as amended, or the Code, a corporation is generally allowed a deduction for net operating losses, or NOLs, carried over from a prior taxable year. Under that provision, we can carryforward our NOLs to offset our future taxable income, if any, until such NOLs are used or expire. The same is true of other unused tax attributes, such as tax credits.

Under the Tax Cut and Jobs Act of 2017, or the Tax Act, federal net operating losses incurred in 2018 and in future years may be carried forward indefinitely, but the deductibility of such federal net operating losses is limited. It is uncertain if and to what extent various states will conform to the newly enacted federal tax law.

In addition, under Section 382 of the Code, and corresponding provisions of state law, if a corporation undergoes an "ownership change," which is generally defined as a greater than 50 percent change, by value, in its equity ownership over a three-year period, the corporation's ability to use its pre-change net operating loss carryforwards and other pre-change tax attributes to offset its post-change income or taxes may be limited. We may experience ownership changes in the future as a result of subsequent shifts in our stock ownership, some of which may be outside of our control. If an ownership change occurs and our ability to use our net operating loss carryforwards or other tax attributes is materially limited, it would harm our future operating results by effectively increasing our future tax obligations.

Since corporate partnering is a significant part of our strategy to fund the development and commercialization of our development programs, if any of our collaborative partners fail to fund our collaborative programs, or if we cannot obtain additional partners, we may have to delay or stop progress on our drug development programs.

To date, corporate partnering has played a significant role in our strategy to fund our development programs and to add key development resources. We plan to continue to rely on additional collaborative arrangements to develop and commercialize our unpartnered medicines. However, we may not be able to negotiate favorable collaborative arrangements for these drug programs. If we cannot continue to secure additional collaborative partners, our revenues could decrease and the development of our medicines could suffer.

Our corporate partners are developing and/or funding many of the medicines in our development pipeline. If any of these pharmaceutical companies stops developing and/or funding these medicines, our business could suffer and we may not have, or be willing to dedicate, the resources available to develop these medicines on our own.

Our collaborators can terminate their relationships with us under certain circumstances, many of which are outside of our control. For example, as part of a reprioritization of its pipeline and strategic review of its rare disease business, GSK declined its option on TEGSEDI and IONIS-FB-L_{Rx}.

Even with funding from corporate partners, if our partners do not effectively perform their obligations under our agreements with them, it would delay or stop the progress of our drug development and commercial programs.

In addition to receiving funding, we enter into collaborative arrangements with third parties to:

- conduct clinical studies;
- seek and obtain marketing authorization; and
- manufacture, market and sell our medicines.

Once we have secured a collaborative arrangement to further develop and commercialize one of our drug development programs, such as our collaborations with AstraZeneca, Bayer, Biogen, GSK, Janssen, Novartis and Roche, these collaborations may not continue or result in commercialized medicines, or may not progress as quickly as we first anticipated.

For example, a collaborator such as AstraZeneca, Bayer, Biogen, GSK, Janssen, Novartis or Roche, could determine that it is in its financial interest to:

- pursue alternative technologies or develop alternative products that may be competitive with the medicine that is part of the collaboration with us;
- pursue higher-priority programs or change the focus of its own development programs; or
- choose to devote fewer resources to our medicines than it does for its own medicines.

If any of these occur, it could affect our partner's commitment to the collaboration with us and could delay or otherwise negatively affect the commercialization of our medicines, including SPINRAZA.

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 medicine will enter the clinic, when we anticipate completing a clinical study, or when we anticipate filing an application for, or obtaining, marketing authorization. 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' expectations, including milestones related to SPINRAZA, TEGSEDI and WAYLIVRA, the price of our securities could decrease.

If we cannot protect our patents 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 develop and secure intellectual property rights to proprietary products and services. However, we may not receive issued patents on any of our pending patent applications in the U.S. or in other countries. In addition, the scope of any of our issued 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.

Intellectual property litigation could be expensive and prevent us from pursuing our programs.

From time to time we have to defend our intellectual property rights. If we are involved in an intellectual property dispute, we sometimes need to litigate to defend our rights or assert them against others. Disputes can involve arbitration, litigation or proceedings declared by the U.S. Patent and Trademark Office or the International Trade Commission or foreign patent authorities. Intellectual property litigation can be extremely expensive, and this expense, as well as the consequences should we not prevail, could seriously harm our business.

If a third party claims that our medicines or technology infringe its patents or other intellectual property rights, we 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 U.S. 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.

If we fail to obtain timely funding, we may need to curtail or abandon some of our programs.*

Many of our medicines are undergoing clinical studies or are in the early stages of research and development. Most of our drug programs will require significant additional research, development, preclinical and/or clinical testing, marketing authorization and/or commitment of significant additional resources prior to their successful commercialization. As of September 30, 2019, we had cash, cash equivalents and short-term investments equal to approximately $2.2 billion. If we do not meet our goals to successfully commercialize our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, or to license our medicines and proprietary technologies, we will need additional funding in the future. Our future capital requirements will depend on many factors, such as the following:

- successful commercialization for SPINRAZA, TEGSEDI and WAYLIVRA;
- additional marketing approvals for WAYLIVRA and TEGSEDI;
- the profile and launch timing of our medicines, including TEGSEDI and WAYLIVRA;
- changes in existing collaborative relationships and our ability to establish and maintain additional collaborative arrangements;
- continued scientific progress in our research, drug discovery and development programs;
- the size of our programs and progress with preclinical and clinical studies;
- the time and costs involved in obtaining marketing authorizations; and
- competing technological and market developments, including the introduction by others of new therapies that address our markets.

If we need additional funds, we may need to raise them through public or private financing. Additional financing may not be available at all or on acceptable terms. If we raise additional funds by issuing equity securities, the shares of existing stockholders will be diluted and the price, as well as the price of our other securities, may decline. If adequate funds are not available or not available on acceptable terms, we may have to cut back on one or more of our research, drug discovery or development programs. Alternatively, we may obtain funds through arrangements with collaborative partners or others, which could require us to give up rights to certain of our technologies or medicines.

If our planned management transition is not successful our business could suffer.

In January 2020, Dr. Crooke, our founder and Chief Executive Officer, plans to transition from Chief Executive Officer to Executive Chairman of our Board of Directors. As Executive Chairman, Dr. Crooke will continue to be responsible for the activities of the board and will remain active in the company, providing strategic advice and continuing to participate in the scientific activities. Our board has selected Dr. Monia, who has been our Chief Operating Officer for the last year and a member of our team since our founding nearly 30 years ago, to serve as our Chief Executive Officer starting in January 2020. If this transition is not successful, our business could suffer.

The loss of key personnel, or the inability to 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 our 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 research and development work. We may not be able to attract and retain skilled and experienced scientific personnel on acceptable terms because of intense competition for experienced scientists among many pharmaceutical and health care companies, universities and non-profit research institutions. In addition, failure to succeed in clinical studies may make it more challenging to recruit and retain qualified scientific personnel.

If the price of our securities continues to be highly volatile, this could make it harder for you to liquidate your investment and could increase your risk of suffering a loss.*

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our securities. During the 12 months preceding September 30, 2019, the market price of our common stock ranged from $43.27 to $86.58 per share. Many factors can affect the market price of our securities, including, for example, fluctuations in our operating results, announcements of collaborations, clinical study results, technological innovations or new products being developed by us or our competitors, governmental regulation, marketing authorization, changes in payors' reimbursement policies, developments in patent or other proprietary rights, public concern regarding the safety of our medicines and general market conditions.

We cannot guarantee that we will repurchase shares of common stock under our stock repurchase program or that we will repurchase shares of common stock at favorable prices.*

In September 2019, our board of directors authorized a program to repurchase up to $125 million of our common stock. We can provide no assurance that we will repurchase shares at favorable prices, if at all, as the amount and timing of share repurchases under such program are subject to capital availability and our determination that share repurchases are in the best interest of our shareholders and in compliance with all applicable laws and agreements. Our ability to repurchase shares will depend upon, among other factors, our financial condition, results of operations, cash balances and potential future capital requirements for strategic transactions. In addition, the share repurchase program could impact the trading price of our stock and increase volatility, and any announcement of a reduction in or discontinuance of repurchases by us under such program may result in a decrease in the trading price of our stock.

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 SPINRAZA, TEGSEDI and WAYLIVRA. We have clinical study insurance coverage and commercial product liability insurance coverage. However, this insurance coverage may not be adequate to cover claims against us, or be available to us at an acceptable cost, if at all. Regardless of their merit or eventual outcome, product liability claims may result in decreased demand for our drug products, injury to our reputation, withdrawal of clinical study volunteers and loss of revenues. Thus, whether or not we are insured, 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 research, 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 store most of these materials and various wastes resulting from their use at our facilities in Carlsbad, California pending ultimate use and disposal. We cannot completely eliminate the risk of contamination, which could cause:

- interruption of our research, development and manufacturing 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 research, development or manufacturing 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 affected.

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

We manufacture our research and clinical supplies in a manufacturing facility located in Carlsbad, California. We manufacture the finished drug product for TEGSEDI and WAYLIVRA at third-party contract manufacturers. The facilities and the equipment we and our contract manufacturers use to research, develop and manufacture our medicines would be costly to replace and could require substantial lead time to repair or replace. Our facilities or our contract manufacturers may be harmed by natural or man-made disasters, including, without limitation, earthquakes, floods, fires and acts of terrorism; and if our facilities are affected by a disaster, our 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, our development and commercialization activities could be harmed or delayed by a shutdown of the U.S. government, including the FDA.

Provisions in our certificate of incorporation, other agreements and Delaware law may prevent stockholders from receiving a premium for their shares.

Our certificate of incorporation provides for classified terms for the members of our board of directors. Our certificate also includes a provision that requires at least 66 2/3 percent of our voting stockholders to approve a merger or certain other business transactions with, or proposed by, any holder of 15 percent or more of our voting stock, except in cases where certain directors approve the transaction or certain minimum price criteria and other procedural requirements are met.

Our certificate of incorporation also requires that any action required or permitted to be taken by our stockholders must be taken at a duly called annual or special meeting of stockholders and may not be taken by written consent. In addition, only our board of directors, chairman of the board or chief executive officer can call special meetings of our stockholders. We have in the past, and may in the future, implement a stockholders' rights plan, also called a poison pill, which could make it uneconomical for a third party to acquire our company on a hostile basis. In addition, our board of directors has the authority to fix the rights and preferences of, and issue shares of preferred stock, which may have the effect of delaying or preventing a change in control of our company without action by our stockholders.

The provisions of our convertible senior notes could make it more difficult or more expensive for a third party to acquire us. Upon the occurrence of certain transactions constituting a fundamental change, holders of the notes will have the right, at their option, to require us to repurchase all of their notes or a portion of their notes, which may discourage certain types of transactions in which our stockholders might otherwise receive a premium for their shares over the then current market prices.

These provisions, as well as Delaware law, including Section 203 of the Delaware General Corporation Law, and other of our agreements, may discourage certain types of transactions in which our stockholders might otherwise receive a premium for their shares over then current market prices, and may limit the ability of our stockholders to approve transactions that they think may be in their best interests.

Future sales of our common stock in the public market could adversely affect the trading price of our securities.

Future sales of substantial amounts of our common stock in the public market, or the perception that such sales could occur, could adversely affect trading prices of our securities. For example, we may issue approximately 10.3 million shares of our common stock upon conversion of our convertible senior notes. The addition of any of these shares into the public market may have an adverse effect on the price of our securities.

Our business is subject to changing regulations for corporate governance and public disclosure that has increased both our costs and the risk of noncompliance.

Each year we are required to evaluate our internal controls systems in order to allow management to report on and our Independent Registered Public Accounting Firm to attest to, our internal controls as required by Section 404 of the Sarbanes-Oxley Act. As a result, we continue to incur additional expenses and divert our management's time to comply with these regulations. In addition, if we cannot continue to comply with the requirements of Section 404 in a timely manner, we might be subject to sanctions or investigation by regulatory authorities, such as the SEC, the Public Company Accounting Oversight Board, or PCAOB, or The Nasdaq Global Select Market. Any such action could adversely affect our financial results and the market price of our common stock.

The SEC and other regulators have continued to adopt new rules and regulations and make additional changes to existing regulations that require our compliance. On July 21, 2010, the Dodd-Frank Wall Street Reform and Protection Act, or the Dodd-Frank Act, was enacted. There are significant corporate governance and executive compensation-related provisions in the Dodd-Frank Act that require the SEC to adopt, or where the SEC has adopted, additional rules and regulations in these areas such as "say on pay" and proxy access. Stockholder activism, the current political environment and the current high level of government intervention and regulatory reform may lead to substantial new regulations and disclosure obligations, which may lead to additional compliance costs and impact the manner in which we operate our business.

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

A change in tax laws, treaties or regulations, or their interpretation, of any country in which we operate could materially affect us.

We could be subject to additional tax liabilities.

We are subject to U.S. federal, state, local and sales taxes in the U.S. 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.

Negative conditions in the global credit markets and financial services and other industries may adversely affect our business.

The global credit markets, the financial services industry, the U.S. capital markets, and the U.S. economy as a whole have in the past experienced periods of substantial turmoil and uncertainty characterized by unprecedented intervention by the U.S. federal government and the failure, bankruptcy, or sale of various financial and other institutions. It is possible that a crisis in the global credit markets, the U.S. capital markets, the financial services industry or the U.S. economy may adversely affect our business, vendors and prospects, as well as our liquidity and financial condition. More specifically, our insurance carriers and insurance policies covering all aspects of our business may become financially unstable or may not be sufficient to cover any or all of our losses and may not continue to be available to us on acceptable terms, or at all.

We are dependent on information technology systems, infrastructure and data, which exposes us to data security risks.

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

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

Not applicable.

ITEM 3. DEFAULT UPON SENIOR SECURITIES

Not applicable.

ITEM 4. MINE SAFETY DISCLOSURES

Not applicable.

ITEM 5. OTHER INFORMATION

Not applicable.

ITEM 6. EXHIBITS

a. Exhibits

Exhibit Number	Description of Document
10.1	Amendment No. 1 to the Neurology III Agreement between the Registrant and Biogen MA Inc., dated August 16, 2019 (portions of the exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed).
10.2	Amendment #8 to the Research, Development and License Agreement between the Registrant, Glaxo Group Limited and Glaxosmithkline Intellectual Property Development Limited, dated July 29, 2019 (portions of the exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed).
10.3	Consent to Collateral Addition and Amendment to Loan Documents between the Registrant, Ionis Gazelle, LLC, Wells Fargo Bank, National Association, as Trustee for the Benefit of the Registered Holders of UBS Commercial Mortgage Trust 2017-C3, Commercial Mortgage Pass-Through Certificates, Series 2017-C3, dated August 1, 2019.
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 Ionis Pharmaceuticals, Inc. Quarterly Report on Form 10-Q for the quarter ended September 30, 2019, formatted in Inline Extensible Business Reporting Language (iXBRL): (i) condensed consolidated balance sheets, (ii) condensed consolidated statements of operations, (iii) condensed consolidated statements of comprehensive income (loss), (iv) condensed consolidated statements of stockholders' equity, (v) condensed consolidated statements of cash flows and (vi) notes to condensed consolidated financial statements (detail tagged).
104	Cover Page Interactive Data File (formatted in iXBRL and included in exhibit 101).

* 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.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the Registrant and in the capacities and on the dates indicated.

Signatures	Title	Date
/s/ STANLEY T. CROOKE Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board, President, and Chief Executive Officer (Principal executive officer)	November 6, 2019
/s/ ELIZABETH L. HOUGEN Elizabeth L. Hougen	Senior Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	November 6, 2019

EXHIBIT 10.1

CERTAIN IDENTIFIED INFORMATION HAS BEEN EXCLUDED FROM THE EXHIBIT BECAUSE IT IS BOTH (I) NOT MATERIAL AND (II) WOULD BE COMPETITIVELY HARMFUL IF PUBLICLY DISCLOSED. SUCH EXCLUDED INFORMATION HAS BEEN MARKED WITH "[***]".

August 16, 2019

Biogen MA Inc.
225 Binney Street
Cambridge, MA 02142
Attention: Chris Henderson, VP, Neuromuscular and Movement Disorders

Re: Amendment No. 1 to the Neurology III Agreement

Dear Chris:

Ionis and Biogen are parties to the New Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement dated April 19, 2018 (the "***Neurology III Agreement***") between Ionis Pharmaceuticals, Inc. ("***Ionis***") and Biogen MA Inc. ("***Biogen***"). Any capitalized terms not defined in this letter agreement (the "***Letter Agreement***") will have the meanings set forth in the Neurology III Agreement, unless expressly specified otherwise.

Ionis and Biogen hereby acknowledge and agree that the Neurology III Agreement is hereby amended as follows:

1. The following new Section 1.2.3(g) is added to the Neurology III Agreement:

1.2.3(g). *Expanded High Interest Targets*.

(i) The Parties, through the Neurology JRC, may add up to [***] gene targets to the High Interest Target List, beyond the [***]-target limit set forth in Section 1.2.3(a), under this Section 1.2.3(g) (each, an "***Expanded High Interest Target***").

ionispharma.com

2855 Gazelle Court
Carlsbad, CA 92010

(760) 931-9200

(ii) Before adding an Expanded High Interest Target to the High Interest Target List, the Parties must mutually agree upon and submit to the Neurology JRC for approval a research plan that meets the requirements of either Section 1.2.3(g)(ii)(A) or Section 1.2.3(g)(ii)(B) (each, an "***Expanded High Interest Target Plan***") for each such proposed Expanded High Interest Target.

(A) An Expanded High Interest Target Plan may consist of an initial plan to conduct limited research by the Parties that clearly defines the scope of work to be performed by each Party. Ionis and Biogen will use Commercially Reasonable Efforts to conduct their respective activities under the Expanded High Interest Target Plan.

(B) An Expanded High Interest Target Plan may consist of a Target Sanction Plan.

(iii) The Neurology JRC will review and, in its discretion, approve the addition of a proposed Expanded High Interest Target to the High Interest Target List along with the Expanded High Interest Target Plan corresponding to such proposed Expanded High Interest Target.

(iv) With respect to each proposed Expanded High Interest Target, if the Neurology JRC, in good faith, does not unanimously agree to (1) add such proposed Expanded High Interest Target to the High Interest Target List and (2) adopt the Expanded High Interest Target Plan corresponding to such proposed Expanded High Interest Target, then the proposed Expanded High Interest Target will not be added to the High Interest Target List under this Section 1.2.3(g). Such gene target may be added to the High Interest Target List in accordance with Section 1.2.3(b) or may be pursued independently by the Parties in accordance with Section 1.2.3(f).

(v) With respect to any Expanded High Interest Target Plan under Section 1.2.3(g)(ii)(A), once the Parties complete all work under such plan and present the results of such research to the Neurology JRC or [***] days following approval of such Expanded High Interest Target Plan by the Neurology JRC, whichever is earlier, the Neurology JRC will have [***] days within which to unanimously agree upon a Target Sanction Plan for such Expanded High Interest Target. If the Neurology JRC does not unanimously agree upon a Target Sanction Plan for such Expanded High Interest Target within such [***]-day period, then the Expanded High Interest Target will be removed from the High Interest Target List. Such gene target may be added to the High Interest Target List in accordance with Section 1.2.3(b) or may be pursued independently by the Parties in accordance with Section 1.2.3(f).

(vi) An Expanded High Interest Target that is approved by the Neurology JRC to add to the High Interest Target List will not be subject to the terms of Section 1.2.3(a), Section 1.2.3(b), or Section 1.2.3(d)(i) of this Agreement.

(vii) Once approved by the Neurology JRC, an Expanded High Interest Target will become a High Interest Target for all purposes under this Agreement except as expressly set forth in this Section 1.2.3(g), and the Expanded High Interest Target Plan approved by the Neurology JRC for such Expanded High Interest Target will become part of the Neurological Disease Research Plan.

(viii) If, on or after the [***] anniversary of the date an Expanded High Interest Target was added to the High Interest Target List, such target remains or becomes an Inactive Target, then, unless the Parties mutually agree through the Neurology JRC that such Expanded High Interest Target may remain on the High Interest Target List, such Expanded High Interest Target will automatically be removed from the High Interest Target List and will no longer be an Expanded High Interest Target. However, during the remainder of the Research Term, such target will remain a Neurology Target and the Parties may add such target to the High Interest Target List in accordance with Section 1.2.3(b) or again add such target to the High Interest Target List in accordance with this Section 1.2.3(g).

(ix) The maximum number of Expanded High Interest Targets set forth in Section 1.2.3(g)(i) may be increased or decreased by the Neurology JRC, and any such change will be reflected in the minutes of the meeting of the Neurology JRC where such increase or decrease occurred and subsequently formalized in a letter between the Parties.

2. Section 1.14.4(a) is deleted and replaced in its entirety with the following:

1.14.4(a). review and approve amendments to the Core Research Plan and the Neurological Disease Research Plan, as described in Section 1.2.2 and 1.2.3(d)(iv), and review and approve Expanded High Interest Targets to add to the High Interest Target List, as well as the Expanded High Interest Target Plans corresponding to such Expanded High Interest Targets, as described in Section 1.2.3(g);

Except as expressly set forth in this Letter Agreement, nothing in this Letter Agreement will otherwise modify or amend any provision of the Neurology III Agreement.

This Letter Agreement may be executed in counterparts, each of which will be deemed an original, notwithstanding variations in format or file designation that may result from electronic transmission, storage and printing of copies of this Letter Agreement from separate computers or printers. Facsimile signatures and signatures transmitted via electronic mail in PDF format will be treated as original signatures.

If the terms of this Letter Agreement are acceptable to Biogen, please so indicate by executing a copy of this Letter Agreement and returning it to Ionis.

Very truly yours,

/s/ Brett Monia
Brett Monia
Chief Operating Officer
IONIS PHARMACEUTICALS, INC.

AGREED TO AND CONFIRMED BY BIOGEN MA INC.:

By: /s/ Chris Henderson
Name: Chris Henderson
Title: VP, Neuromuscular and Movement Disorders

EXHIBIT 10.2

CERTAIN IDENTIFIED INFORMATION HAS BEEN EXCLUDED FROM THE EXHIBIT BECAUSE IT IS BOTH (I) NOT MATERIAL AND (II) WOULD BE COMPETITIVELY HARMFUL IF PUBLICLY DISCLOSED. SUCH EXCLUDED INFORMATION HAS BEEN MARKED WITH "[***]".

AMENDMENT #8 TO THE RESEARCH, DEVELOPMENT AND LICENSE AGREEMENT

This **AMENDMENT #8 TO THE RESEARCH, DEVELOPMENT AND LICENSE AGREEMENT** (this "***Amendment No. 8***") is entered into and made effective as of the 29th day of July 2019 (the "***Amendment No. 8 Effective Date***") by and between **IONIS PHARMACEUTICALS, INC.**, a Delaware corporation, having its principal place of business at 2855 Gazelle Court, Carlsbad, CA 92010 (formerly "Isis Pharmaceuticals, Inc.") ("***Ionis***"), and **GLAXO GROUP LIMITED**, a company existing under the laws of England and Wales, having its registered office at 980 Great West Road, Brentford London TW8 9GS, United Kingdom ("***GGL***"), and **GLAXOSMITHKLINE INTELLECTUAL PROPERTY DEVELOPMENT LIMITED,** a company existing under the laws of England and Wales, having its registered office at 980 Great West Road, Brentford London TW8 9GS, United Kingdom ("***GSK IPDL***"). GGL and GSK IPDL are referred to together as "***GSK***". Ionis and GSK are each referred to herein by name or as a "***Party***" or, collectively, as "***Parties***."

RECITALS

WHEREAS, Ionis and GGL are parties to the Research, Development and License Agreement dated March 30, 2010, as amended (the "***Agreement***") and (to the extent applicable) GGL has sub-licensed its rights under the Agreement to GSK IPDL;

WHEREAS, Ionis and GSK entered into Amendment No. 5 to the Agreement dated June 27, 2014 (the "***Amendment No. 5***") and Amendment No. 7 to the Agreement dated March 4, 2016 (the "***Amendment No. 7***") to amend certain terms of the Agreement solely with respect to the HBV Program, a Collaboration Program focused on hepatitis B virus;

WHEREAS, Ionis and GSK wish to agree to amend the Agreement to provide that certain Isis Product-Specific Patents will only be exclusively licensed and not assigned to GSK following the exercise of the Option for the HBV Program on the terms and conditions set forth herein.

NOW, THEREFORE, in consideration of the premises and mutual covenants herein contained, and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, and solely with respect to the HBV Program, the Parties, intending to be legally bound, do hereby agree as follows:

Capitalized terms used but not defined herein will have the meaning ascribed to such terms in the Agreement, Amendment No. 5 and Amendment No. 7.

1. **Definitions.** **"*Non-Assignable Ionis Product-Specific Patents***" means the Ionis Product-Specific Patents set forth in Appendix A to this Amendment No. 8.

2. **Amendment of the Agreement.** Solely with respect to the HBV Program, the Agreement is hereby amended as follows:

a. The first paragraph of Section 4.1.1 is deleted and replaced in its entirety with: "Development and Commercialization License. On a Collaboration Program-by-Collaboration Program basis, subject to the terms and conditions of this Agreement, Ionis hereby grants to GSK (a): a worldwide, exclusive, royalty-bearing, sublicensable (in accordance with Section 4.1.2) license under the Licensed IP (other than the Ionis Product-Specific Patents) to Manufacture, Develop, and Commercialize Licensed Compounds and Licensed Products, and (b) a worldwide, exclusive, royalty-bearing, sublicensable, perpetual, irrevocable (except pursuant to Section 10.1) license under the Ionis Product-Specific Patents for any purpose related to the treatment of hepatitis B [***].

b. Section 6.2.2(b) is deleted and replaced in its entirety with: "Ionis Patents After Exercise of Option. After GSK has obtained the applicable license under Section 4.1.1 and following review and approval of a majority of the members of the Joint Patent Committee, Ionis will assign to GSK all Ionis Product-Specific Patents that Cover Licensed Compounds, Licensed Products and/or the Collaboration Target included in such Collaboration Program, excluding the Non-Assignable Ionis Product-Specific Patents which Ionis shall license to GSK pursuant to Section 4.1.1, and GSK will thereafter control and be responsible for all aspects of the Prosecution and Maintenance of all such Ionis Product-Specific Patents (for clarity, including the Non-Assignable Ionis Product-Specific Patents) related to the treatment of hepatitis B viral infections, subject to Section 6.2.4."

c. Section 10.1 is deleted and hereby replaced in its entirety with the following: "Reversion Rights. Ionis may elect to continue to Develop and Commercialize any Discontinued Products that are the subject of a termination (i) by GSK under Section 9.2.1, or (ii) by Ionis under Section 9.2.2 or Section 9.2.3, by notice in writing to GSK after such termination (an "***Election Notice***") that Ionis is exercising its rights under this Section 10.1, in which case GSK will grant to Ionis a sublicensable, worldwide, exclusive license or sublicense, as the case may be, to all GSK Technology Controlled by GSK as of the date of the Election Notice solely as they are necessary to make, have made, use, sell, offer for sale, have sold and import Discontinued Products. Such license will be sublicensable by Ionis in accordance with Section 4.1.2, *mutatis mutandis*. In addition, if Ionis provides GSK an Election Notice within ninety (90) days of such termination, then (A) GSK will (x) assign back to Ionis any GSK Orange Book Patents (or any other Patent Rights) that relate to such Discontinued Products assigned by Ionis to GSK under this Agreement, and (y) transfer to Ionis for Ionis' use with respect to the Development and Commercialization of the Discontinued Products, any Know-How data, results, regulatory information, filings, and files in the possession of GSK as of the date of the Election Notice that relate to such Discontinued Products, and any other information or material specified in Section 4.2.1 and (B) the licenses granted by Ionis under Section 4.1.1 with respect to the Non-Assignable Ionis Product-Specific Patents shall terminate.

3. **Governing Law; Counterparts**. This Amendment No. 8 and any dispute arising from the performance or breach hereof will be governed by and construed and enforced in accordance with the laws of the State of Delaware, U.S.A., without reference to conflicts of laws principles. This Amendment No. 8 may be signed in counterparts, each and every one of which will be deemed an original, notwithstanding variations in format or file designation which may result from the electronic transmission, storage and printing of copies of this Amendment No. 8 from separate computers or printers. Facsimile signatures and signatures transmitted via PDF will be treated as original signatures.

* * * *

[Signature page follows]

IN WITNESS WHEREOF, the Parties have caused this Amendment No. 8 to be executed by their duly authorized representatives as of the Amendment No. 8 Effective Date.

IONIS PHARMACEUTICALS, INC.

By: /s/ Brett Monia
Name: Brett Monia
Title: Chief Operating Officer
Date: July 29, 2019

GLAXO GROUP LIMITED

By: /s/ Edinburgh Pharmaceutical Industries Limited, Corporate Director
Name: Authorized Representative of Edinburgh Pharmaceuticals Industries Limited

By: /s/ The Wellcome Foundation Limited, Corporate Director
Name: Authorized Representative of The Wellcome Foundation

GLAXOSMITHKLINE INTELLECTUAL PROPERTY DEVELOPMENT LIMITED

By: /s/ Edinburgh Pharmaceutical Industries Limited, Corporate Director
Name: Authorized Representative of Edinburgh Pharmaceuticals Industries Limited

By: /s/ Glaxo Group Limited, Corporate Director
Name: Authorized Representative of Glaxo Group Limited

APPENDIX A

Non-Assignable Ionis Product-Specific Patents

[***]

EXHIBIT 10.3

Midland Loan Services
10851 Mastin Blvd., Suite 300
Overland Park, Kansas 66210
Attention: Mr. Tad Janssen

Loan Numbers: 030298801; 030298824; and 030298825

CONSENT TO COLLATERAL ADDITION AND AMENDMENT TO LOAN DOCUMENTS

This CONSENT TO COLLATERAL ADDITION AND AMENDMENT TO LOAN DOCUMENTS (this "Agreement") is entered into as of August 1, 2019 by and among **IONIS GAZELLE, LLC**, a Delaware limited liability company ("Borrower"), with an address of 2855 Gazelle Court, Carlsbad, California 92010, **IONIS PHARMACEUTICALS, INC.**, a Delaware corporation ("Principal"), with an address of 2855 Gazelle Court, Carlsbad, California 92010, and **WELLS FARGO BANK, NATIONAL ASSOCIATION, AS TRUSTEE FOR THE BENEFIT OF THE REGISTERED HOLDERS OF UBS COMMERCIAL MORTGAGE TRUST 2017-C3, COMMERCIAL MORTGAGE PASS-THROUGH CERTIFICATES, SERIES 2017-C3** ("Lender"), with an address of c/o Midland Loan Services, a Division of PNC Bank, National Association, 10851 Mastin Boulevard, Suite 300, Overland Park, Kansas 66210, Re: Loan Numbers 030298801, 030298824, and 030298825.

RECITALS

A. Borrower is the owner the property (the "Original Property") encumbered by the Original Security Instrument (defined below) executed by Borrower, which Original Property is more particularly described in the Original Security Instrument.

B. By assignment, Lender is the owner and holder of certain documents (collectively, the "Original Loan Documents") evidencing, securing and otherwise pertaining to a loan (the "Loan") made by UBS AG, by and through its branch office at 1285 Avenue of the Americas, New York, New York ("Original Lender"), to Borrower in the original principal amount of $51,350,000.00, including, without limitation, the following:

(i) Promissory Note A-1, dated July 18, 2017, in the original principal amount of $36,350,000.00, executed by Borrower, as maker, in favor of Original Lender ("Note A-1");

(ii) Promissory Note A-2, dated July 18, 2017, in the original principal amount of $5,000,000.00, executed by Borrower, as maker, in favor of Original Lender ("Note A-2");

(iii) Promissory Note A-3, dated July 18, 2017, in the original principal amount of $10,000,000.00, executed by Borrower, as maker, in favor of Original Lender ("Note A-3"; and Note A-1, Note A-2 and Note A-3 are herein referred to collectively as the "Note");

(iv) Loan Agreement, dated as of July 18, 2017, executed by Borrower and Original Lender (the "Loan Agreement");

(v) Deed of Trust and Security Agreement dated as of July 18, 2017, executed by Borrower in favor of Original Lender, filed for record in the Office of the Register of Deeds, Recorder of Deeds or County Clerk, as applicable, in and for the County of San Diego, California (the "Recording Office") as Document #2017-0323134, aforesaid records, as assigned to Lender pursuant to that certain Assignment of Deed of Trust and Security Agreement, recorded in the Recording Office as Document #2017-0512265 (the "Original Security Instrument");

(vi) Assignment of Leases and Rents, dated as of July 18, 2017, executed by Borrower for the benefit of Original Lender, filed for record in the Recording Office as Document #2017-0323135, as assigned to Lender pursuant to that certain Assignment of Assignment of Leases and Rents, recorded in the Recording Office as Document #2017-0512266 (the "Assignment of Leases");

(vii) Environmental Indemnity Agreement, dated as of July 18, 2017, executed by Borrower and Principal in favor of Original Lender (the "Environmental Indemnity");

(viii) Guaranty, dated as of July 18, 2017, executed by Principal in favor of Original Lender (the "Guaranty");

(ix) Cash Management Agreement, dated as of July 18, 2017, executed by Borrower, Original Lender and Wells Fargo Bank, N.A. ("Wells");

(x) Deposit Account Control Agreement, dated as of July 18, 2017, executed by Borrower, Wells and Original Lender; and

(xi) certain UCC financing statements naming Borrower, as debtor, and Original Lender, as secured party, which financing statements have been assigned to Lender.

The Original Loan Documents and all related documents, agreements, notes, certificates and financing statements evidencing or securing the Loan to which Borrower and/or Principal is a party (as amended or restated by this Agreement or the other New Loan Documents (defined below)), and this Agreement and the other New Loan Documents are hereinafter referred to collectively herein as the "Loan Documents". Unless the context requires otherwise, references in this Agreement to the Loan Documents shall be deemed to refer to such documents as the same may be further amended, modified, supplemented, extended or replaced from time to time. Capitalized terms used but not defined herein have the meaning given such terms in the Loan Agreement, as amended hereby.

C. Midland Loan Services, a Division of PNC Bank, National Association ("Servicer"), services the Loan for Lender, as master servicer, pursuant to that certain Pooling and Servicing Agreement dated as of August 1, 2017 (the "Pooling and Servicing Agreement").

D. On the date hereof, (i) Principal conveyed to Borrower that certain parcel of land described on Exhibit "A" attached hereto (the "Additional Parcel", and the Original Property and the Additional Parcel and all improvements and fixtures from time to time located on the Additional Parcel are herein sometimes referred to collectively as the "Property") (such conveyance is referred to herein as the "Conveyance"); and (ii) Borrower and Principal entered into that certain Ground Lease dated as of the date hereof pursuant to which Borrower is leasing the entirety of the Additional Parcel to Principal (the "Ground Lease"). Principal intends to construct an approximately 70,000 square foot conference center (the "Conference Center") and related improvements (collectively, the "Improvements") in accordance with the plans and specifications for the Improvements delivered to Lender (as amended from time to time in accordance with the terms of this Agreement, the "Plans"), a description of which is attached hereto as Exhibit B, the budget for the Improvements delivered to Lender, a copy of which is attached hereto as Exhibit C (as amended from time to time in accordance with the terms of this Agreement, the "Improvements Budget") and the construction timeline delivered to Lender (as amended from time to time in accordance with the terms of this Agreement, the "Construction Timeline"), a copy of which is attached hereto as Exhibit D. The Conveyance, the Ground Lease and the construction of the Improvements are collectively referred to herein as the "Transactions".

E. Borrower and Principal have requested that Lender consent to the Transactions. Subject to the terms and conditions of this Agreement and the other New Loan Documents, Lender has agreed to consent to the Transactions.

AGREEMENT

NOW, THEREFORE, for good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, the parties agree as follows:

1. **CONSENT TO TRANSACTIONS**. Subject to satisfaction of all of the terms and conditions contained in Section 3 hereof, Lender consents to the Transactions. This consent is strictly limited to the Transactions described in this Agreement. This Agreement shall not constitute a waiver or modification of any requirement of obtaining Lender's consent (to the extent Lender's consent is required by the Loan Documents) to any future acquisition of any property by Borrower or any future alteration or renovation of the Property, nor shall it constitute a modification of the terms, provisions, or requirements in the Original Loan Documents in any respect, except as expressly set forth herein, and the other New Loan Documents.

2. **LOAN INFORMATION**. Borrower, Principal and Lender agree that as of the date hereof:

(a) The outstanding principal balance of the Note is $51,350,000.00.

(b) The interest rate of the Note is a fixed rate of 3.88% per annum.

(c) The maturity date of the Loan is August 6, 2027.

(d) The following listed payments are due and payable on the sixth (6th) day of each and every calendar month as of the Closing Date (as hereinafter defined):

(i) interest installments only[1];

(ii) Monthly Tax Deposits[2];

(iii) Monthly Insurance Deposits[3];

(iv) $2,933.33 Monthly Capital Expenditure Deposits[4]; and

(v) $29,333.33 Monthly Rollover Deposit[5].

(e) The current balance of each escrow account held by Lender with respect to the Loan is:

(i) $00.00 Tax Account;

(ii) $00.00 Insurance Account;

(iii) $00.00 Capital Expenditures Account; and

(iv) $00.00 Rollover Account.

(f) All required payments due through July 6, 2019 under the Loan Documents have been paid.

(g) Lender is the current owner and holder of the Original Loan Documents.

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[1] The Loan is interest only until August 6, 2022. On September 6, 2022 and on each Monthly Payment Date thereafter until the maturity date, Borrower shall make monthly payments of principal and interest in the amount of $241,643.01.

[2] The Monthly Tax Deposit is not required so long as each of the Tax Reserve Waiver Conditions Precedent are satisfied.

[3] The Monthly Insurance Deposit is not required so long as each of the Insurance Reserve Waiver Conditions Precedent are satisfied.

[4] The Monthly Capital Expenditure Deposit is not required so long as each of the Capital Expenditure Reserve Waiver Conditions Precedent are satisfied.

[5] The Monthly Rollover Deposit is not required so long as each of the Rollover Reserve Waiver Conditions Precedent are satisfied.

3. **CONDITIONS**. In addition to any other conditions set forth herein or required by Lender, the following are conditions precedent that must be satisfied prior to Lender's consent to the Transactions set forth in this Agreement becoming effective (the "Closing" and the date all such conditions have been satisfied is herein referred to as the "Closing Date"):

(a) The execution and delivery of this Agreement by all of the parties hereto concurrently with the Closing.

(b) Lender's receipt of fully executed copies of the following documents (collectively, the "Transaction Documents"): (i) the Ground Lease in form and substance satisfactory to Lender, (ii) a subordination, non-disturbance and attornment agreement for the Ground Lease in form and substance satisfactory to Lender, (iii) the "Construction Contracts" and other "Construction and Development Documents" (as such terms are defined hereinbelow) entered into by Principal or obtained by Principal as of the date hereof.

(c) Lender's receipt of evidence satisfactory to it that all insurance over the Property required by the Loan Documents (the "Required Insurance") is in full force and effect as of the Closing, with all required premiums paid, and contains a mortgagee's clause (the "Mortgagee's Clause") satisfactory to Lender in favor of Lender, and its successors and/or assigns, c/o Midland Loan Services, Master Servicer, 10851 Mastin Boulevard, Suite 300, Overland Park, Kansas 66210; re: Loan Numbers 030298801; 030298824; and 030298825.

(d) Lender's receipt of a satisfactory Title Endorsement or Title Policy (as such terms hereinafter defined), or an irrevocable commitment by the applicable title company to issue such Title Endorsement or Title Policy.

(e) Borrower's execution and delivery to Lender of the Settlement Statement (hereinafter defined) and Lender's receipt of all of the Required Payments (hereinafter defined).

(f) Delivery to Lender of such legal opinions from counsel for Borrower and Principal as Lender may require, each in form and substance satisfactory to Lender.

(g) Lender's receipt of a REMIC opinion from counsel to Lender in form and substance satisfactory to Lender.

(h) Lender's receipt of required third party consents (e.g., special servicer, directing certificateholder and rating agencies).

(i) Lender's receipt of an IRS W9 form from Borrower and Principal.

(j) Lender's receipt of evidence satisfactory to Lender of (i) the consummation of the Conveyance, which evidence shall include, without limitation, fully-executed copies of the quitclaim deed, closing statement and other documents evidencing the Conveyance and (ii) the payment of all charges in connection with the Conveyance, including any transfer taxes.

(k) Execution by Borrower and delivery to Lender of an Amended and Restated Deed of Trust and Security Agreement (the "Restated Security Instrument") and an amendment to the Assignment of Leases (collectively, the "Recorded Documents Amendment") in form and substance satisfactory to Lender and the recordation thereof in the Recording Office.

(l) The recordation or filing, as applicable, of one or more amendments to existing financing statements amending the legal description attached thereto.

(m) Receipt by Lender of a tenant estoppel certificate from Principal related to the Ground Lease in form and substance satisfactory to Lender.

(n) Approval by Lender of any amendments or modifications to Borrower's operating agreement and Lender's receipt of executed copies of same.

4. FEES, PAYMENTS AND EXPENSES. Borrower covenants and agrees to pay to Lender, at Closing, the following (the "Required Payments"):

(a) $192,562.50, which represents a consent fee for Lender's consent to the Transactions.

(b) $3,850.00, which represents the attorneys' fees for the REMIC opinion.

(c) $1,000.00, which represents the fees due Lender's environmental counsel.

(d) $2,362.00, which represents the fees due Omega Risk Management for its insurance review.

(e) $7,500.00, which represents fees due Fitch in connection with its review of the Transactions.

(f) $15,846.00, which represents fees due Kroll in connection with its review of the Transactions.

The Required Payments and any other fees, expenses and adjustments due and owing under the Loan Documents or in connection with the Transactions shall be paid in accordance with Lender's settlement charges statement (the "Settlement Statement") delivered at Closing for signature by Borrower. In addition, at Closing, Borrower shall pay all of Lender's reasonable attorneys' fees and expenses incurred in connection with this Agreement and the Transactions in the amounts set forth on the Settlement Statement, which amounts shall be deemed Required Payments pursuant to the terms of this Agreement.

5. TITLE ENDORSEMENT. At Closing, Borrower shall (a) cause Fidelity National Title Insurance Company to issue such endorsements to Lender's mortgagee title insurance policy (Policy No. 25008546L) in such form as Lender may require (collectively, the "Title Endorsement"), including, without limitation, showing that Borrower is the owner of the Property, showing Lender as the insured under such title policy, changing the effective date and time of such title policy (and all endorsements thereto) to the date and time of the recordation of the Restated Security Instrument, showing that the Restated Security Instrument is in a first lien position, and changing the legal description to match the legal description attached to the Restated Security Instrument and (b) pay the cost of the Title Endorsement, any escrow, filing or recording fees applicable to the Transactions, and any other costs and expenses incurred in connection with this Agreement or the Transactions. As an alternative to Borrower's providing a Title Endorsement to Lender's existing mortgagee title insurance policy, Borrower shall (a) provide at Closing to Lender a new mortgagee's policy of title insurance issued by Fidelity National Title Insurance Company (the "New Title Policy") providing the same title insurance coverage as provided in Lender's existing mortgagee title insurance policy (including the endorsements thereto) with such changes as would be required by the Title Endorsement, including showing that Borrower is the owner of the Property, showing Lender as the insured under the New Title Policy, providing that the effective date and time of the New Title Policy is the date and time of the recordation of the Restated Security Instrument, and showing that the Restated Security Instrument is in a first lien position subject to no exceptions other than those set forth in Lender's existing title policy and otherwise acceptable to Lender, which New Title Policy and endorsements thereto must be satisfactory to Lender in its sole and absolute discretion and (b) pay the cost of the New Title Policy, any escrow, filing or recording fees applicable to the Transactions, and any other costs and expenses incurred in connection with this Agreement or the Transactions.

6. **RATIFICATION OF LOAN OBLIGATIONS**. Borrower hereby represents, warrants, acknowledges and agrees that, following the Transactions, all obligations and liabilities of Borrower under the Original Loan Documents, as modified by this Agreement and the other New Loan Documents, are and shall remain obligations and liabilities of Borrower. Borrower hereby expressly ratifies and confirms its obligation to pay the unpaid balance due and owing on the Loan and all interest thereon as provided in the Note and to pay and perform all other obligations under the Loan Documents to which it is a party. Borrower's acknowledgment and ratification of the foregoing obligations (x) is absolute, unconditional and is not subject to any defenses, waivers, claims or offsets (including, without limitation, any defense that may arise as a result of or in connection with the Transactions) and (y) shall not be affected or impaired by any agreement, condition, statement or representation of any person or entity other than Lender.

Principal hereby represents, warrants, acknowledges and agrees that, following the Transactions, all obligations and liabilities of Principal under the Original Loan Documents, as modified herein or in the other New Loan Documents, to which it is a party shall be and remain obligations and liabilities of Principal. Principal hereby expressly ratifies and confirms all of its obligations under the Loan Documents to which it is a party. Principal's acknowledgment and ratification of the foregoing obligations (x) is absolute, unconditional and is not subject to any defenses, waivers, claims or offsets (including, without limitation, any defense that may arise as a result of or in connection with the Transactions), and (y) shall not be affected or impaired by any agreement, condition, statement or representation of any person or entity other than Lender.

7. **NO REPRESENTATIONS OF LENDER**. Borrower and Principal agree that (a) neither Lender nor Servicer has made any representations or warranties, either express or implied regarding Borrower, Principal, the Loan or the Loan Documents, the Original Property, the Additional Parcel or the Improvements (including, without limitation, the Plans, the Improvements Budget, the Construction Timeline, or any of the Construction and Development Documents) or the effect of the Transactions on the Original Property or its value, use or operation, and Lender has and shall have no responsibility or liability whatsoever with respect to the Property or the construction of the Improvements or the effect thereof on the Property, including, without limitation, its value, its condition, or its use, occupancy or status, and (b) no claims relating to the Property or the construction of the Improvements or the effect thereof on the Property, including, without limitation, its value, its condition, or its use, occupancy or status, will be asserted against Lender or its agents, employees, professional consultants, affiliated entities, successors or assigns, either affirmatively or as a defense.

8. **BORROWER'S GENERAL REPRESENTATIONS, WARRANTIES AND COVENANTS**. Borrower hereby represents, warrants, and acknowledges to Lender, and agrees and covenants with Lender, that:

(a) Borrower is the owner of the Property, and Borrower has the power to, and is duly authorized to, execute, deliver and perform (i) this Agreement and the other New Loan Documents to which it is a party and (ii) the Transaction Documents to which it is a party and to consummate the Transactions and the other transactions contemplated hereby and thereby.

(b) Any court or third-party consents and/or approvals necessary for Borrower to enter into this (i) Agreement and the other New Loan Documents to which it is a party and (ii) the Transaction Documents to which it is a party and to consummate the Transactions and the other transactions contemplated hereby and thereby have been obtained and remain in full force and effect.

(c) The entities and/or persons, as applicable, executing and delivering (i) this Agreement and the other New Loan Documents to which Borrower is a party and (ii) the Transaction Documents to which it is a party, on behalf of Borrower, are duly authorized to so execute and deliver this Agreement and such other New Loan Documents and Transaction Documents.

(d) This Agreement, the other New Loan Documents to which it is a party and the other Loan Documents and Transaction Documents to which Borrower is a party are in full force and effect and the agreements and obligations of Borrower contained herein and therein constitute and, following consummation of the Transactions shall continue to constitute, the valid and binding obligations of Borrower, enforceable against Borrower in accordance with their respective terms and have not been modified either orally or in writing, except as expressly set forth herein.

(e) There is no existing Default or Event of Default under any of the Loan Documents.

(f) All taxes and assessments applicable to the Property that would be delinquent as of the Closing if not paid have been paid.

(g) There is no bankruptcy, receivership or insolvency proceeding pending or threatened in writing against Borrower.

(h) Borrower is not subject to any judgment, order, writ, injunction or consent decree. There are no actions, suits or proceedings pending or, to its knowledge, threatened in writing, (i) against or involving Borrower or the Property or (ii) which relate to or may affect the Transactions or any of the other transactions contemplated by this Agreement, the other New Loan Documents or the other Loan Documents.

(i) Borrower has no intention to do any of the following prior to the Closing or within the 180 days following the Closing: (i) seek entry of any order for relief as debtor and a proceeding under the Code (hereinafter defined), (ii) seek consent to or not contest the appointment of a receiver or trustee for itself or for all or any part of its property, (iii) file a petition seeking relief under any bankruptcy, arrangement, reorganization or other debtor relief laws, or (iv) make a general assignment for the benefit of its creditors.

(j) All of the insurance required under the Loan Documents is in full force and effect, with all required premiums paid, and contains the required Mortgagee's Clause.

(k) Borrower has no defenses, setoffs, claims, counterclaims or causes of action of any kind or nature whatsoever against Original Lender, Lender or any servicer of the Loan (including, without limitation, Servicer) with respect to or arising out of (i) the Loan or the Loan Documents, including, without limitation, the administration or funding of the Loan, (ii) this Agreement or any of the other New Loan Documents or the transactions contemplated hereby or thereby, or (iii) any acts or omissions of Original Lender, Lender or any servicer of the Loan (including, without limitation, Servicer) or any past or present officers, agents or employees of Original Lender, Lender or any servicer of the Loan (including, without limitation, Servicer) and Borrower does hereby expressly waive, release and relinquish any and all such defenses, setoffs, claims, counterclaims and causes of action, if any.

(l) Borrower has not requested that Lender waive, and to Borrower's knowledge Lender has not waived, any requirements of the Loan Documents nor any of Lender's rights thereunder.

(m) The Conveyance has been consummated, and the Ground Lease has been executed and delivered by Borrower and Principal.

(n) The ownership structure of Borrower is accurately described in each and every material respect on Schedule 3.1.28 attached to the Loan Agreement.

(o) Neither the consummation of the Transactions nor Borrower's execution and delivery of, and performance of its obligations under, this Agreement or the other New Loan Documents or the Transaction Documents to which it is a party will violate, conflict with or result in a default under (i) any of its organizational documents, (ii) any law, rule, regulation, order, decree or judgment applicable to or binding upon Borrower or the Property, or (iii) any agreement or other instrument to which Borrower is a party or by which Borrower or the Property is or may be bound or affected.

(p) All information provided to Lender or Servicer by Borrower or any of its employees, officers, directors, partners, members, managers or representatives (and, to the best of Borrower's knowledge, all information contained in any third party report obtained by Borrower with respect to the Property), in connection with or relating to (i) this Agreement or the Transactions contemplated hereby or (ii) the Property contains no untrue statement of material fact and does not omit a material fact necessary in order to make such information not misleading, and the provision of any such information by Lender or Servicer to any rating agency is expressly consented to by Borrower.

(q) Borrower is a limited liability company duly organized, validly existing and in good standing under the laws of the State of Delaware and is qualified to do business in the State of California, and there has not been any amendment, modification or supplement to the certificate of formation, operating agreement or other organizational documents of Borrower since the date of the closing of the Loan.

(r) No funds used (or to be used) to close all or any part of the Transactions or to be used to construct the Improvements are secured, directly or indirectly, by an interest in Borrower, the Property or any other collateral for the Loan.

(s) All representations and warranties of Borrower herein and in the Loan Documents to which it is a party and the certifications made by Borrower in that certain Officer's Certificate delivered to Richards, Layton & Finger, P.A. with respect to the non-consolidation opinion are and shall be true and correct as of the date of this Agreement and the Closing and shall survive the Closing.

Lender is entitled to rely, and has relied, upon these representations, warranties, acknowledgments, agreements and covenants in the execution and delivery of this Agreement and all other documents and instruments executed and delivered by Lender in connection with this Agreement.

Borrower, by its execution of this Agreement, jointly and severally with Principal, agrees to reimburse, indemnify and hold Lender, its officers, agents, loan servicers (including, without limitation, Servicer) and employees harmless from and against any and all liabilities, judgments, costs, claims, damages, penalties, expenses, losses or charges (including, but not limited to, all legal fees and expenses and court costs), which may now or in the future be undertaken, suffered, paid, awarded, assessed or otherwise incurred as a result of or arising out of any breach or inaccuracy of the foregoing representations and warranties or any fraudulent conduct of Borrower in connection with this Agreement or the Transactions contemplated hereby, or the Property, including, without limitation, the misrepresentation of financial and other data presented to Lender in connection with the Transactions.

9. PRINCIPAL'S GENERAL REPRESENTATIONS, WARRANTIES AND COVENANTS. Principal hereby represents, warrants, and acknowledges to Lender, and agrees and covenants with Lender, that:

(a) Borrower is the owner of the Property. Principal has an unencumbered leasehold interest in the Improvements located on the Original Property pursuant to the Ionis Lease (as defined in the Original Loan Agreement) and an unencumbered leasehold interest in the Additional Parcel pursuant to the Ground Lease. Upon the termination of the Ground Lease, all right, title and interest in and to all improvements located on the Additional Parcel (including, without limitation, the Improvements) shall automatically vest in, and become the property of, the owner of the fee title to the Additional Parcel. Principal has the power to, and is duly authorized to, execute, deliver and perform (i) this Agreement and the other New Loan Documents to which it is a party and (ii) the Transaction Documents to which it is a party and to consummate the Transactions and the other transactions contemplated hereby and thereby.

(b) Any court or third-party consents and/or approvals necessary for Principal to enter into this Agreement, the other New Loan Documents to which it is a party and the Transaction Documents to which it is a party and to consummate the Transactions and the other transactions contemplated hereby and thereby have been obtained and remain in full force and effect.

(c) The entities and/or persons, as applicable, executing and delivering (i) this Agreement and the other New Loan Documents to which Principal is a party and (ii) the Transaction Documents to which it is a party, on behalf of Principal, are duly authorized to so execute and deliver this Agreement and such other New Loan Documents and Transaction Documents.

(d) This Agreement, the Guaranty, the Environmental Indemnity, the other New Loan Documents to which Principal is a party and the Transaction Documents to which Principal is a party are in full force and effect and the agreements and obligations of Principal contained herein and therein constitute and, following the consummation of the Transactions, shall continue to constitute, the valid and binding obligations of Principal, enforceable against Principal in accordance with their respective terms and have not been modified either orally or in writing, except for the modification to the Guaranty and Environmental Indemnity effectuated by this Agreement.

(e) There is no existing Default or Event of Default under any of the Loan Documents.

(f) All taxes and assessments applicable to the Property that would be delinquent as of the Closing if not paid have been paid.

(g) There is no bankruptcy, receivership or insolvency proceeding pending or threatened in writing against Principal.

(h) Principal is not subject to any judgment, order, writ, injunction or consent decree. There are no actions, suits or proceedings pending or, to its knowledge, threatened in writing, (i) against or involving Principal that might adversely affect Principal's ability to perform under the Loan Documents to which it is a party, (ii) against, involving or relating to the Property or the construction of the Improvements, or (iii) which relate to or affect the Transactions or any of the other transactions contemplated by this Agreement, the other New Loan Documents, the other Loan Documents or the Transaction Documents.

(i) Principal has no intention to do any of the following prior to the Closing or within the 180 days following the Closing: (i) seek entry of any order for relief as debtor and a proceeding under the Code (hereinafter defined), (ii) seek consent to or not contest the appointment of a receiver or trustee for itself or for all or any part of its property, (iii) file a petition seeking relief under any bankruptcy, arrangement, reorganization or other debtor relief laws, or (iv) make a general assignment for the benefit of its creditors.

(j) All of the insurance required under the Loan Documents is in full force and effect, with all required premiums paid, and contains the required Mortgagee's Clause.

(k) Principal has no defenses, setoffs, claims, counterclaims or causes of action of any kind or nature whatsoever against Original Lender, Lender or any servicer of the Loan (including, without limitation, Servicer) with respect to or arising out of (i) the Loan or the Loan Documents, including, without limitation, the administration or funding of the Loan, (ii) this Agreement or any of the other New Loan Documents or the transactions contemplated hereby or thereby, or (iii) any acts or omissions of Original Lender, Lender or any servicer of the Loan (including, without limitation, Servicer) or any past or present officers, agents or employees of Original Lender, Lender or any servicer of the Loan (including, without limitation, Servicer) with respect to the Loan and Principal does hereby expressly waive, release and relinquish any and all such defenses, setoffs, claims, counterclaims and causes of action, if any.

(l) Principal has not requested that Lender waive, and to Principal's knowledge Lender has not waived, any requirements of the Loan Documents nor any of Lender's rights thereunder.

(m) The Conveyance has been consummated, and the Ground Lease has been executed by Borrower and Principal.

(n) The ownership structure of Borrower is accurately described in each and every material respect on Schedule 3.1.28 attached to the Loan Agreement.

(o) Neither the consummation of the Transactions nor Principal's execution and delivery of, and performance of its obligations under, this Agreement or the other New Loan Documents and the Transaction Documents to which it is a party will violate, conflict with or result in a default under (i) any law, rule, regulation, order, decree or judgment applicable to or binding upon Principal or the Property, or (ii) any agreement or other instrument to which Principal is a party or by which Principal or the Property is or may be bound or affected.

(p) All information provided to Lender or Servicer by Principal or any of its representatives (and, to the best of Principal's knowledge, all information contained in any third party report obtained by Principal with respect to the Property), in connection with or relating to (i) this Agreement or the Transactions contemplated hereby or (ii) the Property contains no untrue statement of material fact and does not omit a material fact necessary in order to make such information not misleading, and the provision of any such information by Lender or Servicer to any rating agency is expressly consented to by Principal.

(q) No funds used (or to be used) to close all or any part of the Transactions or to be used to construct the Improvements are secured, directly or indirectly, by an interest in Borrower, the Property or any other collateral for the Loan, or the Improvements.

(r) The Existing Project has been completed in accordance with the terms of the Loan Agreement.

(s) All representations and warranties of Principal herein and in the Loan Documents to which it is a party and the certifications made by Principal in that certain Officer's Certificate delivered to Richards, Layton & Finger, P.A. with respect to the non-consolidation opinion are and shall be true and correct as of the date of this Agreement and the Closing Date and shall survive the Closing.

Lender is entitled to rely, and has relied, upon these representations, warranties, acknowledgments, agreements and covenants in the execution and delivery of this Agreement and all other documents and instruments executed and delivered by Lender in connection with this Agreement.

Principal, by its execution of this Agreement, jointly and severally with Borrower, agrees to reimburse, indemnify and hold Lender, its officers, agents, loan servicers (including, without limitation, Servicer) and employees harmless from and against any and all liabilities, judgments, costs, claims, damages, penalties, expenses, losses or charges (including, but not limited to, all legal fees and court costs), which may now or in the future be undertaken, suffered, paid, awarded, assessed or otherwise incurred as a result of or arising out of any breach or inaccuracy of the foregoing representations and warranties or any fraudulent conduct of Principal in connection with this Agreement or the Transactions contemplated hereby, or the Property, including, without limitation, the misrepresentation of financial and other data presented to Lender in connection with the Transactions.

10. REPRESENTATIONS AND COVENANTS REGARDING IMPROVEMENTS.

(a) Definitions. The parties hereto agree that, for purposes of this Agreement, the following terms shall have the meanings ascribed below unless the context clearly requires otherwise:

"**Architect**" means DG Architects, Inc. dba DGA.

"**Architect's Agreement**" means that certain Owner/Architect Agreement dated November 28, 2018, entered into between Principal and the Architect, as the same has been amended and supplemented by Additional Service Requests 1-4.

"**Construction and Development Documents**" means the Construction Contracts, the Architect's Agreement, the Plans, the Governmental Approvals, and all other instruments, documents and rights relating to the design, construction and development of the Improvements, together with all exhibits and attachments thereto.

"**Construction Contracts**" means the General Construction Contract and the Construction Management Agreement.

"**Construction Management Agreement**" means that certain letter agreement dated January 30, 2018, revised March 2, 2018 between Principal and Construction Manager relating to construction management services with respect to the Improvements.

"**Construction Manager**" means Project Management Advisors, Inc., or such other construction manager as may be approved in writing by Lender prior to Principal's engagement of such other construction manager.

"**Contractor**" means DPR Construction, a General Partnership.

"Engineer" means Pasco Larent Suitor & Associates, Inc.

"**General Construction Contract**" means that certain Standard Form of Agreement Between Owner and Construction Manager as Constructor where the basis of payment is the Cost of the Work Plus a Fee with a Guaranteed Maximum Price, dated August 28, 2018, between Principal and the Contractor.

"**Governmental Approvals**" means all consents, licenses, permits and all other authorizations or approvals required by any Governmental Authority, including, without limitation, that certain letter dated December 13, 2018 from Teri Delcamp, Principal Planner for the City of Carlsbad, California to Mr. Jon Olson of DGA Architects and all agreements entered into with any Governmental Authority, with respect to or in connection with the development, construction, completion, use and occupancy of the Improvements.

(b) Covenants. Borrower and Principal covenant and agree with Lender as follows:

(i) Construction. Principal is and shall be solely responsible for the design, construction and completion of the Improvements and the payment of all costs and expenses in connection therewith and Borrower shall have no obligations or liability under any Construction and Development Document or any other agreement relating to the design or construction of the Improvements.

(ii) Payment of Costs. Principal agrees to, and Borrower agrees to cause Principal to, promptly pay all costs and expenses incurred in connection with the development of the Additional Parcel and the design and construction of the Improvements as and when the same become due and payable.

(iii) Compliance With Construction and Development Documents and Other Agreements. Principal agrees to, and Borrower agrees to cause Principal to, comply with the Construction and Development Documents to which Principal is a party. Principal agrees to, and Borrower agrees to cause Principal to, deliver to Lender copies of any notices of default sent by or to Principal under or with respect to the Construction Contracts, the Architect's Agreement, any Governmental Approvals and any other agreement relating to the design, construction or development of the Improvements requiring payments of $500,000.00 or more, or under any REA in connection with or related to the design or construction of the Improvements.

(iv) Construction and Completion of Improvements. Principal has commenced construction of the Improvements but has ceased construction activity. Principal agrees to, and Borrower agrees to cause Principal to, recommence construction of the Improvements on or before August 31, 2019 and thereafter Principal agrees to, and Borrower agrees to cause Principal to, diligently and continuously (subject to commercially reasonable reasons for delay (such as force majeure events and unknown geological conditions)) prosecute the completion of construction of the Improvements in accordance with the Plans in a good and workmanlike matter, free of all defects (other than immaterial "punchlist" items) and liens (other than those being contested in accordance with the terms hereof), and in compliance with the Construction and Development Documents, the Improvements Budget (as the same may be increased as permitted hereunder) and all Legal Requirements including, without limitation, the REAs. The Improvements shall be completed in accordance with the terms of this Agreement prior to August 6, 2022. The Improvements shall comply with all Governmental Approvals, all applicable Legal Requirements of all Governmental Authorities having jurisdiction over the Additional Parcel and all applicable insurance requirements (including, without limitation, applicable building codes, special use permits, environmental regulations, and requirements of insurance underwriters) and any other restrictions encumbering the Additional Parcel, including, without limitation, the REAs.

(v) Changes in Construction and Development Documents. Lender's approval shall not be required for changes in the Plans, the Improvements Budget, the Construction Timeline or the other Construction and Development Documents, provided that Principal has obtained, and delivers to Lender with the quarterly reporting required hereunder copies of, all Governmental Approvals and other approvals required by or under any Legal Requirements (including the REA) in connection with any changes in the Plans, the Improvements Budget, the Construction Timeline or other Construction and Development Documents and, with respect to amendments to the Construction Timeline, the completion date does not extend beyond August 6, 2022. Principal shall (and Borrower agrees to cause Principal to) deliver to the Lender documentation as reasonably required by Lender pertaining to any change referred to in this Section.

(vi) Insurance. In addition to any insurance required under the Loan Documents, at all times during the construction of the Improvements, Principal shall require that the general contractor name the Lender as additional insured for ongoing and completed operations of the general contractors liability insurance. Principal shall deliver to Lender written evidence confirming its compliance herewith as requested by Lender from time to time.

(vii) Intentionally Omitted.

(viii) Quarterly Deliverables. Within ten (10) days after the end of each calendar quarter, Principal shall furnish to Lender and directly to Servicer at mlsassetmanagement@midlandls.com with a copy to Chuck Hendricks, of Servicer, at chendric@midlandls.com, the following documents:

(a) a report prepared by Construction Manager or the senior officer of Principal responsible for the oversight of the construction of the Improvements detailing the status of construction of the Improvements, including whether construction is on, ahead of or behind the Construction Timeline and whether the construction of the Improvements is on budget and the cost to complete the Improvements in accordance with the Plans, all Legal Requirements and all Governmental Approvals. Additionally, if any significant dispute arises between or among Principal, Contractor, Architect, or any subcontractor, supplier or any other party to a contract requiring payments, individually or in the aggregate, equal to or greater than $500,000.00, said report will contain a written summary of the nature of such dispute;

(b) copies of all Governmental Approvals obtained for the construction of the Improvements in the prior calendar quarter;

(c) copies of AIA Forms G702/703 for costs and invoices for all soft costs relating to the design or construction of the Improvements, in each case received by Principal in the prior calendar quarter and, upon Lender's request, Contractor and subcontractor invoices;

(d) payment receipts and lien releases/waivers from the Contractor and all subcontractors under contracts having an aggregate payment obligation of $500,000.00 or more covering all payments in the prior calendar quarter;

(e) copies of any (i) contracts relating to the design or construction of the Improvements for amounts equal to or greater than $500,000.00 entered into in the prior calendar quarter and (ii) changes to the Plans, Construction Contracts, Architect's Agreement or any construction or supply agreements having payments (individually or in the aggregate) equal to or greater than $500,000.00 (including change orders) made in the prior calendar quarter; and

(f) copies of any amendments made to the Improvements Budget or Construction Timeline in the prior calendar quarter.

(ix) Liens. Notwithstanding anything to the contrary contained in any Loan Document, any lien claimed or filed against any part of the Property for labor done or materials or services furnished in connection with the construction of the Improvements shall be discharged, by bond or otherwise, within thirty (30) days after the date of Borrower's or Principal's receipt of actual notice of the filing thereof. Notwithstanding the foregoing, after prior notice to Lender provided with said 30 day period, Principal, at its own expense, may contest by appropriate legal proceeding, conducted in good faith and with due diligence, the amount or validity of any claims (including claims for labor, services, materials and supplies) for sums that have become due and payable and that by law have or may become a lien upon the Property (collectively, "Contestable Liens"); provided that (i) no Event of Default has occurred and remains uncured; (ii) such proceeding shall be permitted under and be conducted in accordance with all applicable statutes, laws and ordinances, and the terms, conditions and provisions of any applicable document encumbering the Property; (iii) neither the Property nor any part thereof or interest therein will be in danger of being sold, forfeited, terminated, canceled or lost; (iv) Principal shall promptly upon final determination thereof pay the amount of any such Contestable Liens, together with all costs, interest and penalties which may be payable in connection therewith; (v) such proceeding shall suspend the collection of such Contestable Liens from the Property; and (vi) Principal shall deposit with Lender cash, or other security as may be reasonably approved by Lender, in an amount equal to 110% of the contested amount (or such higher amount as may be required by applicable law), to insure the payment of any such Contestable Liens, together with all interest and penalties thereon. Lender may pay over any such cash or other security held by Lender to the claimant entitled thereto at any time when, in the reasonable judgment of Lender, the entitlement of such claimant is established. If Principal shall fail promptly to either (i) discharge any such lien, or (ii) post a bond which fully removes such lien within said thirty (30) day period after the date of the filing thereof or (iii) contest such lien in accordance with the terms of this subsection, Lender may, at its election (but shall not be required to), procure the release and discharge of any such claim and any judgment or decree thereon and, further, may in its sole discretion effect any settlement or compromise of the same, or may furnish such security or indemnity to the title insurer, and any amounts so expended by Lender, including premiums paid or security furnished in connection with the issuance of bonds, shall be added to the Debt, shall be immediately due and payable, and shall bear interest at the Default Rate from the date of disbursement until paid in full. In settling, compromising or discharging any claims for lien, Lender shall not be required to inquire into the validity or amount of any such claim.

(x) Notices. Within ten (10) days after Borrower or Principal acquires knowledge of or receives notice of a defect in the Improvements or any departure from the Plans, or any other requirement of this Agreement, Borrower or Principal, as applicable, will notify Lender and Principal shall proceed with diligence to correct all such defects and departures in accordance with the requirements contained herein.

(xi) Cessation in Construction. Once commenced, construction of the Improvements shall not be abandoned for a period of thirty (30) consecutive days or more, absent a commercially reasonable reason for doing so. Principal shall promptly notify Lender if construction has stopped for a period of thirty (30) or more consecutive days and the reason therefor.

(xii) No Security Interest. No materials, equipment, fixtures or articles of personal property placed in or on the Additional Parcel in connection with the construction of the Improvements shall be purchased by or installed under any security agreement, financing lease or other agreement whereby the seller reserves or purports to reserve title, a lien, a security interest, the right of removal or repossession or the right to consider such items personal property after their incorporation into the Improvements, unless previously authorized by Lender in writing.

(xiii) Governmental and Other Approvals. Principal is and shall be solely responsible for obtaining all necessary approvals in connection with all site work and construction of the Improvements, including, without limitation, any approvals required under any REA and all Governmental Approvals, including, without limitation, certificates of completion and occupancy, required by any Governmental Authority or otherwise necessary for the construction, use, occupancy and operation of the Improvements.

(xiv) Construction and Development Documents. Other than the New Loan Documents to which it is a party, Borrower has not entered into, and will not enter into, any contract or agreement (whether written or oral) in connection with the development, construction or provision of labor, materials or design or supervisory services with respect to the Improvements.

(xv) Obligation upon Completion. Upon completion of the Improvements, (i) Principal shall deliver to Lender a certificate from the Architect that the Improvements have been completed in accordance with the Plans (in all material respects), all applicable Governmental Approvals and all Legal Requirements, (ii) Principal shall provide to Lender written evidence reasonably acceptable to Lender in all respects that the Property continues to comply with all applicable insurance requirements (including, without limitation, applicable building codes, special use permits, environmental regulations, and requirements of insurance underwriters) and any other restrictions encumbering the Property, including, without limitation, the REAs; (iii) Borrower or Principal shall deliver to Lender a copy of the certificate of occupancy with respect to the Improvements and any other evidence obtained by Borrower or Principal that the Improvements comply with all applicable Legal Requirements; (iv) Borrower shall cause to be issued and delivered to Lender an endorsement to the Title Insurance Policy insuring the continued priority of the Lien of the Restated Security Instrument and evidence of payment of any premium payable in connection with such endorsement; (v) Principal shall deliver to Lender notice of such completion of the Improvements, together with an Officer's Certificate certifying that all of the requirements of this Section 10(b) have been satisfied; and (vi) within forty-five (45) days of the completion of the Improvements, Borrower or Principal shall deliver to Lender a Survey of the Additional Parcel and the improvements thereon (including the Improvements) reasonably acceptable to Lender in all respects.

(xvi) Net Worth and Liquidity. Principal agrees that until the Improvements have been completed in accordance with this Agreement, Principal shall maintain (x) a Net Worth of not less than $51,350,000.00 plus the estimated cost of the Improvements (excluding Principal's interest in the Original Property, Additional Parcel and Improvements) and (y) Liquid Assets of not less than $5,135,000.00 plus the estimated cost of the Improvements.

(c) Representation and Warranties**.** Borrower and Principal represent and warrant to Lender as follows:

(i) Governmental and Other Approvals. All Governmental Approvals necessary to construct the Improvements in accordance with the Plans have been or will be obtained by Principal and are or will be valid and in full force and effect, and in each case will remain as such. Principal has delivered true, correct and complete copies of all Governmental Approvals obtained by Principal to Lender as of the date hereof. The Improvements comply with all applicable requirements set forth in the REAs, and all approvals required pursuant to the terms of any REA have been obtained by Borrower or Principal, as applicable, and copies of any such approvals have been provided to Lender. To Borrower's and Principal's knowledge, the Improvements, if completed in accordance with the Plans, will comply with all applicable Governmental Approvals, all applicable Legal Requirements of all Governmental Authorities having jurisdiction over the Additional Parcel and all applicable insurance requirements (including, without limitation, applicable building codes, special use permits, environmental regulations, and requirements of insurance underwriters) and any other restrictions encumbering the Additional Parcel, including, without limitation, the REAs. Neither the construction nor use of the Improvements as a conference center with office and uses ancillary thereto constitutes or will constitute or cause a violation, breach or default by Borrower or Principal under any Governmental Approval, Legal Requirement or document or agreement to which Borrower or Principal is a party or the Original Property or Additional Parcel is bound. The Plans submitted to the City of Carlsbad, California (the "City") and approved by the City are the same Plans heretofore delivered to Lender.

(ii) Plans. As of the date hereof, the Plans (y) are satisfactory to Borrower and Principal and (z) have been approved by each Governmental Authority having jurisdiction over the Property and any others whose approval of the Plans, in whole or in part, is required by any applicable Legal Requirement (including the REA).

(iii) Construction and Development Documents. Lender has been furnished true, correct and complete copies of all Construction and Development Documents entered into or obtained, as applicable, by Principal as of the date hereof. As of the date hereof, the Architect's Agreement and the Construction Contracts constitute all agreements executed by or for the benefit of Principal in connection with the design or construction of the Improvements. As of the date hereof, the Architect's Agreement and the Construction Contracts cover all work and services necessary or desirable for the design and construction of the Improvements, including all work and services necessary for the Improvements to be completed in accordance with all Governmental Approvals and any and all requirements of all applicable Legal Requirements.

(iv) Improvement Budget. As of the date hereof, to the best of Principal's knowledge after consultation with the Architect and Contractor, the Improvements Budget attached hereto as Exhibit C (x) is true, correct and complete in all material respects, (y) shows all sources and uses of funds and (z) provides for all costs and expenses to be incurred in connection with the construction and equipping of the Improvements, and all other items of cost and expense to be incurred in connection with the design and construction of the Improvements, including, without limitation, all costs and expenses to be incurred pursuant to the Construction and Development Documents. As of the date hereof, neither Borrower nor Principal is aware of any other costs, expenses or fees which are material to the completion of the Improvements and are not covered by the Improvements Budget. The amount required to complete the Improvements as set forth on the Improvements Budget ($54,718,029.00) is available and has been allocated by Principal in advance of the commencement of the construction of the Improvements and such amount shall be used solely to complete the Improvements.

(v) Utilities. No utility or other municipal services necessary for the use and occupancy of the Original Property and improvements located thereon will be adversely affected by the construction of the Improvements. All utility and municipal services necessary for the use and occupancy of the Improvements are currently available to the Adjacent Parcel.

(vi) Construction Timeline. As of the date hereof, to the best of Principal's knowledge after consultation with the Architect and Contractor, the Construction Timeline attached hereto as Exhibit D (y) is true, correct and complete in all material respects, and (z) is a fair and reasonable timeline for completing the Improvements in accordance with the terms of this Agreement.

(d) Right to Complete/Raze Improvements. In addition to, and without limiting, any of Lender's other rights and remedies under the Loan Documents, at law or in equity, Lender shall have the further right upon an Event of Default under the Loan Agreement or any of the other Loan Documents, to enter the Property and take any and all actions necessary, in its judgment, to secure, protect and preserve the Improvements and any materials or supplies located on the Property, to complete in part or in full the construction of the Improvements, including, but not limited to, making changes in the Plans (but not to the scope of the Improvements or the quality of the Improvements), and entering into, and, subject to the terms thereof, modifying or terminating the Construction and Development Documents and other contractual arrangements. Alternatively, upon the occurrence of an Event of Default, Lender may elect to demolish and remove any partially completed Improvements in accordance with all Legal Requirements. If Lender elects to continue with the construction of the Improvements or to demolish such Improvements, Lender will not assume any liability to Borrower, Principal or any other Person for completing the Improvements or for the manner or quality of construction of the Improvements or for demolishing and removal of the Improvements and Borrower and Principal each expressly waive any such liability, except to the extent that such liability shall be caused directly by the gross negligence or willful misconduct of Lender. Borrower and Principal each irrevocably appoint Lender as its attorney-in-fact, with full power of substitution, to complete, upon exercise of the Lender's rights following an Event of Default, the Improvements in Borrower's or Principal's name or the Lender may elect to complete construction of the Improvements or demolish and remove the Improvements in the name of Lender or a subsidiary of Lender. In any event, all sums actually expended by Lender, or its subsidiary, in completing construction of the Improvements, demolishing and removing the Improvements or otherwise exercising its rights hereunder or under the other Loan Documents will be part of the Debt, be secured by the Security Instrument and all other Loan Documents and shall bear interest at the Default Rate.

(e) Visitation and Inspection. Borrower and Principal agree that the officers or authorized employees and agents (including any construction consultant engaged by Lender) of Lender or Servicer will have the right, upon not less than forty-eight hours prior notice and at any reasonable time, to enter upon the Additional Parcel and inspect the construction work and all materials, plans, specifications and other matters relating to construction of the Improvements. Borrower and Principal further agree that (i) neither Lender nor Servicer has any duty to examine, supervise or inspect the Plans, the Construction and Development Documents or the construction of the Improvements, (ii) any inspection or examination by Lender, Servicer or their employees or agents is for the sole purpose of protecting the security interests granted in favor of the Lender and preserving its rights under this Agreement and the other Loan Documents, (iii) no default or breach of Principal or Borrower will be waived by any inspection by Lender, Servicer or their employees or agents, nor will any such inspection constitute a representation that there has been or will be compliance with the Plans or any other Construction and Development Documents or any Legal Requirement, or that the construction of the Improvements is free from defective materials or workmanship, (iv) no inspection of the construction of the Improvements or any other inspection constitutes a warranty or representation by Lender or Servicer (or any of their employees or agents) as to the adequacy or safety of construction or any physical condition or feature of the Additional Parcel or the Improvements and (v) neither Borrower nor Principal shall assert any position contrary to any of the foregoing

11. NO RELEASE OF BORROWER OR PRINCIPAL. Each of Borrower and Principal hereby acknowledges, covenants and agrees that nothing contained in this Agreement or any other New Loan Document, the consummation of the Transactions or otherwise, shall be deemed or construed to release Borrower or Principal from any liability or other obligations under the Loan Documents to which it is a party, including, without limitation, Borrower's liability under the terms of the Note and Security Instrument and Principal's liability under the Guaranty. Each of Borrower's and Principal's acknowledgement of the foregoing obligations (i) is absolute, unconditional and is not subject to any defenses, waivers, claims or offsets, and (ii) shall not be affected or impaired by any agreement, condition, statement or representation of any person or entity.

12. **RELEASE OF LENDER**. Each of Borrower and Principal, for itself and for its agents, employees, representatives, officers, directors, general partners, limited partners, members, managers, shareholders, beneficiaries, trustees, administrators, subsidiaries, affiliates, servants, attorneys, heirs, successors and assigns (collectively, the "Releasing Parties") jointly and severally release and forever discharge Original Lender, Lender and Servicer and each other servicer under the Pooling and Servicing Agreement, and their respective predecessors, successors, assigns, managers, partners, directors, officers, employees, agents, attorneys, administrators, trustees, subsidiaries, affiliates, beneficiaries, shareholders and representatives from all liabilities, obligations, costs, expenses, claims and damages, at law or in equity, known or unknown, which any of the Releasing Parties may now or hereafter hold or claim to hold under common law, statutory right or otherwise, arising in any manner out of, or relating to, any matters of any kind or nature whatsoever in connection with (x) the Property (including, without limitation, the ownership or operation thereof), the Loan (including, without limitation, the funding, administration or servicing thereof), any of the Loan Documents or any of the documents, instruments or any other transactions relating thereto or (y) the Ground Lease, the construction of the Improvements and the other transactions contemplated by the Loan Documents. Without limiting the generality of the foregoing, this release shall include the following matters: all aspects of this Agreement, the other New Loan Documents and the other Loan Documents and the transactions contemplated hereby and thereby, any negotiations, demands or requests with respect hereto or thereto. The Releasing Parties agree that this release is a full, final and complete release and that it may be pleaded as an absolute bar to any or all suit or suits pending or which may thereafter be filed or prosecuted by any of the Releasing Parties, or anyone claiming by, through or under any of the Releasing Parties. The Releasing Parties agree that this release is binding upon each of them and their respective agents, employees, representatives, officers, directors, general partners, limited partners, members, managers, shareholders, beneficiaries, trustees, administrators, subsidiaries, affiliates, servants, attorneys, heirs, successors and assigns. Lender agrees that the foregoing release does not apply to any act or omission of Lender first occurring after the Closing Date.

13. **REFERENCES IN THE LOAN DOCUMENTS**. The parties hereto hereby acknowledge and agree that the terms "Lender" and/or "Indemnitee" that may be contained in any of the Loan Documents shall be deemed to refer to Lender and its successors and/or assigns. From and after the date of this Agreement, this Agreement and the other New Loan Documents shall each be deemed a "Loan Document" for all purposes under the Loan Agreement and the other Loan Documents.

14. **RATIFICATION AND CONFIRMATION OF THE LOAN**. Borrower and Principal agree to perform each and every obligation under the Loan Documents to which it is a party, as specifically modified by this Agreement or the other New Loan Documents, and under any other loan documents to which it is a party executed on or about the date of this Agreement and evidencing, securing or otherwise relating to the Loan (this Agreement and such other loan documents being executed in connection herewith, collectively, the "New Loan Documents") in accordance with their respective terms and conditions. Borrower and Principal ratify, affirm, reaffirm, acknowledge, confirm and agree that the Original Loan Documents to which it is a party or by which it is bound, as specifically modified by this Agreement or the other New Loan Documents, remain in full force and effect and, together with this Agreement and all other New Loan Documents to which it is a party or by which it is bound, represent legal, valid and binding obligations of each of Borrower and Principal, as applicable, enforceable against Borrower and Principal, as applicable, in accordance with their terms. Borrower and Principal hereby restate, ratify and confirm, as of the date hereof and after giving effect to each of the Transactions, each of the representations and warranties of Borrower or Principal, as applicable, under the Original Loan Documents, after giving effect to the modification affected by this Agreement and the other New Loan Documents, as if fully set forth herein. Without limiting the foregoing, Borrower acknowledges that the foregoing restatement of the representations and warranties in the Original Loan Documents (as so modified or restated) regarding the "Property" includes the Additional Parcel and the representations and warranties regarding the "Improvements" includes the Improvements (as defined herein). Borrower and Principal agree that neither this Agreement nor any other New Loan Document diminishes, impairs, releases or relinquishes the liens, powers, titles, security interests and rights securing or guaranteeing payment of the Loan, including the validity or first priority of the liens and security interests encumbering the Property granted Lender by the Loan Documents or the New Loan Documents.

15. **NONWAIVER**. The parties hereto acknowledge and agree that (a) any performance or non-performance of the Original Loan Documents prior to the date of this Agreement or Closing does not affect or diminish Lender's ability to require future compliance with the Loan Documents, as the same may be modified from time to time in accordance with the terms thereof, and (b) in the future, Lender will require strict compliance with and performance of the Loan Documents, as the same may be modified from time to time in accordance with the terms thereof. Nothing contained herein shall be construed as a waiver of any of Lender's rights or remedies with respect to any default, "Default" or "Event of Default" under this Agreement, any other New Loan Document and/or any other Loan Document.

16. **FURTHER ASSURANCES**. The parties hereto agree to do any act or execute any additional documents required by Lender, from time to time, to correct errors in the documenting of the Transactions, to effectuate the purposes of this Agreement or to better assure, convey, assign, transfer, perfect or confirm unto Lender the property and rights intended to be given it in the Loan Documents.

17. **LIABILITY**. If any party hereto consists of more than one person and/or entity, (a) the obligations and liabilities of each such person and/or entity hereunder shall be joint and several, (b) the representations, covenants and agreements of such party shall be deemed made by each person and/or entity comprising such party, and (c) each reference to such party shall be deemed a reference to each person and/or entity comprising such party. This Agreement shall be binding upon and inure to the benefit of the parties hereto and their respective heirs, estates, legal representatives (acting on behalf of such party or its estate), successors and assigns forever.

18. **SEVERABILITY**. If any term, covenant or condition of this Agreement is held to be invalid, illegal or unenforceable in any respect, this Agreement shall be construed without such term, covenant or condition and the validity or enforceability of the remaining terms, covenants or conditions shall not in any way be affected.

19. **APPLICABLE LAW; JURISDICTION**. This Agreement shall be governed and construed in accordance with the laws of the State of New York. The parties hereto submit to personal jurisdiction in the state courts located in said state and the federal courts of the United States of America located in said state for the enforcement of any obligations hereunder and waive any and all personal rights under the law of any other state to object to jurisdiction within such state for the purposes of any action, suit, proceeding or litigation to enforce such obligations.

20. **DEFINITIONS**. Unless the context clearly indicates a contrary intent or unless otherwise specifically provided herein, words used in this Agreement (including pronouns) shall include the corresponding masculine, feminine or neuter forms, and the singular form of such words shall include the plural and vice versa. The words "included", "includes" and "including" shall each be deemed to be followed by the phrase, "without limitation." The words "herein", "hereby", "hereof", and "hereunder" shall each be deemed to refer to this entire Agreement and not to any particular paragraph, article or section hereof. Notwithstanding the foregoing, if any law is amended so as to broaden the meaning of any term defined in it, such broader meaning shall apply subsequent to the effective date of such amendment. Where a defined term derives its meaning from a statutory reference, any regulatory definition is broader than the statutory reference and any reference or citation to a statute or regulation shall be deemed to include any amendments to that statute or regulation and judicial and administrative interpretations of it.

21. **COMPLIANCE WITH ERISA**. As of the date of this Agreement, Borrower does not maintain any employee benefit plan which requires compliance with the Employee Retirement Income Security Act of 1974, as amended ("ERISA"). If at any time Borrower shall institute any employee benefit plans, it shall at all times comply with the requirements of ERISA. Principal shall at all times comply with the requirements of ERISA.

22. **SOLE DISCRETION OF LENDER**. Wherever pursuant to this Agreement, Lender exercises any right given to it to approve or disapprove, or any arrangement or term is to be satisfactory to Lender, Lender's decision to approve or disapprove or to decide that arrangements or terms are satisfactory or not satisfactory shall be in the sole and absolute discretion of Lender and shall be final and conclusive, except as may be otherwise expressly and specifically provided herein.

23. **HEADINGS, ETC.** The headings and captions of various paragraphs of this Agreement are for convenience of reference only and are not to be construed as defining or limiting, in any way, the scope or intent of the provisions hereof.

24. **COUNTERPARTS**. This Agreement may be executed in any number of counterparts, each of which shall be deemed to be an original and all of which when taken together shall constitute one and the same agreement.

25. **INTEGRATION, SURVIVAL**. This Agreement, the other New Loan Documents and the Original Loan Documents, as modified or restated hereby or by another New Loan Document, embody the entire agreement by and between the parties hereto with respect to the Loan, and any and all prior correspondence, discussions or negotiations are deemed merged therein. Except as otherwise specifically provided herein, all obligations of any party contained in this Agreement, the other New Loan Documents or the Loan Documents, as modified hereby or by another New Loan Document, shall survive the Closing, and Lender hereby preserves all of its rights against all persons or entities and all collateral securing the Loan, including, without limitation, the Property.

26. **NO ORAL CHANGE**. This Agreement, and any provisions hereof, may not be modified, amended, waived, extended, changed, discharged or terminated orally or by any act or failure to act on the part of any party hereto, but only by an agreement in writing signed by the party against whom enforcement of any modification, amendment, waiver, extension, change, discharge or termination is sought. In addition, nothing contained in any document submitted for Lender's review, including, without limitation any organizational documents of Borrower, Principal or any of their respective managers/members, partners, trustees or officers, shall modify, amend, waive, extend, change, discharge or terminate any term or provision of the Loan Documents or constitute Lender's consent to any matter in the Loan Documents requiring Lender's consent unless and until such time, if any, as an agreement specifically allowing such modification, amendment, waiver, extension, change, discharge or termination or consenting to such matter has been executed in writing by Lender. Furthermore, notwithstanding the delivery to Lender of any current title examinations and/or commitments for the Property, (a) this Agreement shall not constitute Lender's consent or approval to the existence of any matters reflected in such title examinations and/or commitments to the extent such matters are not also reflected in the Lender's mortgagee title insurance policy issued in connection with the Transactions and (b) Lender does not waive, shall not be deemed to have waived and hereby reserves, any and all rights it has under the Loan Documents, with respect to any lien or encumbrance on the Property not expressly permitted under the Loan Documents.

27. **NOTICES**. Except as otherwise specified herein, any notice, consent, request or other communication required or permitted hereunder shall be in writing and shall be deemed properly given if delivered in accordance with the notice requirements contained in the Loan Agreement using the address for a party hereto set forth at the top of the first page of this Agreement (as each such address may be changed from time to time by any such party by delivering notice thereof to the other parties hereto in the manner provided herein). Any notices or other communications required or permitted under any of the other Loan Documents shall be provided in accordance with the requirements therefor as set forth in each such Loan Document; provided, however, that from and after the date hereof the address of Lender, shall, subject to change as provided in the Loan Documents, be as set forth at the top of the first page of this Agreement.

28. **WAIVER OF JURY TRIAL**. **THE PARTIES HERETO KNOWINGLY, VOLUNTARILY AND INTENTIONALLY WAIVE ANY RIGHT THEY MAY HAVE TO A TRIAL BY JURY IN RESPECT OF ANY LITIGATION BASED ON THE LOAN OR ARISING OUT OF, UNDER OR IN CONNECTION WITH THIS AGREEMENT, THE OTHER NEW LOAN DOCUMENTS, OR THE OTHER LOAN DOCUMENTS, OR ANY COURSE OF CONDUCT, COURSE OF DEALING, STATEMENT (WHETHER VERBAL OR WRITTEN) OR ACTION OF ANY PARTY HERETO. THIS PROVISION IS A MATERIAL INDUCEMENT FOR LENDER'S CONSENT TO THE TRANSACTIONS. EACH PARTY REPRESENTS AND WARRANTS THAT IT HAS REVIEWED THIS WAIVER WITH ITS LEGAL COUNSEL AND THAT IT KNOWINGLY AND VOLUNTARILY WAIVES ITS JURY TRIAL RIGHTS FOLLOWING CONSULTATION WITH LEGAL COUNSEL.**

29. AMENDMENTS TO LOAN AGREEMENT. The following amendments to the Loan Agreement shall be effective as of the Closing Date:

(a) Section 1.1 of the Loan Agreement is amended as follows:

(i) By inserting the following new defined term and definition thereof after the defined term "Condemnation":

""Consent to Additional Collateral" shall mean that certain Consent to Collateral Addition and Amendment to Loan Documents dated August 1, 2019 by and among Borrower, Guarantor and Lender."

(ii) By deleting the definition of "Ionis Lease" and inserting in lieu thereof the following new definition:

""Ionis Lease" shall mean, collectively, (i) that certain Lease Agreement, dated as of the date hereof, between Ionis, as tenant and Borrower, as landlord, demising the Original Property (as defined in the Consent to Additional Collateral) to Ionis, as the same may be amended, restated, replaced, supplemented or otherwise modified from time to time in accordance with the terms of this Agreement and (ii) that certain Ground Lease, dated as of August 1, 2019, between Ionis, as tenant and Borrower, as landlord, demising the Additional Parcel (as defined in the Consent to Additional Collateral) to Ionis, as the same may be amended, restated, replaced, supplemented or otherwise modified from time to time in accordance with the terms of this Agreement."

(iii) By inserting at the end of the definition of "Loan Documents" the following: "Loan Documents shall specifically include the Consent to Additional Collateral and any "New Loan Document" (as defined in the Consent to Additional Collateral."

(iv) By inserting at the end of the definition of the "Property" the following: "Notwithstanding anything to the contrary contained herein or in any other Loan Document, "Property" shall include the "Additional Parcel" (as defined in the Consent to Additional Collateral) and all right, title and interest of Borrower in the improvements now or hereafter erected, situated or installed thereon and the personal property located therein."

(v) By deleting the definition of "Security Instrument" and inserting in lieu thereof the following new definition:

""Security Instrument" shall mean that certain first priority Amended and Restated Deed of Trust, Assignment of Leases and Rents, Security Agreement and Fixture Filing, dated as of August 1, 2019, executed and delivered by Borrower as security for the Loan and encumbering the Property, as the same may be amended, restated, replaced, supplemented or otherwise modified from time to time."

(b) Section 3.1.45 of the Loan Agreement is amended by inserting the following at the end thereof: "Additionally, upon completion of same, the Property will consist of an approximately 70,000 square foot conference center as contemplated by the Consent to Additional Collateral."

(c) Section 10.1 of the Loan Agreement is amended (x) by deleting "or" at the end of clause (xviii), (y) by deleting the period at the end of clause (xix) and inserting "; or" in lieu thereof, and (z) inserting the following new clauses (xx) and (xxi):

"(xx) If any of the representations and warranties made by Borrower or Guarantor in Section 10(c) of the Consent to Additional Collateral shall have been false or misleading in any material respect at the time such representation or warranty was made.

(xxi) If (I) Borrower or Guarantor shall default in the performance of any covenant contained in clauses (i), (iii) (with respect to delivery of notices only), (vi), (ix), (x), (xi), (xii), (xiv) or (xvi) of Section 10(b) of the Consent to Additional Collateral or (II) Guarantor shall default in the performance of the covenant contained in clause (viii) of Section 10(b) of the Consent to Additional Collateral and such default shall continue for more than ten (10) days after written notice to Guarantor from Lender; provided, however, notwithstanding the foregoing, Guarantor shall only be entitled to one notice of a default under Section 10(b)(viii) per 365 day period and any subsequent default under section 10(b)(viii) within such 365 day period shall be an immediate Event of Default or (III) Borrower or Guarantor shall default in the performance of any covenant contained in Section 10(b) of the Consent to Additional Collateral other than those contained in clauses (i), (iii) (with respect to delivery of notices only), (vi), (viii), (ix), (x), (xi), (xii), (xiv) or (xvi) of Section 10(b), and if Borrower or Guarantor, as applicable, shall continue to be in default (y) for ten (10) days after written notice to Borrower or Guarantor, as applicable, from Lender, in the case of any default which can be cured by the payment of a sum of money, or (z) for thirty (30) days after written notice from Lender in the case of any other default; provided, however, that if such non-monetary default is susceptible of cure but cannot reasonably be cured within such thirty (30) day period and provided further that Borrower or Guarantor, as applicable, shall have commenced to cure such default within such thirty (30) day period and thereafter diligently and expeditiously proceeds to cure the same, such thirty (30) day period shall be extended for such time as is reasonably necessary for Borrower or Guarantor, as applicable, in the exercise of due diligence to cure such default, such additional period not to exceed sixty (60) days."

(d) Section 11.22 of the Loan Agreement is amended by (i) inserting the following at the end of clause (xii) thereof: "including specifically, but without limitation, the "Improvements" (as defined in the Consent to Additional Collateral), (ii) by deleting clause (xviii) in its entirety and inserting the following new clause (xviii) in lieu thereof: "(xviii) any indemnification and/or other obligations to the City of Carlsbad or any other Governmental Authority or Person under any indemnification agreement, hold harmless agreement, maintenance agreement, notice of restrictions or other agreement of any kind or nature whatsoever executed by Guarantor and/or Borrower in connection with or pursuant to any Governmental Approval or other consents and approvals issued in connection with the construction of the Improvements (as defined in the Consent to Additional Collateral) or the conveyance of the Additional Parcel (as defined in the Consent to Additional Collateral)" (and (iii) by (x) deleting "or" at the end of clause (9) of the penultimate paragraph of Section 11.22, (y) deleting the period at the end of clause (10) of said paragraph and inserting "; or" in lieu thereof and (z) inserting the following new clause (11): "(11) the "Improvements" (as defined in the Consent to Additional Collateral) have not been completed in accordance with the terms of the Consent to Collateral Addition as of the date that is the earlier to occur of (A) August 6, 2025 or (B) the date Lender notifies Borrower in writing of the occurrence of an Event of Default under Sections 10.1(a)(i), (ii), (iii) or (iv) of this Agreement".

(e) Schedule 3.1.22 attached to the Loan Agreement is hereby deleted in its entirely and is replaced with Schedule 3.1.22 attached hereto.

(f) Schedule 3.1.28 attached to the Loan Agreement is hereby deleted in its entirely and is replaced with Schedule 3.1.28 attached hereto.

All references to the Loan Agreement in the Loan Documents shall be references to the Loan Agreement, as amended by this Agreement.

30. AMENDMENT TO ENVIRONMENTAL INDEMNITY. The following amendments to the Environmental Indemnity shall be effective as of the Closing Date:

(a) All references in the Environmental Indemnity to "Environmental Report" shall be deemed to include references to that certain Phase I Environmental Site Assessment Report dated May 1, 2019, prepared by AEI Consultants in respect of Lot 25.

(b) All references in the Environmental Indemnity to "Property" shall mean the Original Property and the Additional Parcel and improvements located thereon.

31. INTENTIONALLY OMITTED.

32. ANTI-MONEY LAUNDERING PROVISIONS.

(a) For purposes of this Section 32:

(i) "Advances" shall mean any and all disbursement of proceeds of the Loan funded by Lender to or for the benefit of Borrower in accordance with the terms and conditions set forth in the Loan Documents; provided, that Lender has no further obligation to so disburse any such proceeds.

(ii) "Anti-Terrorism Laws" shall mean any Laws relating to terrorism, trade sanctions programs and embargoes, import/export licensing, money laundering or bribery, and any regulation, order, or directive promulgated, issued or enforced pursuant to such Laws, all as amended, supplemented or replaced from time to time.

(iii) "Collateral" shall mean all real property and personal property now or hereafter securing the Loan, including, without limitation, the Property.

(iv) "Covered Entity" shall mean (a) Borrower, each of Borrower's subsidiaries, all guarantors under the Loan and all pledgors of Collateral and (b) each Person that, directly or indirectly, is in control of a Person described in clause (a) above. For purposes of this definition, control of a Person shall mean the direct or indirect (x) ownership of, or power to vote, twenty-five percent (25%) or more of the issued and outstanding equity interests having ordinary voting power for the election of directors of such Person or other Persons performing similar functions for such Person, or (y) power to direct or cause the direction of the management and policies of such Person whether by ownership of equity interests, contract or otherwise.

(v) "Governmental Body" shall mean any nation or government, any state or other political subdivision thereof or any entity, authority, agency, division or department exercising the executive, legislative, judicial, taxing, regulatory or administrative powers or functions of or pertaining to a government (including any supra-national bodies such as the European Union or the European Central Bank) and any group or body charged with setting financial accounting or regulatory capital rules or standards (including, without limitation, the Financial Accounting Standards Board, the Bank for International Settlements or the Basel Committee on Banking Supervision or any successor or similar authority to any of the foregoing).

(vi) "Law(s)" shall mean any law(s) (including common law), constitution, statute, treaty, regulation, rule, ordinance, opinion, issued guidance, release, ruling, order, executive order, injunction, writ, decree, bond, judgment, authorization or approval, lien or award of or any settlement arrangement, by agreement, consent or otherwise, with any Governmental Body, foreign or domestic.

(vii) "Person" shall mean any individual, corporation, partnership (whether general or limited), joint venture, limited liability company, limited liability partnership, estate, trust, joint stock company, unincorporated association, any federal, state, county or municipal government or political subdivision or any bureau, department or agency thereof and any fiduciary acting in such capacity on behalf of any of the foregoing or any other entity.

(viii) "Reportable Compliance Event" shall mean that any Covered Entity becomes a Sanctioned Person, or is charged by indictment, criminal complaint or similar charging instrument, arraigned, or custodially detained in connection with any Anti-Terrorism Law or any predicate crime to any Anti-Terrorism Law, or has knowledge of facts or circumstances to the effect that it is reasonably likely that any aspect of its operations is in actual or probable violation of any Anti-Terrorism Law.

(ix) "Sanctioned Country" shall mean a country subject to a sanctions program maintained under any Anti-Terrorism Law.

(x) "Sanctioned Person" shall mean any individual person, group, regime, entity or thing listed or otherwise recognized as a specially designated, prohibited, sanctioned or debarred person, group, regime, entity or thing, or subject to any limitations or prohibitions (including but not limited to the blocking of property or rejection of transactions), under any Anti-Terrorism Law.

(b) Borrower and Principal hereby warrant and represent to Lender that no Covered Entity is a Sanctioned Person, and that no Covered Entity, either in its own right or through any third party, (i) has any of its assets in a Sanctioned Country or in the possession, custody or control of a Sanctioned Person in violation of any Anti-Terrorism Law; (ii) does business in or with, or derives any of its income from investments in or transactions with, any Sanctioned Country or Sanctioned Person in violation of any Anti-Terrorism Law; or (iii) engages in any dealings or transactions prohibited by any Anti-Terrorism Law.

(c) Borrower and Principal hereby covenant and agree with Lender that no Covered Entity will become a Sanctioned Person, and that no Covered Entity, either in its own right or through any third party, will (i) have any of its assets in a Sanctioned Country or in the possession, custody or control of a Sanctioned Person in violation of any Anti-Terrorism Law; (ii) do business in or with, or derive any of its income from investments in or transactions with, any Sanctioned Country or Sanctioned Person in violation of any Anti-Terrorism Law; (iii) engage in any dealings or transactions prohibited by any Anti-Terrorism Law; or (iv) use the Advances to fund any operations in, finance any investments or activities in, or, make any payments to, a Sanctioned Country or Sanctioned Person in violation of any Anti-Terrorism Law. Borrower and Principal hereby further covenant and agree with Lender that the funds used to repay the Debt will not be derived from any unlawful activity, and that each Covered Entity shall comply with all Anti-Terrorism Laws. Borrower covenants and agrees with Lender that Borrower shall promptly notify Lender in writing upon the occurrence of a Reportable Compliance Event.

(d) It shall be an Event of Default under the Loan Documents if (i) any representation or warranty contained in Section 32(b) above is or becomes false or misleading at any time, or (ii) any covenant or agreement of Borrower or Principal contained in Section 32(c) above is breached by Borrower or Principal, and, notwithstanding any provision to the contrary contained in any of the other Loan Documents, none of the Borrower or Principal shall be entitled to (x) any notice of any such false or misleading warranty or representation or of any breach of any such covenant or agreement, nor to (y) any grace period or any cure right with respect to any such false or misleading warranty or representation or any breach of any such covenant or agreement.

(e) If and to the extent that any of the other Loan Documents contain any anti-money laundering provisions, same are hereby deleted and shall be deemed to be replaced by the terms and provisions set forth in this Section 32.

34. CFIUS.

(a) Borrower hereby represents and warrants to Lender that neither Borrower's acquisition of the Additional Parcel nor the Ground Lease is a Covered Transaction (as defined below).

(b) Borrower and Principal agree that during the term of the Loan, Borrower and Principal shall, and shall cause the holders of direct and/or indirect, legal and/or beneficial, interests in Borrower (other than public shareholders of Principal for so long as Principal is a publicly traded company on a recognized stock exchange in the United States of America) to, (a) within five (5) days of receipt of the same, notify Lender, and provide Lender with a copy of, any inquiry received from CFIUS (as defined herein) or any other Governmental Authority related to each of the Borrower's acquisition of the Additional Parcel and/or the Ground Lease, (b) make any filing requested by CFIUS related to the Borrower's acquisition of the Property and/or the Ground Lease, (c) cooperate with, and fully respond to any CFIUS Review related to the Borrower's acquisition of the Property and/or the Ground Lease, in each case within the time permitted by CFIUS or such Governmental Authority, as applicable, and (d) subject to the terms and conditions of the Loan Documents, take any mitigation measures requested by CFIUS and/or any Governmental Authority in connection with the CFIUS Review.

For purposes of this Section:

"**CFIUS**" shall mean (i) the Committee on Foreign Investment in the United States first established pursuant to Executive Order 11858 of May 7, 1975, and (ii) any replacement or successor thereto, including, without limitation, pursuant to FIRRMA.

"**CFIUS Review**" shall mean CFIUS's review and/or investigation, including any inquiries received from, CFIUS or any Governmental Authority related to CFIUS's review and/or investigation.

"**Covered Transaction**" shall have the meaning set forth in the DPA.

"**DPA**" shall mean the Defense Production Act of 1950, 50 U.S.C. § 4565, as amended by FIRRMA, H. R. 5515-538 (as the same may have been or may hereafter be amended, restated, supplemented or otherwise modified), all laws and regulations related thereto and all mandates, requirements, powers and similar requirements imposed or exercised thereunder (including, without limitation, any of the foregoing implemented by and/or otherwise relating to CFIUS), as the foregoing may be amended from time to time, any successor statute or statutes and all rules and regulations from time to time promulgated in connection with the foregoing.

"**FIRRMA**" shall mean the Foreign Investment Risk Review Modernization Act of 2018.

"**Governmental Authority**" shall mean any court, board, agency, commission, office or authority of any nature whatsoever or any governmental unit (federal, state, county, district, municipal, city, foreign or otherwise) whether now or hereafter in existence.

[remainder of page intentionally left blank]

IN WITNESS WHEREOF, the parties hereto have caused this Agreement to be executed under seal by their duly authorized representatives as of the day, month and year first above written.

BORROWER:

IONIS GAZELLE, LLC, a Delaware limited liability company

By: Ionis Pharmaceuticals, Inc., a Delaware corporation, its sole member

By: /s/ Elizabeth L. Hougen
Name: Elizabeth L. Hougen
Title: Senior Vice President, Finance and Chief Financial Officer

[signatures continue on next page]

PRINCIPAL:

IONIS PHARMACEUTICALS, INC., a Delaware corporation

By: /s/ Elizabeth L. Hougen
Name: Elizabeth L. Hougen
Title: Senior Vice President, Finance and Chief Financial Officer

[signatures continue on next page]

LENDER:

WELLS FARGO BANK, NATIONAL ASSOCIATION, AS TRUSTEE FOR THE BENEFIT OF THE REGISTERED HOLDERS OF UBS COMMERCIAL MORTGAGE TRUST 2017-C3, COMMERCIAL MORTGAGE PASS-THROUGH CERTIFICATES, SERIES 2017-C3

By: Midland Loan Services, a Division of PNC Bank, National Association, its Attorney-in-Fact

By: /s/ Alan H. Torgler
Name: Alan H. Torgler
Title: Vice President, Servicing Officer

EXHIBIT "A"

Additional Parcel

LOT 25 OF CARLSBAD TRACT NO. 97-13-03, CARLSBAD OAKS NORTH PHASE 3, ACCORDING TO MAP THEREOF NO. 16145, RECORDED IN THE OFFICE OF THE COUNTY RECORDER OF SAN DIEGO COUNTY, CALIFORNIA, ON OCTOBER 13, 2016 AS DOCUMENT NO. 2016-7000438 OF OFFICIAL RECORDS.

APN: 209-120-27-00

EXHIBIT “B”

Plans

EXHIBIT “C”

Improvements Budget

EXHIBIT “D”

Construction Timeline

SCHEDULE 3.1.22

RENT ROLL

SCHEDULE 3.1.28

ORGANIZATIONAL CHART

EXHIBIT 31.1

CERTIFICATION

I, Stanley T. Crooke, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Ionis Pharmaceuticals, 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: November 6, 2019

/s/ STANLEY T. CROOKE
Stanley T. Crooke, M.D., Ph.D.
Chief Executive Officer

EXHIBIT 31.2

CERTIFICATION

I, Elizabeth L. Hougen, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Ionis Pharmaceuticals, 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: November 6, 2019

/s/ ELIZABETH L. HOUGEN
Elizabeth L. Hougen
Chief Financial Officer

Exhibit 32.1

CERTIFICATION

Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, Stanley T. Crooke, the Chief Executive Officer of Ionis Pharmaceuticals, Inc., (the "Company"), and Elizabeth L. Hougen, 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 September 30, 2019, to which this Certification is attached as Exhibit 32.1 (the "Periodic Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

2. The information contained in the Periodic Report fairly presents, in all material respects, the financial condition 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: November 6, 2019

/s/ STANLEY T. CROOKE	/s/ ELIZABETH L. HOUGEN
Stanley T. Crooke, M.D., Ph.D.	Elizabeth L. Hougen
Chief Executive Officer	Chief Financial Officer

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