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DELTA REPORT

10-Q

IONS - IONIS PHARMACEUTICALS INC

10-Q - JUNE 30, 2024 COMPARED TO 10-Q - MARCH 31, 2024

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TOTAL DELTAS 6796

 CHANGES 130

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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

Form 10-Q

(Mark One)

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

For the Quarterly Period Ended **March 31, 2024** **June 30, 2024**

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

(State or other jurisdiction of incorporation or organization)

33-0336973

(IRS Employer Identification No.)

2855 Gazelle Court, Carlsbad, California

(Address of Principal Executive Offices)

92010

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

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

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted 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 such files). Yes No

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

Large Accelerated Filer

Accelerated Filer

Non-accelerated Filer

Smaller Reporting Company

Emerging Growth Company

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

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

IONIS PHARMACEUTICALS, INC.
FORM 10-Q
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TRADEMARKS

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PART I — FINANCIAL INFORMATION

ITEM 1. FINANCIAL STATEMENTS

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

	March 31, 2024 (unaudited)	December 31, 2023	June 30, 2024 (unaudited)	December 31, 2023
ASSETS				
Current assets:				
Cash and cash equivalents	\$ 348,889	\$ 399,266	\$ 293,993	\$ 399,266
Short-term investments	1,857,327	1,931,935	1,784,693	1,931,935
Contracts receivable	5,140	97,778	27,259	97,778
Inventories	30,259	28,425	28,723	28,425
Other current assets	174,060	184,449	194,715	184,449
Total current assets	2,415,675	2,641,853	2,329,383	2,641,853
Property, plant and equipment, net	72,795	71,043	75,902	71,043
Right-of-use assets	169,431	171,896	166,939	171,896
Deposits and other assets	106,027	105,280	118,904	105,280
Total assets	<u>\$ 2,763,928</u>	<u>\$ 2,990,072</u>	<u>\$ 2,691,128</u>	<u>\$ 2,990,072</u>
LIABILITIES AND STOCKHOLDERS' EQUITY				
Current liabilities:				
Accounts payable	\$ 13,082	\$ 26,027	\$ 9,243	\$ 26,027
Accrued compensation	21,537	67,727	35,018	67,727
Accrued liabilities	106,048	147,894	114,330	147,894
Income taxes payable	2,210	2,151	284	2,151
0.125 percent convertible senior notes, net	44,377	44,332	44,422	44,332
Current portion of deferred contract revenue	130,406	151,128	94,066	151,128
Other current liabilities	9,988	8,831	8,799	8,831
Total current liabilities	327,648	448,090	306,162	448,090
Long-term deferred contract revenue	215,088	241,184	188,701	241,184
1.75 percent convertible senior notes, net	562,964	562,285	563,647	562,285
0 percent convertible senior notes, net	626,167	625,380	626,955	625,380
Liability related to sale of future royalties, net	525,072	513,736	533,754	513,736
Long-term lease liabilities	168,674	170,875	166,438	170,875
Long-term obligations	41,800	41,836	41,773	41,836
Total liabilities	<u>2,467,413</u>	<u>2,603,386</u>	<u>2,427,430</u>	<u>2,603,386</u>
Stockholders' equity:				
Common stock, \$0.001 par value; 300,000,000 shares authorized, 145,844,719 and 144,340,526 shares issued and outstanding at March 31, 2024 (unaudited) and December 31, 2023, respectively	146	144		
Common stock, \$0.001 par value; 300,000,000 shares authorized, 146,025,246 and 144,340,526 shares issued and outstanding at June 30, 2024 (unaudited) and December 31, 2023, respectively			146	144
Additional paid-in capital	2,270,047	2,215,098	2,303,369	2,215,098
Accumulated other comprehensive loss	(34,964)	(32,645)	(34,838)	(32,645)
Accumulated deficit	(1,938,714)	(1,795,911)	(2,004,979)	(1,795,911)

Total stockholders' equity	296,515	386,686	263,698	386,686
Total liabilities and stockholders' equity	\$ 2,763,928	\$ 2,990,072	\$ 2,691,128	\$ 2,990,072

See accompanying notes.

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

	Three Months Ended March 31,		Three Months Ended June 30,		Six Months Ended June 30,	
	2024		2023		2024	
	2024	2023	2023	2024	2023	2023
Revenue:						
Commercial revenue:						
JRAZA royalties	\$ 38,455	\$ 50,247	\$ 56,743	\$ 61,012	\$ 95,198	\$ 111,258
NUA royalties	1,125	—	3,781	—	4,907	—
Total commercial revenue	<u>20,013</u>	<u>17,521</u>	<u>11,512</u>	<u>16,885</u>	<u>31,524</u>	<u>34,406</u>
Total commercial revenue	<u>59,593</u>	<u>67,768</u>	<u>72,036</u>	<u>77,897</u>	<u>131,629</u>	<u>145,664</u>
Research and development revenue:						
Collaborative agreement revenue	49,345	38,334	141,524	91,013	190,870	129,347
WAINUA joint development revenue	10,559	24,422	11,690	19,501	22,249	43,924
Total research and development revenue	<u>59,904</u>	<u>62,756</u>	<u>153,214</u>	<u>110,514</u>	<u>213,119</u>	<u>173,271</u>
Total revenue	<u>119,497</u>	<u>130,524</u>	<u>225,250</u>	<u>188,411</u>	<u>344,748</u>	<u>318,935</u>
Expenses:						
Cost of sales	2,151	1,343	4,164	2,537	6,314	3,880
Research, development and patent	214,215	197,813	222,064	229,927	436,280	427,740
Selling, general and administrative	52,644	45,516	65,113	46,142	117,758	91,658
Total operating expenses	<u>269,010</u>	<u>244,672</u>	<u>291,341</u>	<u>278,606</u>	<u>560,352</u>	<u>523,278</u>
Loss from operations	(149,513)	(114,148)	(66,091)	(90,195)	(215,604)	(204,343)
Other income (expense):						
Investment income	26,285	18,627	25,599	20,792	51,884	39,419
Interest expense	(4,151)	(1,608)	(4,490)	(2,291)	(8,641)	(3,899)
Interest expense related to sale of future royalties	(17,959)	(15,515)	(18,296)	(17,655)	(36,254)	(33,170)
Gain (loss) on investments	2,333	(529)	(3,533)	718	(1,200)	189
Other income	<u>277</u>	<u>230</u>	<u>610</u>	<u>11,183</u>	<u>887</u>	<u>11,414</u>
Loss before income tax expense	(142,728)	(112,943)	(66,201)	(77,448)	(208,928)	(190,390)
Income tax expense	(75)	(11,380)	(64)	(7,842)	(140)	(19,223)
Net loss	<u>\$ (142,803)</u>	<u>\$ (124,323)</u>	<u>\$ (66,265)</u>	<u>\$ (85,290)</u>	<u>\$ (209,068)</u>	<u>\$ (209,613)</u>
Basic and diluted net loss per share	<u>\$ (0.98)</u>	<u>\$ (0.87)</u>	<u>\$ (0.45)</u>	<u>\$ (0.60)</u>	<u>\$ (1.43)</u>	<u>\$ (1.47)</u>
Shares used in computing basic and diluted net loss per share	<u>145,538</u>	<u>142,735</u>	<u>145,958</u>	<u>143,098</u>	<u>145,748</u>	<u>142,918</u>

See accompanying notes.

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

	Three Months Ended March 31,		Three Months Ended June 30,		Six Months Ended June 30,	
	2024		2023		2024	
	2024	2023	2024	2023	2024	2023
Net loss	\$ (142,803)	\$ (124,323)	\$ (66,265)	\$ (85,290)	\$ (209,068)	\$ (209,613)
Unrealized losses on debt securities, net of tax	(2,205)	8,393				
Unrealized gains (losses) on debt securities, net of tax			150	(2,000)	(2,056)	6,393
Currency translation adjustment	(114)	104	(24)	70	(137)	174
Comprehensive loss	<u>\$ (145,122)</u>	<u>\$ (115,826)</u>	<u>\$ (66,139)</u>	<u>\$ (87,220)</u>	<u>\$ (211,261)</u>	<u>\$ (203,046)</u>

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
(in thousands)
(Unaudited)

Description	Common Stock		Additional Paid in Capital	Accumulated Comprehensive Loss	Accumulated Deficit	Stockholders' Equity	Common Stock		Additional Paid in Capital	Accumulated Comprehensive Loss
	Shares	Amount					Shares	Amount		
Balance at December 31, 2022	142,058	\$ 142	\$ 2,059,850	\$ (57,480)	\$ (1,429,625)	\$ 572,887				
Balance at March 31, 2023							143,023	\$ 143	\$ 2,089,358	\$ (48,983)
Net loss	—	—	—	—	(124,323)	(124,323)	—	—	—	—
Change in unrealized losses, net of tax	—	—	—	8,393	—	8,393	—	—	—	(2,000)
Foreign currency translation	—	—	—	104	—	104	—	—	—	70
Issuance of common stock in connection with employee stock plans	965	1	2,560	—	—	2,561	144	—	2,390	—
Stock-based compensation expense	—	—	26,948	—	—	26,948	—	—	26,561	—
Balance at March 31, 2023	<u>143,023</u>	<u>\$ 143</u>	<u>\$ 2,089,358</u>	<u>\$ (48,983)</u>	<u>\$ (1,553,948)</u>	<u>\$ 486,570</u>				

Balance at								
June 30,								
2023								
						<u>143,167</u>	<u>\$ 143</u>	<u>\$ 2,118,309</u>
								<u><u>(50,913)</u></u>
Balance at								
December								
31, 2023	<u>144,341</u>	<u>\$ 144</u>	<u>\$ 2,215,098</u>	<u>\$ (32,645)</u>	<u>\$ (1,795,911)</u>	<u>\$ 386,686</u>		
Balance at								
March 31,								
2024						<u>145,845</u>	<u>\$ 146</u>	<u>\$ 2,270,047</u>
								<u><u>(34,964)</u></u>
Net loss	—	—	—	—	(142,803)	(142,803)	—	—
Change in unrealized losses, net of tax	—	—	—	(2,205)	—	(2,205)	—	—
Change in unrealized gains, net of tax	—	—	—	—	—	—	—	150
Foreign currency translation	—	—	—	(114)	—	(114)	—	(24)
Issuance of common stock in connection with employee stock plans	1,504	2	23,609	—	—	23,611	180	2,594
Stock-based compensation expense	—	—	31,340	—	—	31,340	—	30,728
Balance at								
March 31,								
2024	<u>145,845</u>	<u>\$ 146</u>	<u>\$ 2,270,047</u>	<u>\$ (34,964)</u>	<u>\$ (1,938,714)</u>	<u>\$ 296,515</u>		
Balance at								
June 30,								
2024						<u>146,025</u>	<u>\$ 146</u>	<u>\$ 2,303,369</u>
								<u><u>(34,838)</u></u>

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
(in thousands)
(Unaudited)

Description	Common Stock		Additional Paid in Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount				
Balance at December 31, 2022	<u>142,058</u>	<u>\$ 142</u>	<u>\$ 2,059,850</u>	<u>\$ (57,480)</u>	<u>\$ (1,429,625)</u>	<u>\$ 572,887</u>
Net loss	—	—	—	—	(209,613)	(209,613)
Change in unrealized gains, net of tax	—	—	—	6,393	—	6,393
Foreign currency translation	—	—	—	174	—	174
Issuance of common stock in connection with employee stock plans	1,109	1	4,949	—	—	4,950
Stock-based compensation expense	—	—	53,510	—	—	53,510
Balance at June 30, 2023	<u><u>143,167</u></u>	<u><u>\$ 143</u></u>	<u><u>\$ 2,118,309</u></u>	<u><u>\$ (50,913)</u></u>	<u><u>\$ (1,639,238)</u></u>	<u><u>\$ 428,301</u></u>

Balance at December 31, 2023	144,341	\$	144	\$	2,215,098	\$	(32,645)	\$	(1,795,911)	\$	386,686
Net loss	—		—		—		—		(209,068)		(209,068)
Change in unrealized losses, net of tax	—		—		—		(2,056)		—		(2,056)
Foreign currency translation	—		—		—		(137)		—		(137)
Issuance of common stock in connection with employee stock plans	1,684		2		26,203		—		—		26,205
Stock-based compensation expense	—		—		62,068		—		—		62,068
Balance at June 30, 2024	146,025	\$	146	\$	2,303,369	\$	(34,838)	\$	(2,004,979)	\$	263,698

See accompanying notes.

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

	Three Months Ended March 31,		Six Months Ended June 30,	
	2024	2023	2024	2023
Operating activities:				
Net loss	\$ (142,803)	\$ (124,323)	\$ (209,068)	\$ (209,613)
Adjustments to reconcile net loss to net cash used in operating activities:				
Depreciation	2,547	2,604	5,013	5,225
Amortization of right-of-use operating lease assets	2,465	2,395	4,957	4,826
Amortization of other assets	639	607	1,260	1,244
Amortization of discount on investments, net	(9,257)	(5,042)	(19,143)	(12,481)
Amortization of debt issuance costs	1,667	1,486	3,338	2,966
Non-cash royalty revenue related to sale of royalties	(6,623)	—	(16,236)	(12,562)
Non-cash interest related to sale of future royalties	17,806	15,363	35,949	32,915
Stock-based compensation expense	31,340	26,948	62,068	53,510
Loss (gain) on investments	(2,332)	529	1,201	(301)
Gain on early retirement of debt			—	(11,292)
Non-cash losses related to other assets	133	445	389	775
Changes in operating assets and liabilities:				
Contracts receivable	92,638	11,624	70,519	(2,254)
Inventories	(1,834)	(167)	(298)	(3,505)
Other current and long-term assets	13,381	5,312	(9,381)	(19,696)
Income taxes	59	11,037	(1,867)	18,483
Accounts payable	(13,869)	(10,295)	(17,064)	5,517
Accrued compensation	(46,190)	(31,018)	(32,709)	(19,856)
Accrued liabilities and other current liabilities	(42,887)	(28,460)	(39,201)	(37,562)
Deferred contract revenue	(46,818)	(13,037)	(109,545)	(27,695)
Net cash used in operating activities	(149,938)	(133,992)	(269,818)	(231,356)
Investing activities:				
Purchases of short-term investments	(519,001)	(688,278)	(803,867)	(932,362)
Proceeds from sale of short-term investments	600,836	374,363	968,413	701,034
Purchases of property, plant and equipment	(4,493)	(10,472)	(10,727)	(22,483)
Acquisition of licenses and other assets, net	(1,237)	(1,253)	(15,264)	(2,314)
Net cash provided by (used in) investing activities	76,105	(325,640)	138,555	(256,125)
Financing activities:				
Proceeds from equity, net	23,609	2,560	26,205	4,950

Proceeds from issuance of 1.75 percent convertible senior notes			—	575,000
1.75 percent convertible senior notes issuance costs			—	(13,658)
Repurchase of \$434.1 million principal amount of 0.125 percent convertible senior notes			—	(420,158)
Proceeds from sale of future royalties	—	500,000	—	500,000
Payments of transaction costs related to sale of future royalties	—	(10,434)	—	(10,434)
Principal payments on mortgage debt	(39)	(39)	(78)	(75)
Net cash provided by financing activities	<u>23,570</u>	<u>492,087</u>	<u>26,127</u>	<u>635,625</u>
Effects of exchange rates on cash	(114)	104	(137)	174
Net increase (decrease) in cash and cash equivalents	(50,377)	32,559	(105,273)	148,318
Cash and cash equivalents at beginning of period	<u>399,266</u>	<u>276,472</u>	<u>399,266</u>	<u>276,472</u>
Cash and cash equivalents at end of period	<u>\$ 348,889</u>	<u>\$ 309,031</u>	<u>\$ 293,993</u>	<u>\$ 424,790</u>
Supplemental disclosures of cash flow information:				
Interest paid	\$ 95	\$ 89	\$ 5,569	\$ 529
Income taxes paid	\$ 13	\$ 293	\$ 1,992	\$ 510
Supplemental disclosures of non-cash investing and financing activities:				
Amounts accrued for capital and patent expenditures	\$ 924	\$ 3,058	\$ 1,453	\$ 251

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
March 31, June 30, 2024
(Unaudited)

1. Organization and Basis of Presentation

Organization and Business Activity

We incorporated in California on January 10, 1989. In conjunction with our initial public offering, we reorganized as a Delaware corporation in April 1991. We are a leader in the discovery and development of RNA-targeted therapeutics.

Basis of Presentation

We prepared the unaudited interim condensed consolidated financial statements for the three and six months ended **March 31, 2024** **June 30, 2024** and 2023 on the same basis as the audited financial statements for the year ended December 31, 2023. 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. Our operating results for the interim periods may not be indicative of what our operating results will be 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, 2023 included in our Annual Report on Form 10-K filed with the Securities and Exchange Commission, or SEC.

In our condensed consolidated financial statements, we included the accounts of Ionis Pharmaceuticals, Inc. and the consolidated results of our wholly owned subsidiary, Akcea Therapeutics, Inc. and its wholly owned subsidiaries ("we", "us" or "our").

We operate as a single segment, Ionis operations, because our chief decision maker reviews operating results on an aggregate basis and manages our operations as a single operating segment.

Use of Estimates

We prepare our condensed consolidated financial statements in conformity with accounting principles generally accepted in the United States, or U.S., that require 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 our estimates.

2. Significant Accounting Policies

Our significant accounting policies have not changed substantially from those included in our Annual Report on Form 10-K for the year ended December 31, 2023.

Recently Adopted Issued Accounting Standards

We do not expect any recently issued accounting standards to have a material impact to our financial results.

3. Supplemental Financial Data

Inventories

Our inventory consisted of the following (in thousands):

	March 31, 2024	December 31, 2023	June 30, 2024	December 31, 2023
Raw materials:				
Raw materials - clinical	\$ 23,317	\$ 20,985	\$ 22,211	\$ 20,985
Raw materials - commercial	705	1,809	2,412	1,809
Total raw materials	24,022	22,794	24,623	22,794
Work in process	6,037	5,477	3,614	5,477
Finished goods	200	154	486	154
Total inventories	\$ 30,259	\$ 28,425	\$ 28,723	\$ 28,425

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Accrued Liabilities

Our accrued liabilities consisted of the following (in thousands):

	March 31, 2024	December 31, 2023	June 30, 2024	December 31, 2023
Clinical development expenses	\$ 75,929	\$ 105,967	\$ 82,017	\$ 105,967
In-licensing expenses	6,436	7,454	10,603	7,454
Commercial expenses	4,739	4,875	4,583	4,875
Other miscellaneous expenses	18,944	29,598	17,127	29,598
Total accrued liabilities	\$ 106,048	\$ 147,894	\$ 114,330	\$ 147,894

4. Revenues

During the three and six months ended **March 31, 2024** **June 30, 2024** and 2023, our revenues were comprised of the following (in thousands):

	Three Months Ended March 31,		Three Months Ended June 30,		Six Months Ended June 30,	
	2024	2023	2024	2023	2024	2023
Revenue:						
Commercial revenue:						
JRAZA royalties	\$ 38,455	\$ 50,247	\$ 56,743	\$ 61,012	\$ 95,198	\$ 111,258
NUA royalties	1,125	—	3,781	—	4,907	—
Total commercial revenue	8,628	6,478	8,192	10,655	16,820	17,133
TEGSEDI and WAYLIVRA revenue, net	11,385	11,043	3,320	6,230	14,704	17,273
Licensing and other royalty revenue	20,013	17,521	11,512	16,885	31,524	34,406
Total other commercial revenue	59,593	67,768	72,036	77,897	131,629	145,664
Total commercial revenue	89,206	85,244	91,827	94,560	163,853	175,779
Research and development revenue:						
Collaborative agreement revenue	49,345	38,334	141,524	91,013	190,870	129,347
WAINUA joint development revenue	10,559	24,422	11,690	19,501	22,249	43,924
Total research and development revenue	59,904	62,756	153,214	110,514	213,119	173,271
Total revenue	\$ 119,497	\$ 130,524	\$ 225,250	\$ 188,411	\$ 344,748	\$ 318,935

Revenue Sources

The following are sources of revenue and when we typically recognize revenue.

Commercial Revenue: SPINRAZA royalties and WAINUA royalties

We earn commercial revenue primarily in the form of royalty payments on net sales of SPINRAZA. In 2024, we began earning royalties from WAINUA sales.

Commercial Revenue: TEGSEDI and WAYLIVRA revenue, net

We earn commercial revenue from TEGSEDI and WAYLIVRA sales under our distribution agreements with Sobi. In addition, we receive royalties from PTC Therapeutics International Limited, or PTC, for TEGSEDI and WAYLIVRA sales.

Commercial Revenue: Licensing and other royalty revenue

We also recognize as commercial revenue sales milestone payments and royalties we earn under our partnerships. For example, we earn royalty revenue on net sales of QALSDODY, which is included in Licensing and other royalty revenue.

Research and development revenue under collaboration agreements

We 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.

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Upfront payments: When we enter into a collaboration agreement and receive 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. If part or all of the upfront payment is a license fee, we recognize as revenue the portion related to the license when we deliver the license to our partner because our partner has full use of the license and we do not have any additional performance obligations related to the license after delivery.

Milestone payments: We include variable 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 typically there is considerable uncertainty in the R&D processes that trigger these payments. 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, when we achieve a milestone payment from a partner for advancing a clinical study under a collaboration agreement, we add the milestone payment to the transaction price if the milestone relates to an ongoing R&D services performance obligation and recognize revenue related to the milestone payment over our estimated period of performance. If we have partially completed our performance obligation, then we record a cumulative-effect adjustment in the period we add the milestone payment to the transaction price.

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.

License fees: We recognize as revenue the total amount we determine to be the relative stand-alone selling price of a license when we deliver the license to our partner because our partner has full use of the license and we do not have any additional performance obligations related to the license after delivery.

WAINUA (Eplontersen) Collaboration with AstraZeneca

In 2021, we entered into a joint development and commercialization agreement with AstraZeneca to develop and commercialize WAINUA for the treatment of transthyretin amyloidosis, or ATTR. We jointly developed and are preparing to commercialize WAINUA with AstraZeneca in the U.S. for the treatment of adults with polyneuropathy caused by hereditary ATTR, or ATTRv-PN. We initially granted AstraZeneca exclusive rights to commercialize WAINUA outside the U.S., except for certain Latin American countries. In 2023, we expanded those rights to include Latin America. Under the terms of the agreement, we received a \$200 million upfront payment in 2021.

We evaluated our WAINUA collaboration under ASC 808 and identified four material components: (i) the license we granted to AstraZeneca in 2021, (ii) the co-development activities that we and AstraZeneca are performing, (iii) the co-commercialization activities that we and AstraZeneca are performing and (iv) the co-medical affairs activities that we and AstraZeneca are performing.

We determined that we had a vendor-customer relationship within the scope of Accounting Standards Codification, or ASC, Topic 606, *Revenue from Contracts with Customers*, or ASC 606, for the license we granted to AstraZeneca and as a result we had one performance obligation. For our sole performance obligation, we determined the transaction price was the \$200 million upfront payment we received. We recognized the upfront payment in full in 2021 because we did not have any remaining performance obligations after we delivered the license to AstraZeneca.

We also concluded that the co-development activities, the co-commercialization activities and the co-medical affairs activities are within the scope of ASC Topic 808, *Collaborative Arrangements*, or ASC 808, because we and AstraZeneca are active participants exposed to the risks and benefits of the activities under the collaboration and

therefore do not have a vendor-customer relationship. AstraZeneca is currently responsible for 55 percent of the costs associated with the ongoing global Phase 3 development program. Because we are leading the Phase 3 development program, we made an accounting policy election to recognize as non-customer revenue the cost-share funding from AstraZeneca, net of our share of AstraZeneca's development expenses, in the same period we incur the related development expenses. As AstraZeneca is responsible for the majority of the commercial and medical affairs costs in the U.S. and all costs associated with bringing WAINUA to market outside the U.S., we made an accounting policy election to recognize cost-share funding we receive from AstraZeneca related to commercial and medical affairs activities as reductions of our selling, general and administrative, or SG&A, expense and R&D expense, respectively.

5. Collaborative Arrangements and Licensing Agreements

Below, we have included our AstraZeneca, Biogen, Otsuka and Biogen Roche collaborations, which are the collaborations with substantive changes during 2024 from those included in Part IV, Item 15, Note 4, *Collaborative Arrangements and Licensing Agreements*, of our audited financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2023.

AstraZeneca

We have two collaborations with AstraZeneca, one focused on the joint development and commercialization of WAINUA for the treatment of transthyretin amyloidosis, or ATTR, and one focused on the treatment of cardiovascular, renal and metabolic diseases. From inception through **March 31, June 30, 2024**, we have received **nearly** more than \$910.920 million from these collaborations.

Over the term of our WAINUA collaboration, we are eligible to receive up to \$3.6 billion, which is comprised of a \$200 million upfront payment, up to \$485 million in development and approval milestone payments and up to \$2.9 billion in sales milestone payments. The agreement includes territory-specific development, commercial and medical affairs cost-sharing provisions. In addition, we are eligible to receive up to mid-20 percent royalties for sales in the U.S. and tiered royalties up to the high teens for sales outside the U.S.

In January 2024, we and AstraZeneca launched WAINUA in the U.S. for the treatment of adults with polyneuropathy caused by hereditary transthyretin amyloidosis, or ATTRv-PN. As a result, we began earning royalties from WAINUA sales, which we recognize as commercial revenue in our condensed consolidated statements of operations. We will achieve the next payment of up to \$30 million upon regulatory approval of WAINUA for ATTRv-PN in the European Union, or EU, under this collaboration.

During the three and six months ended **March 31, 2024** **June 30, 2024** and 2023, we earned the following revenue from our relationship with AstraZeneca (in thousands, except percentage amounts):

	Three Months Ended March 31,		Three Months Ended June 30,		Six Months Ended June 30,	
	2024		2023		2024	
	\$ 11,685	\$ 24,425	\$ 15,960	\$ 59,501	\$ 27,645	\$ 83,926
Revenue from our relationship with AstraZeneca			10 %	19 %	7 %	32 %
Percentage of total revenue					8 %	26 %

Our condensed consolidated balance sheet at **March 31, 2024** **June 30, 2024** included deferred contract revenue of \$1.9 million from our relationship with AstraZeneca. We did not have any deferred contract revenue from our relationship with AstraZeneca at December 31, 2023.

Biogen

We have several strategic collaborations with Biogen focused on using antisense technology to advance the treatment of neurological disorders. We developed and licensed to Biogen SPINRAZA, our approved medicine to treat people with spinal muscular atrophy, or SMA. QALSODY, our medicine to treat patients with superoxide dismutase 1 amyotrophic lateral sclerosis, or SOD1-ALS, received accelerated approval **in** from the U.S. **Food and Drug Administration**, or FDA, in April **2023**, **2023** and marketing authorization under exceptional circumstances from the European Medicines Agency, or EMA, in May 2024. In addition, we and Biogen are currently developing numerous other investigational medicines to treat neurodegenerative diseases, including medicines in development to treat people with amyotrophic lateral sclerosis, or ALS, SMA, Angelman Syndrome, or AS, Alzheimer's disease, or AD, and Parkinson's disease, or PD. 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 **March 31, 2024** **June 30, 2024**, we have received more than \$3.8 billion \$3.9 billion in payments from our Biogen collaborations, including payments to purchase our stock.

Under our 2013 strategic neurology collaboration, we earned a \$20 million milestone payment from Biogen when the EMA approved Biogen's Marketing Authorization Application, or MAA, filing of QALSODY in the second quarter of 2024. We recognized this milestone payment as R&D revenue in full in the second quarter of 2024 because we did not have any remaining performance obligations related to the milestone payment. We will achieve the next milestone payment for QALSODY of \$10 million if the Ministry of Health, Labour and Welfare of Japan approves Biogen's Japanese New Drug Application filing of QALSODY.

In the second quarter of 2024, Biogen's option to license ION582, an investigational antisense medicine for the potential treatment of Angelman Syndrome, expired unexercised. As a result, we recognized \$30 million of R&D revenue from previously deferred milestone payments related to the ION582 study because we did not have any remaining performance obligations. We will achieve the next milestone payment of \$25 million if Biogen advances IONIS-MAPT_{RX} into Phase 3 development under our 2012 neurology collaboration.

During the three and six months ended **March 31, 2024** **June 30, 2024** and 2023, we earned the following revenue from our relationship with Biogen (in thousands, except percentage amounts):

	Three Months Ended March 31,		Three Months Ended June 30,		Six Months Ended June 30,	
	2024		2023		2024	
	\$ 59,236	\$ 70,501	\$ 138,159	\$ 97,402	\$ 197,395	\$ 167,903
Revenue from our relationship with Biogen						
Percentage of total revenue	50%	54%	61%	52%	57%	53%

Our condensed consolidated balance sheets at **March 31, 2024** **June 30, 2024** and December 31, 2023 included deferred contract revenue of **\$287.2 million** **\$241.8 million** and \$307.4 million, respectively, from our relationship with Biogen.

Otsuka

In 2023, we entered into an agreement with Otsuka Pharmaceutical Co., Ltd., or Otsuka, to commercialize donidalorsen in Europe. In the second quarter of 2024, we expanded the agreement to include commercialization rights for donidalorsen in the Asia-Pacific region in addition to Europe. As a result, we received a \$20 million upfront payment from Otsuka. Under the amended agreement, we are eligible to receive up to \$290 million, which is comprised of \$85 million in upfront payments, up to \$65 million in regulatory milestone payments and up to \$140 million in sales milestone payments over the term of the collaboration. In addition, we are eligible to receive tiered royalties up to 30 percent on net sales. We are responsible for completing the ongoing development of donidalorsen. We retained the rights to commercialize donidalorsen in the U.S. and in the rest of the world, assuming regulatory approvals. From inception through June 30, 2024, we have received \$85 million in payments from Otsuka.

We identified two performance obligations under our amended agreement for the Asia-Pacific region, comprised of our license of donidalorsen to Otsuka and R&D services for donidalorsen. We allocated the transaction price of \$20 million based on the estimated stand-alone selling price of each performance obligation as follows:

- \$17.5 million for the license of donidalorsen; and
- \$2.5 million for the R&D services for donidalorsen.

In the second quarter of 2024, we recognized \$17.5 million as revenue in full because Otsuka had full use of the license without any continuing involvement from us. We are recognizing revenue for our R&D services performance obligation as we perform services based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. We currently estimate we will satisfy our R&D services performance obligation in March 2026. We will achieve the next payment of \$15 million if the EMA accepts a MAA filing for donidalorsen in the EU under this collaboration.

During the three and six months ended June 30, 2024 and 2023, we earned the following revenue from our relationship with Otsuka (in thousands, except percentage amounts):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2024		2023	
	\$ 18,905	\$ —	\$ 19,691	\$ —
Revenue from our relationship with Otsuka				
Percentage of total revenue	8 %	0 %	6 %	0 %

Our condensed consolidated balance sheets at June 30, 2024 and December 31, 2023 included deferred contract revenue of \$8.8 million and \$8.5 million, respectively, from our relationship with Otsuka.

Roche

We have three collaborations with Hoffmann-La Roche Inc. and F. Hoffmann-La Roche Ltd, collectively Roche: one to develop treatments for Huntington's disease, or HD, one to develop IONIS-FB-L_{Rx} for the treatment of immunoglobulin A, or IgA, nephropathy, or IgAN, and one to develop RNA-targeted programs for AD and HD. From inception through June 30, 2024, we have received more than \$345 million in payments from our Roche collaborations.

In July 2024, Roche discontinued development of IONIS-FB-L_{Rx} for the treatment of geographic atrophy, or GA, following the completion of the Phase 2 study, which showed a favorable safety profile and target engagement, but insufficient efficacy to advance into Phase 3 development.

Over the term of the IONIS-FB-L_{Rx} collaboration for the treatment of IgAN, we are eligible to receive up to \$430 million, which is comprised of a \$35 million license fee, up to \$25 million in development milestone payments, up to \$90 million in regulatory milestone payments and up to \$280 million in sales milestone payments. We will achieve the next payment of \$23.5 million if Roche advances IONIS-FB-L_{Rx} for the treatment of IgAN under this collaboration.

During the three and six months ended June 30, 2024 and 2023, we earned the following revenue from our relationship with Roche (in thousands, except percentage amounts):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2024	2023	2024	2023
	\$ 11,089	\$ 5,754	\$ 22,595	\$ 8,121
Revenue from our relationship with Roche				
Percentage of total revenue	5 %	3 %	7 %	3 %

Our condensed consolidated balance sheets at June 30, 2024 and December 31, 2023 included deferred contract revenue of \$15.0 million and \$36.7 million, respectively, from our relationship with Roche.

6. Basic and Diluted Net Loss Per Share

Basic net loss per share

We calculated our basic net loss per share for the three and six months ended March 31, 2024 June 30, 2024 and 2023 by dividing our net loss by our weighted-average number of common shares outstanding during the period.

Diluted net loss per share

For the three and six months ended March 31, 2024 June 30, 2024 and 2023, 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:

- 1.75 percent convertible senior notes, or 1.75% Notes;
- 0 percent convertible senior notes, or 0% Notes;
- Note hedges related to the 0% Notes;
- 0.125 percent convertible senior notes, or 0.125% Notes;
- Note hedges related to the 0.125% Notes;
- Dilutive stock options;
- Unvested restricted stock units, or RSUs;
- Unvested performance restricted stock units, or PRSUs; and
- Employee Stock Purchase Plan, or ESPP.

For the three months ended March 31, 2024, common stock underlying the 1.75 percent convertible senior notes, or 1.75% Notes, would also have had an anti-dilutive effect on net loss per share.

Additionally, as of March 31, 2024 June 30, 2024 and 2023, we had warrants related to our 0% and 0.125% Notes outstanding. We will include the shares issuable under these warrants in our calculation of diluted earnings per share when the average market price per share of our common stock for the reporting period exceeds the strike price of the warrants.

7. Investments

The following table summarizes the contract maturity of the available-for-sale securities we held as of March 31, 2024 June 30, 2024:

One year or less	69.75 %
After one year but within two years	26.21 %
After two years but within three and a half years	5.4 %
Total	100 %

As illustrated above, at March 31, 2024 June 30, 2024, 95.96 percent of our available-for-sale securities had a maturity of less than two years.

All of our available-for-sale debt 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.

We invest in debt securities with strong credit ratings and an investment grade rating at or above A-1, P-1 or F-1 by Standard & Poor's, Moody's or Fitch, respectively.

At **March 31, 2024** **June 30, 2024**, we had an equity ownership interest of less than 20 percent in seven private companies and three public companies with which we conduct business.

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

	Amortized		Gross Unrealized		Estimated Fair Value	Amortized		Gross Unrealized		Estimated Fair Value
	Cost	Gains	Losses	Cost		Gains	Losses			
March 31, 2024										
June 30, 2024										
Available-for-sale debt securities:										
Corporate debt securities (1)	\$ 529,593	\$ 87	\$ (1,990)	\$ 527,690	\$ 552,837	\$ 36	\$ (1,569)	\$ 551,304		
Debt securities issued by U.S. government agencies	179,632	24	(409)	179,247	121,781	5	(310)	121,476		
Debt securities issued by the U.S. Treasury (1)	582,782	38	(1,372)	581,448	650,997	12	(1,105)	649,904		
Debt securities issued by states of the U.S. and political subdivisions of the states	15,017	29	(77)	14,969	18,083	14	(42)	18,055		
Total debt securities with a maturity of one year or less	1,307,024	178	(3,848)	1,303,354	1,343,698	67	(3,026)	1,340,739		
Corporate debt securities	248,548	405	(890)	248,063	218,639	191	(874)	217,956		
Debt securities issued by U.S. government agencies	115,152	134	(187)	115,099	115,349	72	(317)	115,104		
Debt securities issued by the U.S. Treasury	204,535	133	(1,086)	203,582	127,240	12	(1,135)	126,117		
Debt securities issued by states of the U.S. and political subdivisions of the states	1,420	—	(3)	1,417	1,668	—	(8)	1,660		
Total debt securities with a maturity of more than one year	569,655	672	(2,166)	568,161	462,896	275	(2,334)	460,837		
Total available-for-sale debt securities	\$ 1,876,679	\$ 850	\$ (6,014)	\$ 1,871,515	\$ 1,806,594	\$ 342	\$ (5,360)	\$ 1,801,576		
Equity securities:										
Publicly traded equity securities included in other current assets (2)	\$ 11,897	\$ 319	\$ (3,756)	\$ 8,460	\$ 11,897	\$ 334	\$ (5,377)	\$ 6,854		
Privately held equity securities included in deposits and other assets (3)	23,115	25,001	(5,125)	42,991	23,115	25,001	(7,093)	41,023		
Total equity securities	35,012	25,320	(8,881)	51,451	35,012	25,335	(12,470)	47,877		
Total available-for-sale debt and equity securities	\$ 1,911,691	\$ 26,170	\$ (14,895)	\$ 1,922,966	\$ 1,841,606	\$ 25,677	\$ (17,830)	\$ 1,849,453		
December 31, 2023										
Available-for-sale debt securities:										
Corporate debt securities (1)	\$ 559,967	\$ 157	\$ (2,625)	\$ 557,499						
Debt securities issued by U.S. government agencies	224,711	64	(611)	224,164						
Debt securities issued by the U.S. Treasury (1)	513,784	152	(1,889)	512,047						
Debt securities issued by states of the U.S. and political subdivisions of the states	17,757	42	(113)	17,686						
Total debt securities with a maturity of one year or less	1,316,219	415	(5,238)	1,311,396						
Corporate debt securities	243,151	1,270	(692)	243,729						
Debt securities issued by U.S. government agencies	110,138	547	(21)	110,664						
Debt securities issued by the U.S. Treasury	294,873	1,239	(480)	295,632						
Debt securities issued by states of the U.S. and political subdivisions of the states	3,466	7	(4)	3,469						
Total debt securities with a maturity of more than one year	651,628	3,063	(1,197)	653,494						
Total available-for-sale debt securities	\$ 1,967,847	\$ 3,478	\$ (6,435)	\$ 1,964,890						
Equity securities:										
Publicly traded equity securities included in other current assets (2)	\$ 11,897	\$ 236	\$ (5,832)	\$ 6,301						
Privately held equity securities included in deposits and other assets (3)	23,115	25,001	(5,125)	42,991						
Total equity securities	35,012	25,237	(10,957)	49,292						
Total available-for-sale debt and equity securities	\$ 2,002,859	\$ 28,715	\$ (17,392)	\$ 2,014,182						

(1) Includes investments classified as cash equivalents in our condensed consolidated balance sheets.

(2) Our publicly traded equity securities are included in other current assets. We recognize publicly traded equity securities at fair value. In the **three** **six** months ended **March 31, 2024** **June 30, 2024**, we recorded a **\$2.2 million** **\$0.6 million** net unrealized gain in our condensed consolidated statements of operations related to changes in the fair value of our investments in publicly traded companies.

(3) Our privately held equity securities are included in deposits and other assets. We recognize our privately held 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, which are Level 3 inputs. In the **three** **six** months ended **March 31, 2024** **June 30, 2024**, **there were** **we recorded a loss of \$no 2.0 million** in our condensed consolidated statements of operations related to changes in the fair value of our investments in privately held companies.

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The following is a summary of our investments we consider to be temporarily impaired at **March 31, 2024** **June 30, 2024** (in thousands, except for number of investments):

	Number of Investments	Less than 12 Months of Temporary Impairment		More than 12 Months of Temporary Impairment		Total Temporary Impairment		Number of Investments	Less than 12 Months of Temporary Impairment		More than 12 Months of Temporary Impairment	
		Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses		Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses
Corporate debt securities	392	\$ 487,939	\$ (1,361)	\$ 96,219	\$ (1,519)	\$ 584,158	\$ (2,880)	440	\$ 517,394	\$ (1,155)	\$ 142,390	\$ (2,880)
Debt securities issued by U.S. government agencies	80	176,956	(360)	12,375	(236)	189,331	(596)	108	173,618	(482)	25,892	(596)
Debt securities issued by the U.S. Treasury	64	588,958	(1,773)	86,772	(685)	675,730	(2,458)	71	561,363	(862)	154,006	(2,458)
Debt securities issued by states of the U.S. and political subdivisions of the states	53	7,978	(22)	5,703	(58)	13,681	(80)	45	8,449	(23)	9,319	(80)
Total temporarily impaired securities	589	\$ 1,261,831	\$ (3,516)	\$ 201,069	\$ (2,498)	\$ 1,462,900	\$ (6,014)	664	\$ 1,260,824	\$ (2,522)	\$ 331,607	\$ (6,014)

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 rather than underlying credit deterioration for any of the issuers. We believe it is more likely than not that we will be able to hold our debt securities with declines in value to maturity. Therefore, we intend to hold these securities to maturity and anticipate full recovery of our debt securities' amortized cost basis at maturity.

8. Fair Value Measurements

The following tables present the major security types we held at **March 31, 2024** **June 30, 2024** and December 31, 2023 that we regularly measure and carry at fair value. The following tables segregate each security type by the level within the fair value hierarchy of the valuation techniques we utilized to determine the respective security's fair value (in thousands):

	At March 31, 2024	Quoted Prices in Active Markets (Level 1)		Significant Other Observable Inputs (Level 2)		At June 30, 2024	Quoted Prices in Active Markets (Level 1)		Significant Other Observable Inputs (Level 2)			
		\$	263,639	\$	263,639		\$	212,489	\$	212,489	\$	—
Cash equivalents (1)												
Corporate debt securities (2)		775,753	—		775,753		769,260	—		769,260		
Debt securities issued by U.S. government agencies (3)		294,346	—		294,346		236,580	—		236,580		

Debt securities issued by the U.S. Treasury (3)	785,030	785,030	—	776,021	776,021	—
Debt securities issued by states of the U.S. and political subdivisions of the states (3)	16,386	—	16,386	19,715	—	19,715
Publicly traded equity securities included in other current assets (4)	8,460	8,460	—	6,854	6,854	—
Total	\$ 2,143,614	\$ 1,057,129	\$ 1,086,485	\$ 2,020,919	\$ 995,364	\$ 1,025,555

		At December 31, 2023	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents (1)		\$ 185,424	\$ 185,424	\$ —
Corporate debt securities (5)		801,228	—	801,228
Debt securities issued by U.S. government agencies (3)		334,828	—	334,828
Debt securities issued by the U.S. Treasury (3)		807,679	807,679	—
Debt securities issued by states of the U.S. and political subdivisions of the states (3)		21,155	—	21,155
Publicly traded equity securities included in other current assets (4)		6,301	6,301	—
Total		\$ 2,156,615	\$ 999,404	\$ 1,157,211

The following footnotes reference lines in our condensed consolidated balance sheets:

- (1) Included in cash and cash equivalents.
- (2) \$14.2 million was included in cash and cash equivalents, with the difference included in short-term investments.
- (3) Included in short-term investments.
- (4) Included in other current assets.
- (5) \$33.0 million was included in cash and cash equivalents, with the difference included in short-term investments.

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Convertible Notes

Our 1.75% Notes, 0% Notes and 0.125% Notes had a fair value of \$601.1 million \$634.4 million, \$627.8 million \$649.6 million and \$42.4 million \$43.4 million at March 31, 2024 June 30, 2024, respectively. Our 1.75% Notes, 0% Notes and 0.125% Notes had a fair value of \$661.1 million, \$667.8 million and \$42.4 million at December 31, 2023, respectively. 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.

9. Stock-based Compensation Expense

The following table summarizes stock-based compensation expense for the three and six months ended March 31, 2024 June 30, 2024 and 2023 (in thousands):

	Three Months Ended March 31,		Three Months Ended June 30,		Six Months Ended June 30,	
			2024	2023	2024	2023
	\$ 204	\$ 119	\$ 246	\$ 118	\$ 450	\$ 237
Cost of sales						
Research, development and patent expense	22,225	19,567	22,766	19,249	44,991	38,816
Selling, general and administrative expense	8,911	7,262	7,716	7,194	16,627	14,457
Total	\$ 31,340	\$ 26,948				
Total stock-based compensation expense			\$ 30,728	\$ 26,561	\$ 62,068	\$ 53,510

As of March 31, 2024 June 30, 2024, total unrecognized estimated stock-based compensation expense related to non-vested stock options, RSUs and PRSUs was \$71.1 million \$61.6 million, \$112.8 million \$96.7 million and \$16.8 million \$13.8 million, respectively. Our actual expenses may differ from these estimates because we will adjust our unrecognized stock-based compensation expense for future forfeitures, including any PRSUs that do not vest. We expect to recognize the cost of stock-based compensation expense related to our non-vested stock options, RSUs and PRSUs over a weighted average amortization period of 1.4 1.3 years, 1.8 1.6 years and 2.2 1.9 years, respectively.

Refer to Part IV, Item 15, Note 1, *Organization and Significant Accounting Policies*, of our audited financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2023 for further details on how we determine the fair value of stock options granted, RSUs, PRSUs and stock purchase rights under the ESPP.

For the ~~three~~ six months ended **March 31, 2024** **June 30, 2024** and 2023, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	Three Months Ended March 31,		Six Months Ended June 30,	
			2024	2023
	2024	2023	2024	2023
Risk-free interest rate	4.0%	3.6%	4.1%	3.6%
Dividend yield	0.0%	0.0%	0.0%	0.0%
Volatility	44.0%	47.5%	43.9%	47.3%
Expected life	6.3 years	6.3 years	6.3 years	6.3 years

ESPP:

	Three Months Ended March 31,		Six Months Ended June 30,	
			2024	2023
	2024	2023	2024	2023
Risk-free interest rate	5.3%	5.2%	5.3%	5.2%
Dividend yield	0.0%	0.0%	0.0%	0.0%
Volatility	38.4%	36.7%	38.4%	36.7%
Expected life	6 months	6 months	6 months	6 months

RSUs:

The weighted-average grant date fair value of RSUs granted to employees for the ~~three~~ six months ended **March 31, 2024** **June 30, 2024** and 2023 was **\$53.54** **\$52.60** and **\$39.85** **\$39.50** per share, respectively.

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PRSUs:

Under the terms of the PRSUs we granted in 2024 and 2023, 100 percent of the PRSUs may vest at the end of the three-year performance period based on our relative TSR as compared to a peer group of companies and as measured at the end of the performance period. Under the terms of the grants, no number of PRSUs is guaranteed to vest and the actual number of PRSUs that will vest at the end of each performance period may be anywhere from zero to 200 percent of the target number depending on our relative TSR.

The weighted-average grant date fair value of PRSUs we granted to our executive officers for the ~~three~~ six months ended **March 31, 2024** **June 30, 2024** and 2023 was \$78.41 and \$58.99 per share, respectively.

10. Income Taxes

We recorded income tax expense of \$0.1 million and \$0.1 million for the three and six months ended **March 31, 2024** **June 30, 2024**, respectively, compared to \$11.4 million \$7.8 million and \$19.2 million for the same period periods in 2023. The decrease in income tax expense relates primarily to the impact of the royalty purchase agreement with Royalty Pharma on income tax expense for the three and six months ended **March 31, 2023** **June 30, 2023**. We reflected the Royalty Pharma transaction as a taxable sale, which required us to include the proceeds from the sale, net of currently deductible issuance costs, as taxable income in 2023.

We continue to maintain a full valuation allowance on all of our net deferred tax assets.

11. Liability Related to Sale of Future Royalties

In January 2023, we entered into a royalty purchase agreement with Royalty Pharma to monetize a portion of our future SPINRAZA and pelacarsen royalties we are entitled to under our arrangements with Biogen and Novartis, respectively. As a result, we received an upfront payment of \$500 million and we are eligible to receive up to \$625 million in additional milestone payments. Under the terms of the agreement, Royalty Pharma will receive 25 percent of our SPINRAZA royalty payments from 2023 through 2027, increasing to 45 percent of royalty payments in 2028, on up to \$1.5 billion in annual sales. In addition, Royalty Pharma will receive 25 percent of any future royalty payments on pelacarsen, our medicine in development to treat patients with elevated lipoprotein(a)-driven cardiovascular disease. Royalty Pharma's royalty interest in SPINRAZA will revert to us after total SPINRAZA royalty payments to Royalty Pharma reach either \$475 million or \$550 million, depending on the timing and occurrence of FDA approval of pelacarsen.

We recorded the upfront payment of \$500 million as a liability related to the sale of future royalties, net of transaction costs of \$10.4 million, which we are amortizing over the estimated life of the arrangement using the effective interest rate method. We recognize royalty revenue in the period in which the counterparty sells the related product and recognizes the related revenue. We record royalty payments made to Royalty Pharma as a reduction of the liability.

We determine the effective interest rate used to record interest expense under this agreement based on an estimate of future royalty payments to Royalty Pharma. As of **March 31, 2024** **June 30, 2024**, the estimated effective interest rate under the agreement was 13.5 percent.

The following table sets forth information on our liability related to sale of future royalties (in thousands):

Proceeds from sale of future royalties in January 2023	\$ 500,000	\$ 500,000
Issuance costs related to sale of future royalties	(10,434)	(10,434)
Royalty payments to Royalty Pharma	(44,628)	(44,628)
Interest expense related to sale of future royalties	68,238	68,238
Amortization of issuance costs related to sale of future royalties	560	560
Net liability related to sale of future royalties as of December 31, 2023	<u>513,736</u>	<u>513,736</u>
Royalty payments to Royalty Pharma	(6,623)	(16,236)
Interest expense related to sale of future royalties	17,806	35,949
Amortization of issuance costs related to sale of future royalties	153	305
Net liability related to sale of future royalties as of March 31, 2024	<u>\$ 525,072</u>	<u>\$ 533,754</u>
Net liability related to sale of future royalties as of June 30, 2024		

There are numerous factors, most of which are not within our control, that could materially impact the amount and timing of royalty payments from Biogen and Novartis, and result in changes to our estimate of future royalty payments to Royalty Pharma. Such factors include, but are not limited to, the commercial sales of SPINRAZA, the regulatory approval and commercial sales of pelacarsen, competing products or other significant events.

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12. Convertible Debt

1.75 Percent Convertible Senior Notes

In 2023, we completed a \$575.0 million offering of convertible senior notes and used \$488.2 million of the net proceeds from the issuance of the 1.75% Notes to repurchase \$504.4 million in principal of our 0.125% Notes. We expect to use the remaining net proceeds to settle the 0.125% Notes that remain **outstanding**, **outstanding** and for general corporate and working capital purposes.

At **March 31, 2024** **June 30, 2024**, we had the following 1.75% Notes outstanding (in millions except interest rate and price per share data):

	1.75% Notes	1.75% Notes
Outstanding principal balance	\$ 575.0	\$ 575.0
Unamortized debt issuance costs	\$ 12.0	\$ 11.4
Maturity date	June 2028	June 2028
Interest rate	1.75%	1.75%
Effective interest rate	2.3%	2.3%
Conversion price per share	\$ 53.73	\$ 53.73
Total shares of common stock subject to conversion	10.7	10.7

0 Percent Convertible Senior Notes and Call Spread

At **March 31, 2024** **June 30, 2024**, we had the following 0% Notes outstanding (in millions except interest rate and price per share data):

	0% Notes	0% Notes
Outstanding principal balance	\$ 632.5	\$ 632.5
Unamortized debt issuance costs	\$ 6.3	\$ 5.5
Maturity date	April 2026	April 2026
Interest rate	0 %	0 %
Effective interest rate	0.5 %	0.5 %
Conversion price per share	\$ 57.84	\$ 57.84
Effective conversion price per share with call spread	\$ 76.39	\$ 76.39

In conjunction with the 2021 offering, we entered into a call spread transaction, which was comprised of purchasing note hedges and selling warrants, to minimize the impact of potential economic dilution upon conversion of our 0% Notes by increasing the effective conversion price on our 0% Notes. We increased our effective conversion price to \$76.39 with the same number of underlying shares as our 0% Notes. The call spread cost us \$46.9 million, of which \$136.7 million was for the note hedge purchase, offset by \$89.8 million we received for selling the warrants. Similar to our 0% Notes, our note hedges are subject to adjustment. Additionally, our note hedges are exercisable upon conversion of the 0% Notes. The note hedges will expire upon maturity of the 0% Notes, or April 2026. The note hedges and warrants are separate transactions and are not part of the terms of our 0% Notes. The holders of the 0% Notes do not have any rights with respect to the note hedges and warrants.

We recorded the amount we paid for the note hedges and the amount we received for the warrants in additional paid-in capital in our condensed consolidated balance sheets. Refer to Part IV, Item 15, Note 1, *Organization and Significant Accounting Policies*, of our audited financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2023 for our Call Spread accounting policy. We reassess our ability to continue to classify the note hedges and warrants in shareholders' equity at each reporting period.

0.125 Percent Convertible Senior Notes and Call Spread

As discussed above, in 2023, we repurchased \$504.4 million of our 0.125% Notes.

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At **March 31, 2024** **June 30, 2024**, we had the following 0.125% Notes outstanding with interest payable semi-annually (in millions except interest rate and price per share data):

	0.125% Notes
Outstanding principal balance	\$ 44.5
Unamortized debt issuance costs	\$ 0.1
Maturity date	December 2024
Interest rate	0.125 %
Effective interest rate	0.5 %
Conversion price per share	\$ 83.28
Effective conversion price per share with call spread	\$ 123.38
Total shares of common stock subject to conversion, excluding shares related to 0.125% Notes that we have repurchased and are currently holding in treasury	0.5

In conjunction with the issuance of our 0.125% Notes in 2019, we entered into a call spread transaction, which was comprised of purchasing note hedges and selling warrants, to minimize the impact of potential economic dilution upon conversion of our 0.125% Notes by increasing the effective conversion price on our 0.125% Notes. We increased our effective conversion price to \$123.38 with the same number of underlying shares as our 0.125% Notes. The call spread cost us \$52.6 million, of which \$108.7 million was for the note hedge purchase, offset by \$56.1 million we received for selling the warrants. Similar to our 0.125% Notes, our note hedges are subject to adjustment. Additionally, our note hedges are exercisable upon conversion of the 0.125% Notes. The note hedges will expire upon maturity of the 0.125% Notes, or December 2024. The note hedges and warrants are separate transactions and are not part of the terms of our 0.125% Notes. The holders of the 0.125% Notes do not have any rights with respect to the note hedges and warrants. As of **March 31, June 30, 2024**, the note hedges and warrants remain outstanding.

We recorded the amount we paid for the note hedges and the amount we received for the warrants in additional paid-in capital in our condensed consolidated balance sheets. We reassess our ability to continue to classify the note hedges and warrants in shareholders' equity at each reporting period.

Other Terms of Convertible Senior Notes

The 1.75%, 0% and 0.125% Notes are convertible under certain conditions, at the option of the note holders. We can 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 notes prior to maturity, and we do not have to provide a sinking fund for them. Holders of the notes may require us to purchase some or all of their notes upon the occurrence of certain fundamental changes, as set forth in the indentures governing the notes, at a purchase price equal to 100 percent of the principal amount of the notes to be purchased, plus any accrued and unpaid interest.

13. Legal Proceedings

From time to time, we are involved in legal proceedings arising in the ordinary course of our business. Periodically, we evaluate the status of each legal matter and assess our potential financial exposure. If we consider the potential loss from any legal proceeding to be probable and we can reasonably estimate the amount, we accrue a liability for the estimated loss. The outcome of any proceeding is not determinable in advance. Therefore, we are required to use significant judgment to determine the probability of a loss and whether the amount of the loss is reasonably estimable. Our assessment of a potential liability and the amount of accruals we recorded are based only on the information available to us at the time. As additional information becomes available, we reassess the potential liability related to the legal proceeding and may revise our estimates.

There are no pending material legal proceedings to which we are a party or of which our property is the subject.

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 wholly owned subsidiary, 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 our commercial medicines, additional medicines in development and technologies. 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 and particularly those inherent in the process of discovering, developing and commercializing medicines that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such medicines. 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, 2023, 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. Except as required by law, we undertake no obligation to update any forward-looking statements for any reason. As a result, you are cautioned not to rely on these forward-looking statements.

Overview

For three decades as a pioneer in RNA-targeted medicines, we have focused on bringing better futures to people with serious diseases. Today, we continue to drive innovation in RNA therapies. A deep understanding of disease biology and an industry-leading drug discovery technology propels our work, coupled with a passion and urgency to deliver better futures for patients.

We currently have five marketed medicines to treat serious diseases: SPINRAZA (nusinersen), QALSODY (tofersen), WAINUA (eplontersen), TEGSEDI (inotersen) and WAYLIVRA (volanesorsen). We also have a rich innovative late- and mid-stage pipeline in neurology, cardiology and other areas of high patient need. We currently have nine medicines in Phase 3 development and multiple additional medicines in early and mid-stage development.

We are using our multiple sources of revenue and **our** capital structure **enable us** to continue investing in our commercial readiness efforts for multiple late-stage programs, our innovative pipeline and our technology. By continuing to focus on these priorities, we believe we are well positioned to drive future growth and to bring next-level value to patients and shareholders.

Marketed Medicines

SPINRAZA is an antisense medicine for the treatment of patients with spinal muscular atrophy, or SMA, a progressive, debilitating and often fatal genetic disease. Our partner, Biogen, is responsible for commercializing SPINRAZA worldwide. From inception through **March 31, 2024** **June 30, 2024**, we have earned more than **\$2.1 billion** **\$2.2 billion** in revenues from our SPINRAZA collaboration, including more than \$1.7 billion in royalties on sales of SPINRAZA.

QALSODY is an antisense medicine that received accelerated approval **in April 2023** from the United States, or U.S., Food and Drug Administration, or FDA, **in April 2023** and marketing authorization under exceptional circumstances from the European Medicines Agency, or EMA, **in May 2024** for the treatment of adult patients with superoxide dismutase 1 amyotrophic lateral sclerosis, or SOD1-ALS, a rare, neurodegenerative disorder that causes progressive loss of motor neurons leading to death. Our partner, Biogen, is responsible for commercializing QALSODY worldwide. **The European Medicines Agency, or EMA, is currently reviewing QALSODY for approval in the European Union, or EU.**

WAINUA is a once monthly, self-administered subcutaneous Ligand-Conjugated Antisense, or LICA, medicine that received **approval from the FDA** **approval** in December 2023 and **Health Canada** in **June 2024** for the treatment of adults with polyneuropathy of hereditary transthyretin-mediated amyloidosis, or ATTRv-PN, a debilitating, progressive, and fatal disease. WAINUA is the only approved medicine for the treatment of ATTRv-PN that can be self-administered via an auto-injector. We and AstraZeneca are commercializing WAINUA in the U.S. with the launch having commenced in January 2024. We and AstraZeneca are seeking regulatory approval for WAINUA in Europe and other parts of the world. AstraZeneca has exclusive rights to commercialize WAINUA outside of the U.S.

TEGSEDI is a once weekly, self-administered subcutaneous medicine approved in the U.S., Europe, Canada and Brazil for the treatment of patients with ATTRv-PN. We sell TEGSEDI in the U.S. and Canada (collectively, North America) and Europe through our distribution agreement with Swedish Orphan Biovitrum AB, or Sobi. In October 2023, our agreement for TEGSEDI in North America was terminated. As a result, Sobi is transitioning responsibilities to us. In February 2024, we began the process to withdraw the TEGSEDI New Drug Application, or NDA. In Latin America, PTC Therapeutics International Limited, or PTC, is commercializing TEGSEDI in Brazil and is pursuing access in additional Latin American countries through its exclusive license agreement with us.

WAYLIVRA is a once weekly, self-administered, subcutaneous medicine approved in Europe and Brazil as an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome, or FCS, and at high risk for pancreatitis. We sell WAYLIVRA in Europe through our distribution agreement with Sobi. In Latin America, PTC is commercializing WAYLIVRA in Brazil for two indications, FCS and familial partial lipodystrophy, or FPL, and is pursuing access in additional Latin American countries through its exclusive license agreement with us.

Medicines in Registration and Phase 3 Studies

We currently have nine medicines in registration or Phase 3 studies for eleven indications, which are:

WAINUA is our medicine to treat patients with transthyretin amyloidosis, or ATTR, that is approved in the U.S. and Canada for the treatment of adults with ATTRv-PN, under regulatory review in other countries for ATTRv-PN and in development for ATTR cardiomyopathy, or ATTR-CM. In January 2024, we launched WAINUA for the treatment of adults with ATTRv-PN in the U.S. In September 2023, The *Journal of the American Medical Association*, or JAMA, published positive results from the Phase 3 NEURO-TTTransform study in patients with ATTRv-PN showing WAINUA halted disease progression and continuously improved quality of life at the 35-, 66- and 85-week analyses. In July 2023, we completed enrollment of the Phase 3 CARDIO-TTTransform study of WAINUA in patients with ATTR-CM with data planned for as early as 2025, expected in 2026. In February 2024, the FDA granted Fast Track designation to WAINUA for the treatment of patients with ATTR-CM. Additionally, in January 2022 and October 2023, the FDA and EMA, respectively, granted Orphan Drug designation to WAINUA for the treatment of ATTR. In June 2024, Health Canada approved WAINUA for the treatment of adults with ATTRv-PN.

Olezarsen is our medicine in development for FCS, an ultra-rare indication and severe hypertriglyceridemia, or sHTG, a much broader indication. We recently submitted an NDA, which is pending acceptance from In June 2024, the FDA accepted our NDA for patients with FCS and are preparing to submit applications for regulatory approval in the EU. Priority Review with a Prescription Drug User Fee Act, or PDUFA, date of December 19, 2024. In April 2024, we presented positive data from the Phase 3 Balance study in patients with FCS and the Phase 2b Bridge study in patients with HTG and sHTG at the American Academy of Cardiology meeting with simultaneous publications in the *New England Journal of Medicine*, or NEJM. Additionally, in April 2024, we opened our Expanded Access Program, or EAP, for patients with FCS in the U.S. In September 2023, we reported positive results from the Phase 3 Balance study in patients with FCS showing statistically significant triglyceride lowering and a substantial reduction in acute pancreatitis events in addition to a favorable safety and tolerability profile. Additionally, we are currently conducting a broad Phase 3 development program for olezarsen for the treatment of sHTG including three Phase 3 studies supporting development (CORE, CORE2 and ESSENCE). We recently completed, which achieved full enrollment of the Phase 3 CORE pivotal study and ESSENCE supportive safety study for sHTG, in 2024. The FDA granted Breakthrough Therapy designation, Orphan Drug designation and Fast Track designation to olezarsen for the treatment of FCS.

Donidalsoren is our medicine in development for hereditary angioedema, or HAE. In January May 2024, we reported presented positive topline data from the Phase 3 OASIS-HAE study in patients treated every four weeks and every eight weeks. We are currently conducting OASIS-Plus, which In addition, we presented positive data from OASISplus, our trial that includes an open-label, or OLE, study in cohort for patients who have completed OASIS-HAE rolling over from the Phase 3 study and a separate "switch study" in cohort for patients who have transitioned to donidalsoren from other prophylactic HAE medications. In May 2024, medications that we opened our EAP for patients refer to as the "switch study," with HAE simultaneous publications in the U.S. NEJM. In December 2023 and June 2024, we licensed European commercialization rights of for donidalsoren to Otsuka Pharmaceutical Co., Ltd., or Otsuka. Otsuka, in Europe and the Asia-Pacific region, respectively. Throughout 2022 and 2023, we reported positive data from the Phase 2 study and Phase 2 OLE study, including two-year OLE data. We are preparing to submit an NDA to the FDA. Otsuka is preparing to submit a Marketing Authorization Application, or MAA, to the EMA. In September 2023 and February 2024, the FDA and EMA, respectively, granted Orphan Drug designation to donidalsoren.

Zilganersen is our medicine in development for Alexander disease, or AxD. In September 2023, July 2024, we advanced zilganersen into completed enrollment in the Phase 3 portion of its the ongoing study for patients with AxD. In September 2020 and October 2019, the FDA and EMA, respectively, granted Orphan Drug designation to zilganersen. Additionally in August 2020, the FDA granted rare pediatric designation to zilganersen.

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Ulefnersen is our medicine in development for amyotrophic lateral sclerosis, or ALS, with mutations in the fused in sarcoma gene, or FUS. We are currently conducting a Phase 3 study of ulefnersen in juvenile and adult patients with FUS-ALS. In August 2023 and September 2023, the FDA and EMA, respectively, granted Orphan Drug designation to ulefnersen.

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QALSODY (tofersen) is our marketed medicine to treat patients with SOD1-ALS. In April 2023, the FDA granted Biogen accelerated approval and in May 2024, the EMA granted Biogen marketing authorization under exceptional circumstances of QALSODY for patients with SOD1-ALS. QALSODY is currently under regulatory review in the EU. Additionally, Biogen is evaluating QALSODY as a potential treatment for presymptomatic SOD1-ALS patients in the ongoing ATLAS study. In September 2016 and August 2016, the FDA and EMA, respectively, granted Orphan Drug designation to QALSODY.

Pelacarsen is our medicine in development to treat patients with elevated lipoprotein(a)-driven cardiovascular disease, disease, or Lp(a)-driven CVD. Novartis is developing pelacarsen, including conducting the ongoing Lp(a) HORIZON Phase 3 cardiovascular outcome study in patients with elevated Lp(a)-driven CVD, which achieved full enrollment in July 2022 with more than 8,000 patients. In April 2020, the FDA granted Fast Track designation to pelacarsen.

Bepirovirsen is our medicine in development for chronic hepatitis B virus, or HBV. GSK is developing bepirovirsen, including conducting the ongoing B-Well Phase 3 program in patients with HBV. HBV, which achieved full enrollment in June 2024. GSK reported positive results from Phase 2 studies in 2023, including durable response data from the Phase 2 B-Sure long-term follow-up study of bepirovirsen in complete responder patients from the Phase 2b B-Clear study of patients with HBV. In February 2024, the FDA granted Fast Track designation to bepirovirsen for the treatment of patients with chronic hepatitis B, or CHB. HBV.

IONIS-FB-L_{Rx} is our medicine in development for immunoglobulin A, or IgA, nephropathy, or IgAN, and geographic atrophy, or GA. IgAN. In the second quarter of 2023, Roche advanced IONIS-FB-L_{Rx} into Phase 3 development in patients with IgAN. In October 2023, we reported positive interim data from the ongoing Phase 2 study of IONIS-FB-L_{Rx} in patients with IgAN. Additionally, IONIS-FB-L_{Rx} is in an ongoing Phase 2 study in patients with geographic atrophy, or GA.

Critical Accounting Estimates

We prepare our condensed consolidated financial statements in conformity with accounting principles generally accepted in the U.S. 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 the audit committee of our board of directors. The following are our significant accounting estimates, which we believe are the most critical to aid in fully understanding and evaluating our reported financial results:

- Assessing the propriety of revenue recognition and associated deferred revenue;
- Determining the appropriate cost estimates for unbilled preclinical studies and clinical development activities; and
- Assessing the appropriate estimate of anticipated future royalty payments under our royalty purchase agreement

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, 2023.

Results of Operations

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

	Three Months Ended March 31		Three Months Ended June 30,		Six Months Ended June 30,	
	2024		2023		2024	
	2024	2023	2024	2023	2024	2023
Total revenue	\$ 119.5	\$ 130.5	\$ 225.3	\$ 188.4	\$ 344.7	\$ 318.9
Total operating expenses	\$ 269.0	\$ 244.7	\$ 291.3	\$ 278.6	\$ 560.4	\$ 523.3
Loss from operations	\$ (149.5)	\$ (114.1)	\$ (66.1)	\$ (90.2)	\$ (215.6)	\$ (204.3)
Net loss	\$ (142.8)	\$ (124.3)	\$ (66.3)	\$ (85.3)	\$ (209.1)	\$ (209.6)

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Revenue

Total revenue for the three and six months ended March 31, 2024 was \$119.5 million June 30, 2024 were \$225.3 million and \$344.7 million, respectively, compared to \$130.5 million \$188.4 million and \$318.9 million for the same period periods in 2023 and was were comprised of the following (in millions):

	Three Months Ended March 31,		Three Months Ended June 30,		Six Months Ended June 30,	
	2024		2023		2024	
	2024	2023	2024	2023	2024	2023
Revenue:						
Commercial revenue:						
JRAZA royalties	\$ 38.5	\$ 50.2	\$ 56.7	\$ 61.0	\$ 95.2	\$ 111.3
NUA royalties	1.1	—	3.8	—	4.9	—
Total commercial revenue:	8.6	6.5	8.2	10.7	16.8	17.1
TEGSEDI and WAYLIVRA revenue, net	11.4	11.0	3.3	6.2	14.7	17.3
Licensing and other royalty revenue	20.0	17.5	11.5	16.9	31.5	34.4
Total other commercial revenue	59.6	67.7	72.0	77.9	131.6	145.7
Total commercial revenue						
Research and development revenue:						
Amortization from upfront payments	41.5	15.6	35.2	15.1	76.7	28.8
Milestone payments	7.0	22.5	53.0	51.1	60.0	73.6
License fees					37.5	20.0
Other services	0.8	0.3	15.9	4.8	16.7	6.9

Collaborative agreement revenue	49.3	38.4	141.6	91.0	190.9	129.3
WAINUA joint development revenue	10.6	24.4	11.7	19.5	22.2	43.9
Total research and development revenue	59.9	62.8	153.3	110.5	213.1	173.2
Total revenue	\$ 119.5	\$ 130.5	\$ 225.3	\$ 188.4	\$ 344.7	\$ 318.9

Commercial revenue for in the three and six months ended March 31, 2024 June 30, 2024 included a new source of royalty revenue with the launch of WAINUA in the U.S. in mid-January late January 2024. While the number of patients on SPINRAZA treatment remained consistent globally, royalties decreased year over year primarily due to the timing of shipments in several markets outside the U.S. Our commercial revenue in the three and six months ended March 31, 2024 June 30, 2024 also included royalties from U.S. the net sales of QALSODY, which Biogen launched in the U.S. in the second quarter of 2023, 2023 and in the EU in the second quarter of 2024.

Research and development, or R&D revenue in the three and six months ended March 31, 2024 included June 30, 2024 increased revenue from compared to the same periods in 2023 primarily due to the amortization of upfront payments compared to from the same period last new collaborations with Roche and Novartis that we entered into during the second half of 2023. In addition, license fees increased year due to the over year as a result of new collaborations we entered into during 2023 the second quarter of 2024, including the expanded donidalorsen licensing agreement with Roche and Novartis. This increase was Otsuka, which now includes the Asia-Pacific region in addition to Europe. These increases were partially offset by decreases the decrease in milestone payments due to timing and WAINUA joint development revenue, which decreased as development activities relating to ATTRv-PN wound down with the launch of WAINUA. WAINUA for this indication.

WAINUA (Eplontersen) Collaboration with AstraZeneca

Our financial results for the three and six months ended March 31, 2024 June 30, 2024 and 2023 reflected the cost-sharing provisions related to our collaboration with AstraZeneca to develop and commercialize WAINUA for the treatment of ATTR. Under the terms of the collaboration agreement, AstraZeneca is currently paying 55 percent of the costs associated with the ongoing global Phase 3 development program. Because we are leading and conducting the Phase 3 development program, we are recognizing as R&D revenue the 55 percent of cost-share funding AstraZeneca is responsible for, net of our share of AstraZeneca's development expenses, in the same period we incur the related development expenses.

As AstraZeneca is responsible for the majority of the medical affairs and commercial costs in the U.S. and all costs associated with bringing WAINUA to market outside the U.S., we are recognizing cost-share funding we receive from AstraZeneca related to these activities as a reduction of our medical affairs and commercialization expenses, which we classify as R&D and selling, general and administrative, or SG&A expenses, respectively. We expect our medical affairs and commercialization expenses to increase with the launch of WAINUA for ATTRv-PN in the U.S. and as WAINUA advances toward the market for ATTR-CM under our collaboration with AstraZeneca.

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The following table sets forth information on revenue and expenses under this collaboration (in millions):

	Three Months Ended March 31,				Three Months Ended June 30,		Six Months Ended June 30,	
	2024		2023		2024	2023	2024	2023
	\$	10.6	\$	24.4	\$ 11.7	\$ 19.5	\$ 22.2	\$ 43.9
WAINUA joint development revenue								
Research and development expenses related to Phase 3 development of WAINUA		22.7		47.1	25.4	38.3	48.1	85.4
Medical affairs expenses for WAINUA		1.3		0.7	1.9	1.1	3.1	1.8
Commercialization expenses for WAINUA		6.0		1.3	6.6	2.5	12.6	3.8

Operating Expenses

The following table sets forth information on operating expenses (in millions):

	Three Months Ended March 31,				Three Months Ended June 30,		Six Months Ended June 30,	
	2024		2023		2024	2023	2024	2023
	\$	237.7	\$	217.7	\$ 260.6	\$ 252.1	\$ 498.3	\$ 469.8
Operating expenses, excluding non-cash compensation expense related to equity awards								
Non-cash compensation expense related to equity awards		31.3		27.0	30.7	26.5	62.1	53.5
Total operating expenses		269.0		244.7	291.3	278.6	560.4	523.3

Operating expenses, excluding non-cash compensation expense related to equity awards, for the three and six months ended March 31, 2024 June 30, 2024 increased compared to the same period periods in 2023. Our SG&A expenses increased year over year primarily due to the launch of WAINUA in the U.S. and launch preparation activities for olezarsen and donidalorsen, donidalorsen, including establishing the field team for olezarsen. Our R&D expenses increased due decreased in the three months ended June 30, 2024 compared to the timing of our late-stage program activities. We expect our R&D expenses will stabilize same period in 2023, and were relatively consistent in the six months ended June 30, 2024 compared to the same period in 2023 as several late-stage studies end and we reallocate resources toward earlier stage programs, have ended. We expect our

operating expenses, excluding non-cash compensation expense related to equity awards, to continue to increase during the remainder of 2024 as we advance our commercialization activities.

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.

Cost of Sales

Our cost of sales is comprised of costs related to our TEGSEDI and WAYLIVRA revenue, which consisted of manufacturing costs, including certain fixed costs, transportation and freight, indirect overhead costs associated with the manufacturing and distribution of TEGSEDI and WAYLIVRA and certain associated period costs.

The following table sets forth information on cost of sales (in millions):

	Three Months Ended March 31,		Three Months Ended June 30,		Six Months Ended June 30,	
	2024		2023		2024	
	\$ 2.0	\$ 1.2	\$ 4.0	\$ 2.4	\$ 5.9	\$ 3.7
Cost of sales, excluding non-cash compensation expense related to equity awards	\$ 2.0	\$ 1.2	\$ 4.0	\$ 2.4	\$ 5.9	\$ 3.7
Non-cash compensation expense related to equity awards	0.2	0.1	0.2	0.1	0.4	0.2
Total cost of sales	\$ 2.2	\$ 1.3	\$ 4.2	\$ 2.5	\$ 6.3	\$ 3.9

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Research, Development and Patent Expenses

Our research, development and patent expenses consist of expenses for drug discovery, drug development, medical affairs, manufacturing and development chemistry and R&D support expenses.

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

	Three Months Ended March 31,		Three Months Ended June 30,		Six Months Ended June 30,	
	2024		2023		2024	
	\$ 192.0	\$ 178.2	\$ 199.3	\$ 210.7	\$ 391.3	\$ 388.9
Research, development and patent expenses, excluding non-cash compensation expense related to equity awards	\$ 192.0	\$ 178.2	\$ 199.3	\$ 210.7	\$ 391.3	\$ 388.9
Non-cash compensation expense related to equity awards	22.2	19.6	22.8	19.2	45.0	38.8
Total research, development and patent expenses	\$ 214.2	\$ 197.8	\$ 222.1	\$ 229.9	\$ 436.3	\$ 427.7

Drug Discovery

We use our proprietary technologies 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 drug discovery research, and that of our partners. Drug discovery is also the function that is responsible for advancing our core technology. This function is also responsible for making investments in complementary technologies to expand the reach of our technologies.

The following table sets forth information on drug discovery expenses (in millions):

	Three Months Ended March 31,		Three Months Ended June 30,		Six Months Ended June 30,	
	2024		2023		2024	
	\$ 28.2	\$ 24.6	\$ 26.7	\$ 27.6	\$ 54.9	\$ 52.2
Drug discovery expenses, excluding non-cash compensation expense related to equity awards	\$ 28.2	\$ 24.6	\$ 26.7	\$ 27.6	\$ 54.9	\$ 52.2
Non-cash compensation expense related to equity awards	4.3	3.9	4.6	4.0	8.9	7.9
Total drug discovery expenses	\$ 32.5	\$ 28.5	\$ 31.3	\$ 31.6	\$ 63.8	\$ 60.1

Drug discovery expenses, excluding non-cash compensation expense related to equity awards, increased were relatively consistent in the three months ended March 31, 2024 June 30, 2024 compared to the same period in 2023, and increased in the six months ended June 30, 2024 compared to the same period in 2023 as we continued to make strategic investments in advancing our technology.

Drug Development

The following table sets forth drug development expenses, including expenses for our marketed medicines and those in Phase 3 development for which we have incurred significant costs (in millions):

	Three Months Ended March 31,				Three Months Ended June 30,		Six Months Ended June 30,	
	2024		2023		2024	2023	2024	2023
	\$	21.7	\$	37.0	\$	24.3	\$	28.7
WAINUA							\$ 46.0	\$ 65.7
TEGSEDI and WAYLIVRA							4.4	2.6
Olezarsen		39.5		26.8		40.0	31.3	79.5
Donidalorsen		4.8		5.3		5.1	7.2	9.9
Zilganersen		2.1		1.7		1.6	2.9	3.7
Jlefnersen		3.5		2.3		3.4	2.9	6.9
Other development projects		25.1		17.4		21.5	31.2	43.4
Development overhead expenses		29.1		25.1		33.9	30.4	63.0
Total drug development expenses, excluding non-cash compensation expense related to equity awards		125.8		115.6		134.2	137.2	260.0
Non-cash compensation expense related to equity awards		10.4		8.8		10.3	8.3	20.7
Total drug development expenses	\$	136.2	\$	124.4	\$	144.5	\$ 145.5	\$ 280.7
							\$ 269.9	

Our drug development expenses, excluding non-cash compensation expense related to equity awards, increased for were relatively consistent in the three months ended March 31, 2024 June 30, 2024 compared to the same period in 2023, and increased in the six months ended June 30, 2024 compared to the same period in 2023 primarily due to the timing of our late-stage program activities. We expect our development expenses will stabilize as several late-stage studies end and we reallocate resources toward earlier stage programs.

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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 medicines 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 medicine. Although we may characterize a medicine 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 medicines based on each medicine's particular needs at that time. This means we are constantly shifting resources among medicines. Therefore, what we spend on each medicine during a particular period is usually a function of what is required to keep the medicines progressing in clinical development, not what medicines 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 medicine to another and cannot be used to accurately predict future costs for each medicine. Because we always have numerous medicines in preclinical and varying stages of 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.

Medical Affairs

Our medical affairs function is responsible for funding and coordinating investigator-sponsored trials, communicating scientific and clinical information to healthcare providers, medical professionals and patients, and managing publications.

The following table sets forth information on medical affairs expenses (in millions):

	Three Months Ended March 31,				Three Months Ended June 30,		Six Months Ended June 30,	
	2024		2023		2024	2023	2024	2023
	\$	4.7	\$	4.3	\$	7.1	\$	4.5
Medical affairs expenses, excluding non-cash compensation expense related to equity awards							\$ 11.8	\$ 8.8
Non-cash compensation expense related to equity awards		0.9		1.0		1.2	0.9	2.1
Total medical affairs expenses	\$	5.6	\$	5.3	\$	8.3	\$	5.4
							\$ 13.9	\$ 10.7

Medical affairs expenses, excluding non-cash compensation expense related to equity awards, slightly increased in the three and six months ended March 31, 2024 June 30, 2024 compared to the same period in 2023 as we continued advancing our late-stage pipeline.

Manufacturing and Development Chemistry

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

The following table sets forth information on manufacturing and development chemistry expenses (in millions):

	Three Months Ended March 31,		Three Months Ended June 30,		Six Months Ended June 30,	
	2024	2023	2024	2023	2024	2023
Manufacturing and development chemistry expenses, excluding non-cash compensation expense related to equity awards	\$ 11.4	\$ 14.7	\$ 14.2	\$ 22.2	\$ 25.6	\$ 36.9
Non-cash compensation expense related to equity awards	2.3	2.1	2.3	2.2	4.6	4.3
Total manufacturing and development chemistry expenses	\$ 13.7	\$ 16.8	\$ 16.5	\$ 24.4	\$ 30.2	\$ 41.2

Manufacturing and development chemistry expenses, excluding non-cash compensation expense related to equity awards, decreased in the three and six months ended **March 31, 2024** **June 30, 2024** compared to the same **period periods** in 2023. In the three and six months ended **March 31, 2023** **June 30, 2023**, our contract manufacturing organizations, or CMOs, manufactured higher quantities of drug product related to several late-stage programs.

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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, information technology costs, procurement costs and waste disposal costs. We call these costs R&D support expenses. expenses.

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

	Three Months Ended March 31,		Three Months Ended June 30,		Six Months Ended June 30,	
	2024	2023	2024	2023	2024	2023
Personnel costs	\$ 7.8	\$ 6.5	\$ 7.2	\$ 6.7	\$ 15.0	\$ 13.2
Occupancy	7.1	7.3	6.7	6.9	13.8	14.2
Computer software and licenses	1.6	0.6	1.7	0.6	3.3	1.2
Insurance	0.9	0.9	0.8	0.9	1.7	1.8
Patent expenses	0.7	1.1	0.7	0.8	1.4	1.9
Consulting expenses	0.6	0.3	—	—	—	—
Other	3.2	2.3	—	3.3	3.8	5.9
Total R&D support expenses, excluding non-cash compensation expense related to equity awards	\$ 21.9	\$ 19.0	\$ 17.1	\$ 19.2	\$ 39.0	\$ 38.2
Non-cash compensation expense related to equity awards	4.3	3.8	4.3	3.8	8.6	7.6
Total R&D support expenses	\$ 26.2	\$ 22.8	\$ 21.4	\$ 23.0	\$ 47.6	\$ 45.8

R&D support expenses, excluding non-cash compensation expense related to equity awards, increased were relatively consistent in the three and six months ended **March 31, 2024** **June 30, 2024** compared to the same **period periods** in 2023. The increase was primarily related to increased personnel costs and computer software and licenses to support advancing our pipeline and our technology. 2023.

Selling, General and Administrative Expenses

SG&A expenses include personnel information technology systems 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 SG&A 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 and QALSOY.

The following table sets forth information on SG&A expenses (in millions):

	Three Months Ended March 31,		Three Months Ended June 30,		Six Months Ended June 30,			
	2024		2023		2024		2023	
	\$	43.7	\$	38.2	\$	57.4	\$	38.9
Selling, general and administrative expenses, excluding non-cash compensation expense related to equity awards							\$ 101.2	\$ 77.2
Non-cash compensation expense related to equity awards		8.9		7.3		7.7	7.2	16.6
Total selling, general and administrative expenses	\$	52.6	\$	45.5	\$	65.1	\$	46.1
							\$ 117.8	\$ 91.7

SG&A expenses, excluding non-cash compensation expense related to equity awards, increased in the three and six months ended March 31, 2024 June 30, 2024 compared to the same period periods in 2023 due to increased expenses related to our launch of WAINUA and launch preparation activities for olezarsen and donidalorsen.

Investment Income

The following table sets forth information on investment income for the three months ended March 31, 2024 was \$26.3 million compared to \$18.6 million for the same period in 2023. (in millions):

	Three Months Ended June 30,				Six Months Ended June 30,			
	2024		2023		2024		2023	
	\$	25.6	\$	20.8	\$	51.9	\$	39.4
Investment income								

Our investment income increased primarily due to an increase in interest rates associated with our investments during the three and six months ended March 31, 2024 June 30, 2024 compared to the same period periods in 2023.

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Interest Expense

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

	Three Months Ended March 31,				Three Months Ended June 30,				Six Months Ended June 30,			
	2024		2023		2024		2023		2024		2023	
	\$	1.6	\$	1.3	\$	1.5	\$	1.4	\$	3.0	\$	2.7
Convertible notes:												
Non-cash amortization of debt issuance costs												
Interest expense payable in cash		2.5		0.2		2.9		0.8		5.4		1.0
Interest on mortgage for manufacturing facility		0.1		0.1		0.1		0.1		0.2		0.2
Total interest expense	\$	4.2	\$	1.6	\$	4.5	\$	2.3	\$	8.6	\$	3.9

In June 2023, we completed a \$575.0 million offering of our 1.75% Notes and repurchased \$504.4 million in principal of our 0.125% Notes. As a result, beginning in the second quarter of 2023, our interest expense related to our convertible notes increased because we began incurring interest expense for our 1.75% Notes.

Interest Expense Related to Sale of Future Royalties

We recorded \$18.0 18.3 million and \$36.3 million of interest expense related to the sale of future royalties in the three and three six months ended March 31, June 30, 2024 as a result of, respectively, compared to \$17.7 million and \$33.2 million in the same periods in 2023, respectively. These amounts are related to the Royalty Pharma transaction, in which we sold a minority interest in our future royalties to Royalty Pharma for a \$500 million upfront payment and \$625 million of potential future payments. Refer to Part I, Item 1, Note 11, *Liability Related to Sale of Future Royalties*, in the Notes to Condensed Consolidated Financial Statements for further details.

Gain (Loss) on Investments

We recorded a net The following table sets forth information on gain (loss) on investments of \$2.3 million for the three months ended March 31, 2024 compared to a net loss (in millions):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2024	2023	2024	2023

	2024	2023	2024	2023
Gain (loss) on investments	\$ (3.5)	\$ 0.7	\$ (1.2)	\$ 0.2

The period-over-period fluctuations in our gain (loss) on investments of \$0.5 million for the same period in 2023 primarily due to were driven by changes in the fair value of our investments in privately held and publicly traded and privately held biotechnology companies.

Other Expense

In the second quarter of 2023, we completed a \$575.0 million offering of our 1.75% Notes and used \$420.4 million of the net proceeds to repurchase \$434.1 million in principal of our 0.125% Notes. As a result, we recorded an \$11.3 million gain on early retirement of debt in the second quarter of 2023, which reflects the difference between the amount we paid to repurchase a portion of our 0.125% Notes and the net carrying balance of the liability at the time that we repurchased the debt. Refer to Part I, Item 1, Note 12, *Convertible Debt*, in the Notes to Condensed Consolidated Financial Statements for further details regarding our convertible debt.

Income Tax Expense

We recorded income tax expense of \$0.1 million and \$0.1 million for the three and six months ended **March 31, 2024** **June 30, 2024**, respectively, compared to \$11.4 million \$7.8 million and \$19.2 million for the same period periods in 2023, 2023, respectively. The decrease in income tax expense relates primarily to the impact of the royalty purchase agreement with Royalty Pharma on income tax expense for the three and six months ended **March 31, 2023** **June 30, 2023**. We reflected the Royalty Pharma transaction as a taxable sale, which required us to include the proceeds from the sale, net of currently deductible issuance costs, as taxable income in 2023.

We continue to maintain a full valuation allowance on all of our net deferred tax assets.

Net Loss and Net Loss per Share

We had a net loss of \$142.8 million \$66.3 million and \$209.1 million for the three and six months ended June 30, 2024, respectively. **March 31, 2024** compared to We had a net loss of \$124.3 million \$85.3 million and \$209.6 million for the same period periods in 2023, which reflects 2023. The period-over-period fluctuations in our net loss were driven by factors discussed in the fluctuations discussed sections above. Our basic Basic and diluted net loss per share for the three and **three** six months ended **March 31, June 30, 2024** and 2023 was were \$0.98 0.45 and \$0.87 1.43, respectively, respectively, compared to \$0.60 and \$1.47 for the same periods in 2023.

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Liquidity and Capital Resources

We have financed our operations primarily from research and development collaborative agreements. We also financed our operations from revenue from SPINRAZA and QALSDY royalties and TEGSEDI and WAYLIVRA commercial revenue. In addition, we began receiving commercial revenue from WAINUA royalties in 2024. From our inception through **March 31, 2024** **June 30, 2024**, we have earned approximately \$7.3 billion \$7.6 billion in revenue. We have also financed our operations through the sale of our equity securities, the issuance of long-term debt and the sale of future royalties. From the time we were founded through **March 31, 2024** **June 30, 2024**, we have raised net proceeds of approximately \$2.1 billion from the sale of our equity securities. Additionally, from our inception through **March 31, 2024** **June 30, 2024**, we have borrowed approximately \$2.7 billion under long-term debt arrangements and received proceeds of \$0.5 billion from the sale of future royalties to finance a portion of our operations.

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From December 31, 2023 to **March 31, June 30, 2024** our working capital decreased as our cash, cash equivalents and short-term investments decreased, while decreased. During the same period, our long-term obligations did not change significantly.

The following table summarizes our contractual obligations, excluding our liability related to the sale of future royalties, as of **March 31, 2024** **June 30, 2024**. 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 (selected balances described below)	Payments Due by Period (in millions)		
	Total	Less than 1 year	More than 1 year
1.75% Notes (principal and interest payable)	\$ 620.3	\$ 10.1	\$ 610.2
0% Notes (principal payable)	632.5	—	632.5
0.125% Notes (principal and interest payable)	44.6	44.6	—
Operating leases	274.9	20.6	254.3
Building mortgage payments (principal and interest payable)	10.1	0.5	9.6
Other obligations (principal and interest payable)	0.7	0.1	0.6
Total	\$ 1,583.1	\$ 75.9	\$ 1,507.2

Contractual Obligations

(selected balances described below)	Payments Due by Period (in millions)		
	Total	Less than 1 year	More than 1 year

1.75% Notes (principal and interest payable)	\$ 615.3	\$ 10.1	\$ 605.2
0% Notes (principal payable)	632.5	—	632.5
0.125% Notes (principal and interest payable)	44.6	44.6	—
Operating leases	269.7	20.6	249.1
Building mortgage payments (principal and interest payable)	9.9	0.5	9.4
Other obligations (principal and interest payable)	0.7	0.1	0.6
Total	\$ 1,572.7	\$ 75.9	\$ 1,496.8

Our contractual obligations consist primarily of our convertible debt. In addition, we also have a facility mortgage, facility leases, equipment financing arrangements and other obligations. We believe our cash, cash equivalents and short-term investments, as well as plans for cash in the future, will be sufficient to fund our planned operations and these obligations. We have not entered into, nor do we currently have, any off-balance sheet arrangements (as defined under SEC rules).

Convertible Debt and Call Spread

Refer to Part I, Item 1, Note 12, *Convertible Debt*, in the Notes to Condensed Consolidated Financial Statements for the significant terms of each convertible debt instrument.

Operating Facilities

Refer to Part IV, Item 15, Note 7, *Long-Term Obligations and Commitments*, of our audited financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2023 for further details on our operating facilities.

Operating Leases

Refer to Part IV, Item 15, Note 7, *Long-Term Obligations and Commitments*, of our audited financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2023 for further details on our operating leases.

Liability Related to Sale of Future Royalties

Refer to Part I, Item 1, Note 11, *Liability Related to Sale of Future Royalties*, in the Notes to Condensed Consolidated Financial Statements for further details on our royalty purchase agreement with Royalty Pharma.

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Other Obligations

In addition to contractual obligations, we had outstanding purchase orders as of **March 31, 2024** **June 30, 2024** for the purchase of services, capital equipment and materials as part of our normal course of business.

We may enter into additional collaborations with partners which could 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, securing lines of credit or executing royalty monetization agreements. 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.

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ITEM 3. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

We are exposed to changes in interest rates primarily from our 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, foreign currency exchange 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 condensed consolidated financial statements.

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 **March 31, 2024** **June 30, 2024**. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to **March 31, 2024** **June 30, 2024**.

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.

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PART II — OTHER INFORMATION

ITEM 1. LEGAL PROCEEDINGS

For details of legal proceedings, refer to Part I, Item 1, Note 13, *Legal Proceedings*, in the Notes to Condensed Consolidated Financial Statements.

ITEM 1A. RISK FACTORS

Investing in our securities involves a high degree of risk. You should carefully consider 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. There were no 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, 2023.

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Summary of Risk Factors

There are a number of risks related to our business and our securities. Some of the principal risks related to our business include the following:

- Our ability to generate substantial revenue from the sale of our medicines;
- The availability of adequate coverage and payment rates for our medicines;
- Our and our partners' ability to compete effectively;
- Our ability to successfully manufacture our medicines;
- Our ability to successfully develop and obtain marketing approvals for our medicines;
- Our ability to secure and maintain effective corporate partnerships;
- Our ability to sustain cash flows and achieve consistent profitability;
- Our ability to protect our intellectual property;
- Our ability to maintain the effectiveness of our personnel;
- The impacts of health epidemics, climate change, war and other global events; and
- Our dependence upon our own and third-party information technology systems;
- Our compliance with laws; and
- The other factors set forth below.

Risks Related to the Commercialization of our Medicines

We have limited experience as a company in commercializing medicines and we will have to invest significant resources to develop our capabilities. If we are unable to establish effective marketing, sales, market access, distribution, and related functions, or enter into agreements with third parties to commercialize our medicines, we may not be able to generate revenue from our medicines.

We currently rely on third parties for the commercialization of our marketed medicines, have limited experience as a company in commercializing medicines and will have to continue to invest significant financial and management resources to develop the infrastructure required to successfully commercialize our medicines. There are significant risks involved in building and managing a sales organization, including our ability to hire, retain and incentivize qualified individuals, generate sufficient sales leads, provide adequate training to sales and marketing personnel, and effectively manage a geographically dispersed sales and marketing team. We will also need to continue to scale-up existing internal support functions to aid our commercialization efforts, in particular, regulatory affairs and medical affairs. Any failure to effectively build or maintain the infrastructure required to successfully commercialize our medicines, including our sales, marketing, market access, distribution, and related capabilities, or scale-up our existing support functions, could adversely impact the revenue we generate from our medicines. In addition, if we choose to rely on third parties to assist us in commercializing our medicines, we may not be able to enter into collaborations or hire consultants or external service providers on acceptable financial terms, or at all. If we continue to engage third parties to assist us in the commercialization of our medicines, our product revenues and profitability may be lower than if we commercialized such medicines ourselves.

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If the market does not accept our medicines, including our commercial medicines and our medicines in development, we are not likely to generate substantial revenues or become consistently profitable.

Even if our medicines are authorized for marketing, our success will depend upon the medical community, patients and third-party payers accepting our medicines as medically useful, cost-effective, safe and convenient. Even when the **United States, or U.S., Food and Drug Administration, or FDA**, or foreign regulatory authorities authorize our or our partners' medicines for commercialization, doctors may not prescribe our medicines to treat patients. Furthermore, we and our partners may not successfully commercialize additional medicines.

Additionally, in many of the markets where we or our partners may sell our medicines in the future, if we or our partners cannot agree with the government or other third-party payers regarding the price we can charge for our medicines, we may not be able to sell our medicines in that market. Similarly, cost control initiatives by governments or third-party payers could decrease the price received for our medicines or increase patient coinsurance to a level that makes our medicines, including our commercial medicines and our medicines in development, economically unviable. If the pricing of any of our medicines decreases for any reason, it will reduce our revenue for such medicine. For example, Biogen has in the past disclosed that SPINRAZA revenue decreased in part due to lower pricing in the U.S. and certain rest-of-world markets.

The degree of market acceptance for our medicines, including our commercial medicines and our medicines in development, depends upon a number of factors, including the:

- receipt and scope of marketing authorizations;
- establishment and demonstration in the medical and patient community of the efficacy and safety of our 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 payers.

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

For example, TEGSEDI requires periodic blood and urine monitoring and is available in the U.S. only through a risk evaluation and mitigation strategy, or REMS program. In addition, the product label for TEGSEDI in the U.S. has a boxed warning for thrombocytopenia and glomerulonephritis. Our main external competitors in the U.S. market for TEGSEDI are patisiran and vutrisiran, both marketed by Alnylam Pharmaceuticals, Inc. Neither patisiran nor vutrisiran has a boxed warning nor does either require use of a REMS program. Additionally, the product label for WAYLIVRA in the European Union, or EU, requires regular blood monitoring. In each case, these label requirements have negatively affected our ability to attract and retain patients for these medicines.

If government or other third-party payers fail to provide adequate coverage and payment rates for our medicines, including our commercial medicines and our medicines in development, 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 payers. The majority of patients 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 medicines 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. Even if favorable coverage status and adequate reimbursement rates are attained, less favorable coverage policies and reimbursement rates may be implemented in the future. Accordingly, our commercial medicines and our medicines in development will face competition from other therapies and medicines for limited financial resources. Furthermore, we or our partners may need to conduct

post-marketing studies to demonstrate the cost-effectiveness of any future products to satisfy third-party payers. These studies might require us to commit a significant amount of management time and financial and other resources. In addition, third-party payers may never consider our future products as cost-effective and adequate third-party coverage and reimbursement might not be available to enable us to maintain price levels sufficient to realize an appropriate return on investment in product development.

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Third-party payers, 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 medicines exists among third-party payers. Therefore, coverage and reimbursement for medicines can differ significantly from payer to payer. For example, the Affordable Care Act, or ACA, was passed in March 2010, and substantially changed the way healthcare is financed by both governmental and private insurers and continues to significantly impact the U.S. pharmaceutical industry. There have been judicial and Congressional challenges to certain aspects of the ACA, as well as efforts to repeal or replace certain aspects of the ACA. It is unclear how future litigation and healthcare reform measures will impact the ACA and our business.

Further, we believe that future coverage, reimbursement and pricing will likely be subject to increased restrictions both in the U.S. and in international markets. In the U.S., recent health reform measures have resulted in reductions in Medicare and other healthcare funding, and there have been several recent U.S. Congressional inquiries, legislation and executive orders designed to, among other things, reduce drug prices, increase competition (including by enhancing support for generic and biosimilar drugs), lower out-of-pocket drug costs for patients, curtail spread pricing practices by pharmacy benefit managers, and foster scientific innovation to promote better health care and improved health. In addition, the Inflation Reduction Act of 2022, or the IRA, includes key actions aimed at reducing the costs of prescription drugs and allows HHS to negotiate the price of certain single-source drugs covered under Medicare and establish a price cap on such drugs. Specifically, in an effort to curb Medicare patients' out-of-pocket costs for prescription drugs, the Part D redesign legislation under the IRA requires, among other things, (1) a cap on out-of-pocket drug spending under Part D, (2) drug manufacturers to pay a rebate to the federal government if prices for drugs covered under Part D and Part B increase faster than the rate of inflation, and (3) drug manufacturers to contribute to the catastrophic coverage phase for Part D drugs as discounts through a manufacturer discount program. The IRA permits HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years. These provisions take effect progressively starting in fiscal year 2023. On August 29, 2023, HHS announced the list of the first ten drugs that will be subject to price negotiations, although the Medicare drug price negotiation program is currently subject to legal challenges. In response to the Biden administration's October 2022 executive order, on February 14, 2023, HHS released a report outlining three new models for testing by the CMS Innovation Center which will be evaluated on their ability to lower the cost of drugs, promote accessibility, and improve quality of care. It is unclear whether the models will be utilized in any health reform measures in the future. Further, on December 7, 2023, the Biden administration announced an initiative to control the price of prescription drugs using march-in rights under the Bayh-Dole Act. On December 8, 2023, the National Institute of Standards and Technology published for comment a Draft Interagency Guidance Framework for Considering the Exercise of March-In Rights which for the first time includes the price of a product as one factor an agency can use when deciding to exercise march-in rights. While march-in rights have not previously been exercised, it is uncertain if that will continue under the new framework. It is unclear whether or how these selected models or similar policy initiatives will impact prescription drug pricing in the future.

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Any reduction in reimbursement from Medicare and other government programs may result in a similar reduction in payments from private payers. Our future product sales may be subject to additional discounts from list price in the form of rebates and discounts provided to covered entities under the Public Health Service Act 340B drug pricing program. Changes to the 340B program or to Medicare or Medicaid programs at the federal or state level, including outcomes of ongoing litigation in our industry, may impact our product prices and rebate liability.

At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. For example, on January 5, 2024, the FDA approved Florida's Section 804 Importation Program, or SIP, proposal to import certain drugs from Canada for specific state healthcare programs. It is unclear how this program will be implemented, including which drugs will be chosen, and whether it will be subject to legal challenges in the United States or Canada. Other states have also submitted SIP proposals that are pending review by the FDA. Any such approved importation plans, when implemented, may result in lower drug prices for products covered by those programs. Third-party coverage and reimbursement for 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.

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If we or our partners fail to compete effectively, our medicines, including our commercial medicines and our medicines in development, will not generate significant revenues.

Our competitors engage in drug discovery throughout the world, are numerous, and include, among others, major pharmaceutical companies and specialized biopharmaceutical firms. In addition, other companies are engaged in developing RNA-targeted technology. Our competitors may succeed in developing medicines that are:

- priced lower than our medicines;
- reimbursed more favorably by government and other third-party payers 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 our commercial medicines and our medicines in development, 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 some of 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 our commercial medicines and our medicines in development.

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 or more successfully commercialize their products.

There are several pharmaceutical and biotechnology companies engaged in the development or commercialization in certain geographic markets of products against targets that are also targets of products in our development pipeline. For example:

- Onasemnogene abeparvovec and risdiplam compete with SPINRAZA;
- Taldefgrobep alfa, Evrysdi + GYM329 and NMD670 could compete with SPINRAZA;
- Patisiran, tafamidis, tafamidis meglumine and vutrisiran compete with TEGSEDI and WAINUA;
- Acoramidis, NTLA-2001 and NNC6019-0001 could compete with TEGSEDI and WAINUA;
- ARO-APOC3 and pegozafermin could compete with WAYLIVRA and olezarsen;
- Lanadelumab-flyo, C1 esterase inhibitor, berotralstat, C1 esterase inhibitor subcutaneous, garadacimab, deucrictibant, NTLA-2002 and STAR-0215 could compete with donidalorsen;
- Olpasiran, zertasiran, leporisiran and muvalaplin could compete with pelacarsen;
- NI-005/AP-101 could compete with QALSODY;
- VIR-2218 + PEG-IFN- α , VIR-3434 \pm VIR-2218 \pm PEG-IFN- α , VIR-2218 + BRII-179, NI-204VIR-2218 + GS-9688 + nivolumab, AB-729, imdusiran + Peg-IFN- α + NA, xalnésiran + RG6084 + NA, xalnésiran + NA, xalnésiran + pegIFN + NA, xalnésiran + RO7049389 + NA, xalnésiran + ruzotolimod + NA, RO7049389 + ruzotolimod + NA could compete with bepirovirsen; and
- Budesonide, sparsentan, atrasentan, iptacopan, zigakibart, sibreprenlimab, atacicept, ravulizumab, vemircopan, felzartamab, povetacicept, avacincaptad pegol, pegcetacoplan, tinlarebant, danicopan, GT005, AVD-104 and ANX007 could compete with IONIS-FB-L_{Rx}.

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SPINRAZA injection for intrathecal use is an antisense medicine indicated for the treatment of SMA patients of all ages approved in over 50 countries. Specifically, SPINRAZA faces competition from onasemnogene abeparvovec, a gene therapy product that was approved in the U.S. in May 2019 and in the EU in May 2020 for the treatment of SMA, as well as risdiplam, an oral product for the treatment of SMA that was approved in the U.S. in August 2020 and in the EU in March 2021. Biogen has in the past disclosed that SPINRAZA revenue decreased due to a reduction in demand as a result of increased competition and that future sales of SPINRAZA may be adversely affected by competing products.

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Additionally, companies that are developing medicines that target the same patient populations as our medicines in development may compete with us to enroll participants in the clinical trials for such medicines, which could make it more difficult for us to complete enrollment for these clinical trials.

Our medicines could be subject to regulatory limitations following approval.

Following approval of a medicine, we and our partners must comply with comprehensive government regulations regarding the manufacture, marketing and distribution of medicines. Promotional communications regarding prescription medicines must be consistent with the information in the product's approved labeling. We or our partners may not obtain the labeling claims necessary or desirable to successfully commercialize our medicines, including our commercial medicines and our medicines in development.

The FDA and foreign regulatory bodies have the authority to impose significant restrictions on an approved medicine 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; and
- in the U.S., TEGSEDI is available only through a REMS program.

Prescription medicines may be promoted only for the approved indication(s) in accordance with the approved label. The FDA and other regulatory authorities actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant

liability.

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, EC or other foreign regulatory authorities may withdraw marketing authorization or may condition continued marketing on commitments from us or our partners that may be expensive and time consuming to fulfill.

If we or others identify side effects after any of our medicines are on the market, or if manufacturing problems occur subsequent to regulatory approval, or if we, our CMOs or our partners fail to comply with regulatory requirements, we or our partners may, among other things, lose regulatory approval and be forced to withdraw products from the market, need to conduct additional clinical studies, incur restrictions on the marketing, distribution or manufacturing of the product, and/or change the labeling of our medicines.

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

We have entered into separate collaborative arrangements with Biogen to develop and commercialize SPINRAZA and QALSODY. We entered into these collaborations primarily to:

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

We are relying on Biogen to obtain additional regulatory approvals for SPINRAZA and QALSODY, generate additional clinical data for SPINRAZA and QALSODY, manufacture SPINRAZA and QALSODY, and successfully commercialize SPINRAZA and QALSODY. In general, we cannot control the amount and timing of resources that Biogen devotes to our collaborations. If Biogen fails to further develop SPINRAZA or QALSODY, obtain additional regulatory approvals for SPINRAZA or QALSODY, manufacture SPINRAZA or QALSODY, or successfully commercialize SPINRAZA or QALSODY, or if Biogen's efforts in any of these respects are ineffective, revenues for SPINRAZA or QALSODY would be negatively affected.

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

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We depend on our collaboration with AstraZeneca for the joint development and commercialization of WAINUA.

We have entered into a collaborative arrangement with AstraZeneca to develop and commercialize WAINUA. Under the terms of the collaboration agreement, we and AstraZeneca will co-develop and co-commercialize WAINUA in the U.S. and AstraZeneca will have the sole right to commercialize WAINUA in all other countries. As a company we do not have experience with co-commercialization arrangements. We also do not have control over the amount and timing of resources that AstraZeneca devotes to our collaboration, particularly outside of the U.S. If the co-commercialization arrangement for WAINUA is not successful for any reason, WAINUA may not meet our commercial objectives and our revenues for WAINUA may be limited.

In addition, a Joint Steering Committee, or JSC, having equal membership from us and AstraZeneca, and various subcommittees oversee and coordinate the development, manufacturing, commercialization and other exploitation activities for WAINUA in the U.S. by mutual agreement. If any subcommittee cannot reach unanimous agreement on any matter within its respective scope of authority, such matter may be referred to the JSC for resolution. If the JSC cannot come to a mutual agreement on any particular matter, this could delay our ability to develop or commercialize WAINUA.

If we are not successful in expanding our manufacturing capabilities or 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 need to optimize and manage large-scale commercial manufacturing capabilities either on a standalone basis or through a third-party manufacturer. As our drug development and commercial pipeline increases and matures, we will have a greater need for clinical trial and commercial manufacturing capacity. While we believe our current capabilities and those we obtain through third-party manufacturers support our manufacturing needs now, it will be important to expand our manufacturing infrastructure in the future, which will likely require substantial expenditures. If we are not successful in executing this expansion, it could limit our ability to meet our manufacturing requirements and commercial objectives in the future.

In addition, 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 or our partners may not be able to manufacture our medicines at a cost or in quantities necessary to make commercially successful products.

Manufacturers, including us, must adhere to the FDA's cGMP regulations and similar regulations in foreign countries, which the applicable regulatory authorities enforce through facilities inspection programs. We, our partners and our contract manufacturers may not comply or maintain compliance with cGMP, or similar foreign regulations. Non-compliance could significantly delay or prevent receipt of marketing authorizations for our medicines, including authorizations for our commercial medicines and our medicines in development, or could result in enforcement action after authorization that might limit the commercial success of our medicines, including our commercial medicines and our medicines in development.

We rely on third-party manufacturers to supply the drug substance and drug product for TEGSEDI and WAINUA and drug product for WAYLIVRA. Any delays or disruption to our own or third-party commercial manufacturing capabilities could limit the commercial success of our medicines.

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Risks Related to the Development and Regulatory Approval of our Medicines

If we or our partners fail to obtain regulatory approval for our medicines and additional approvals for our commercial medicines, 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, it is possible that our commercial medicines may not be approved in additional markets or for additional indications. We and our partners must conduct time-consuming, extensive and costly clinical studies to demonstrate the safety and efficacy of each of our medicines before they can be approved or receive additional approvals for sale. We and our partners must conduct these studies in compliance with FDA regulations and with comparable regulations in other countries.

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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 authorities will not approve our medicines for marketing or our commercial medicines in additional markets or for additional indications. If the FDA or another regulatory authority believes that we or our partners have not sufficiently demonstrated the safety or efficacy of any of our medicines, including our commercial medicines or our medicines in development, the authority will not approve the specific medicine or will require additional studies, which could be time consuming and expensive and delay or harm commercialization of the medicine. For example, in August 2018 we received a complete response letter from the FDA regarding the new drug application for WAYLIVRA in which the FDA determined that the safety concerns identified with WAYLIVRA in our clinical development program outweighed the expected benefits of triglyceride lowering in patients with FCS. We also received a Notice of Non-Compliance Withdrawal Letter, or Non-W, from Health Canada for WAYLIVRA in November 2018.

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

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

Failure to receive marketing authorization for our medicines in development, or failure to receive additional marketing authorizations for our commercial medicines, 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 drug development have 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 in the intended indication(s), we may need to abandon one or more of our drug development programs.

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. If any of our medicines in Phase 3 clinical studies do not show sufficient safety and efficacy in patients with the targeted indication, or if such studies are discontinued for any other reason, it could negatively impact our development and commercialization goals for these medicines and our stock price could decline.

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In the past, we have invested in clinical studies of medicines that have not met the primary clinical endpoints in their Phase 3 studies or have been discontinued for other reasons. For example, in October 2021, Biogen reported that QALSODY did not meet the primary clinical endpoint in the Phase 3 VALOR study; however, trends favoring QALSODY were seen across multiple secondary and exploratory measures of disease activity and clinical function. In addition, in March 2021, Roche decided to discontinue dosing in the Phase 3 GENERATION HD1 study of tominersen in patients with manifest Huntington's disease based on the results of a pre-planned review of data from the Phase 3 study conducted by an unblinded Independent Data Monitoring Committee. Similar results could occur in clinical studies for our other medicines.

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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 or lack of efficacy in the trial;
- we or our partners 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;
- we or our partners, including our independent clinical investigators, contract research organizations and other third-party service providers on which we rely, may not identify, recruit or train suitable clinical investigators at a sufficient number of study sites or timely enroll a sufficient number of study subjects in the clinical study;
- the institutional review board for a prospective site might withhold or delay its approval for the study;
- 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;
- a clinical study site may deviate from the protocol for the study;
- the cost of our clinical studies may be greater than we anticipate;
- our partners may decide not to exercise any existing options to license and conduct additional clinical studies for our medicines; and
- the supply or quality of our medicines or other materials necessary to conduct our clinical studies may be insufficient, inadequate or delayed.

Further, the FDA or other regulatory authorities could request, among other things, 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. This happened in connection with the conditional marketing approval for WAYLIVRA in the EU, as the EC is requiring us to conduct a post-authorization safety study to evaluate the safety of WAYLIVRA on thrombocytopenia and bleeding in FCS patients taking WAYLIVRA. In addition, under accelerated approval the FDA is requiring completion of the ongoing Phase 3 trial for QALSODY to confirm the clinical benefit of QALSODY.

Moreover, our commercial medicines 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 or 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. Any failure or delay in our clinical studies could reduce the commercial potential or viability of our medicines.

We depend on third parties to conduct 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, Medpace, Inc., Parexel International Corporation, Syneos Health, Inc. and Thermo Fisher Scientific Inc. for the clinical studies for our medicines, including WAINUA for the treatment of ATTR-CM, donidalorsen, olezarsen, ulefnersen and zilganersen. 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, but we are responsible for ensuring that such investigators 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. For example, some of our key vendors have in the past experienced labor shortages, which impacted their ability to perform services for us for certain of our clinical trials. Subsequent failures of these third parties to carry out their obligations, or a termination of our relationship with such third parties, could delay or prevent the development, marketing authorization and commercialization of our medicines.

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In addition, while we do not have any clinical trial sites in Russia, Ukraine or Gaza, we do have a limited number of clinical trial sites in Russia and Israel that may be materially impacted by the ongoing war between Russia and Ukraine and military conflicts in Israel and the surrounding areas, as well as related political or economic responses and counter-responses by various global actors, or collectively, conflicts elsewhere in Eastern Europe and the Middle East and could result in difficulties enrolling or completing our clinical trials in such areas on schedule. Furthermore, the U.S. and its European allies have imposed significant sanctions against Russia, including regional embargoes, full blocking sanctions, and other restrictions targeting major Russian financial institutions. The U.S. government has also indicated it will consider imposing additional sanctions and

other similar measures in the future. Our ability to conduct clinical trials in Russia may become restricted under applicable sanctions laws, which would require us to identify alternative trial sites, and could increase our costs and delay the clinical development of certain of our medicines.

Since corporate partnering is a significant part of our strategy to fund the advancement 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 some of 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 funding many of the medicines in our development pipeline. For example, we are relying on:

- AstraZeneca for the joint development and funding of WAINUA;
- Novartis for development and funding of pelacarsen;
- GSK for development and funding of bepivirsen; and
- Roche for development and funding of IONIS-FB-L_{RX}.

If any of these pharmaceutical companies stops developing and 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, in 2022, Pfizer and Bayer decided to discontinue the clinical development programs for vupanorsen and fesomersen, respectively.

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 authorizations; and
- manufacture and commercialize 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, Biogen, GSK, Novartis, Otsuka and Roche, these collaborations may not continue or result in commercialized medicines, or may not progress as quickly as we anticipated.

For example, a collaborator such as AstraZeneca, Biogen, GSK, Novartis, Otsuka 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 to 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 QALSDY, SPINRAZA, WAINUA, bepivirsen, donidalorsen, IONIS-FB-L_{RX} and pelacarsen.

We may not be able to benefit from Orphan Drug designation for our medicines.

In the U.S., under the Orphan Drug Act, the FDA may designate a medicine as an Orphan Drug if it is intended to treat a rare disease or condition affecting fewer than 200,000 individuals in the U.S. Orphan Drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process, but it can provide financial incentives, such as tax advantages and user-fee waivers, as well as longer regulatory exclusivity periods. The FDA has granted Orphan Drug designation to olezarsen for the treatment of patients with FCS, to ulefnersen for the treatment of patients with FUS-ALS, and to ION582 for the treatment of patients with Angelman syndrome. The FDA and European Medicines Agency, or EMA, have granted Orphan Drug designation to WAINUA for the treatment of patients with ATTR, to donidalorsen for the treatment of patients with HAE, to TEGSEDI for the treatment of patients with ATTRv-PN, to WAYLIVRA for the treatment of patients with FCS, to tominersen for the treatment of patients with HD, and to ION356 for the treatment of patients with Pelizaeus-Merzbacher disease. In addition, the EMA has granted Orphan Drug designation to WAYLIVRA for the treatment of

patients with FPL. Even if approval is obtained on a medicine that has been designated as an Orphan Drug, we may lose Orphan Drug exclusivity if the FDA or EMA determines that the request for designation was materially defective or if we cannot assure sufficient quantity of the applicable medicine to meet the needs of patients with the rare disease or condition, or if a competitor is able to gain approval for the same or a substantially similar medicine in a safer or more effective form or that makes a major contribution to patient care. If we lose Orphan Drug exclusivity on any of our medicines, we may face increased competition and lose market share for such medicine.

Risks Associated with our Businesses as a Whole

Risks related to our financial condition

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 programs will require significant additional research, development, manufacturing, preclinical and clinical testing, marketing authorizations, preclinical activities and commitment of significant additional resources prior to their successful commercialization. In addition, as we commercialize more medicines on our own, we will need to invest significant financial resources to continue developing the infrastructure required to successfully commercialize our medicines, including the expansion of our manufacturing capabilities. All of these activities will require significant cash. As of **March 31, 2024** **June 30, 2024**, we had cash, cash equivalents and short-term investments equal to **\$2.2 billion** **\$2.1 billion**. If we or our partners do not meet our goals to successfully commercialize our medicines, including our commercial medicines, or to license certain medicines and proprietary technologies, we will need additional funding in the future. Our future capital requirements will depend on many factors such as:

- successful commercialization of our commercial medicines;
- the profile and launch timing of our medicines in development;
- 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;
- competing technological and market developments, including the introduction by others of new therapies that address our markets; and
- our manufacturing requirements and capacity to fulfill such requirements.

If we need additional funds, we may need to raise them through public or private financing. Additional financing may not be available on acceptable terms or at all. 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, or commercial operations. 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.

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

Because drug discovery and development require substantial lead-time and money prior to commercialization, our expenses have generally exceeded our revenue since we were founded in January 1989. As of **March 31, 2024** **June 30, 2024**, we had an accumulated deficit of approximately **\$1.9 billion** **\$2.0 billion** and stockholders' equity of approximately \$0.3 billion. Most of our income has historically 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. We will now and continuing into the foreseeable future need to invest significant financial resources to develop capabilities to commercialize medicines on our own and expect that our income in the future will be driven primarily by commercial sales. If we do not earn substantial revenue from commercial sales, we may incur additional operating losses in the future, which could restrict our ability to successfully develop additional medicines or sustain future profitability.

We may not be entitled to obtain additional milestone payments under our royalty monetization agreement with Royalty Pharma.

In January 2023, we entered into a Royalty Purchase Agreement with Royalty Pharma Investments. In addition to the \$500 million we received at closing, this agreement makes available to us up to an additional \$625 million in milestone payments. However, these additional milestone payments are subject to satisfaction of certain conditions related to the regulatory approval or commercial sales of pelacarsen, in certain cases by specific deadlines. Should we not satisfy such conditions by the applicable deadlines, or if we fail to meet our obligations or default under this agreement, the actual amount of additional payments to us could be substantially less than the maximum amounts available thereunder.

Risks related to our intellectual property

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

Our success depends to a significant degree upon whether we can continue to develop, secure and maintain 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 and we may not be able to obtain, maintain or enforce our patents and other intellectual property rights, any of which could impact our ability to compete effectively. 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.

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

If we or any licensor partner loses or cannot obtain patent protection for our commercial medicines or any of our medicines in development, it could have a material adverse impact on our business.

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 may need to litigate to defend our rights or assert them against others. Disputes can involve arbitration, litigation or proceedings declared by the U.S. PTO or the International Trade Commission or foreign patent authorities. Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock.

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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.

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Risks related to product liability

We are exposed to potential product liability claims, and insurance against these claims may not be available to us at a reasonable rate 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 our commercial medicines and our medicines in development. 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 medicines, 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.

Risks related to our personnel

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, and as we move towards commercializing medicines on our own, we will become increasingly dependent on the principal members of our commercial team. We do not have employment agreements with any of our employees that would prevent them from leaving us. The loss of our management, key scientific or commercial employees might slow the achievement of important research and development or commercial goals. It is also critical to our success that we recruit and retain qualified scientific personnel to perform research and development work and that we recruit and retain qualified marketing, sales, market access, distribution, and related personnel to commercialize our medicines. We may not be able to attract and retain skilled and experienced personnel on acceptable terms because of intense competition for experienced personnel among many pharmaceutical and health care companies, universities and non-profit research institutions. In addition, failure to succeed in clinical studies or in commercializing our medicines may make it more challenging to recruit and retain qualified personnel.

Risks related to health epidemics, climate change and other events

Our business may be adversely affected by health epidemics, climate change, extreme weather events, earthquakes, war, civil or political unrest, terrorism or other catastrophic events.

Our business could be adversely affected by health epidemics in regions where we or our partners are commercializing our medicines, have concentrations of clinical trial sites or other business operations, and could cause disruption in the operations of third-party manufacturers and contract research organizations upon whom we rely. For example, enrollment in some of our clinical trials was delayed due to the COVID-19 pandemic.

In recent years, extreme weather events and changing weather patterns have become more common. As a result, we are potentially exposed to varying natural disaster or extreme weather risks such as hurricanes, tornadoes, fires, droughts, floods, or other events that may result from the impact of climate change on the environment. The potential impacts of climate change may also include increased operating costs associated with additional regulatory requirements and investments in reducing energy, water use and greenhouse gas emissions. In addition, we currently manufacture most of our research and clinical supplies in a manufacturing facility located in Carlsbad, California. We manufacture the finished drug product for TEGSEDI, WAINUA and WAYLIVRA at third-party contract manufacturers. Biogen manufactures the finished drug product for SPINRAZA and QALSYD. The facilities and the equipment we, our partners 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.

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Our facilities or those of our partners or contract manufacturers may be harmed by natural disasters or other events outside our control, such as earthquakes, war, civil or political unrest, deliberate acts of sabotage, terrorism or industrial accidents such as fire and explosion, whether due to human or equipment error, and if such facilities are affected by a disaster or other event, our development and commercialization efforts would be delayed. Although we possess property damage and business interruption insurance coverage, 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.

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Risks related to cybersecurity, social media and artificial intelligence

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

We are dependent upon our own and 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, particularly as companies (including us) moved to more remote work structures during and following the COVID-19 pandemic. In addition, the number and frequency of cybersecurity events globally may be heightened during times of geopolitical tension or instability between countries, including, for example, the ongoing war between Russia and Ukraine and military conflicts in Israel and the surrounding areas, as well as related political or economic responses and counter-responses by various global actors, or collectively, conflicts in Eastern Europe and the Middle East.

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, delay progress on the development of our medicines, compel us to comply with federal and state breach notification laws and foreign law equivalents, subject us to financial penalties and mandatory and costly 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 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, our efforts may not prevent service interruptions or identify breaches in our systems that could adversely affect our business and operations and result in the loss of critical or sensitive information, which could result in financial, legal, business or reputational harm to us.

The increasing use of social media platforms and artificial intelligence based software presents new risks and challenges.

Social media is increasingly being used to communicate about our medicines and the diseases our therapies are designed to treat. Social media practices in the biopharmaceutical industry continue to evolve and regulations relating to such use are not always clear and create uncertainty and risk of noncompliance with regulations applicable to our business. There is also a risk of inappropriate disclosure of sensitive information or negative or inaccurate posts or comments about us on social media. We may also encounter criticism on social media regarding our company, management, or medicines. Our reputation could be damaged by negative publicity or if adverse information concerning us is posted on social media platforms or similar mediums, which we may not be able to reverse. If any of these events were to occur or we otherwise fail to comply with applicable regulations, we could incur liability, face restrictive regulatory actions or incur other harm to our business.

Additionally, the use of artificial intelligence, or AI, based software is increasingly being used in the biopharmaceutical industry. Use of AI based software may lead to the release of confidential proprietary information, which may impact our ability to realize the benefit of our intellectual property.

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Risks related to our securities and the global credit markets

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 clinical trials, when we anticipate completing a clinical study, or when we anticipate filing an application for, or obtaining, marketing authorization, or when we or our partners plan to commercially launch a medicine. We base our estimates on present facts and a variety of assumptions, many of which are outside of our control. If we do not achieve milestones in accordance with our or our investors' or securities analysts' expectations, including milestones related to our commercial medicines and medicines in development, the price of our securities could decrease.

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If the price of our securities continues to be highly volatile, this could make it harder 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 **March 31, 2024** **June 30, 2024**, the closing market price of our common stock ranged from \$53.55 to **\$34.73** **\$36.45** 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, the commercial success of our approved medicines, governmental regulation, marketing authorizations, changes in payers' reimbursement policies, developments in patent or other proprietary rights and public concern regarding the safety of our medicines.

Broad market factors may materially harm the market price of our common stock irrespective of our operating performance. For example, recent events such as the COVID-19 pandemic, the ongoing conflicts in Eastern Europe and the Middle East, and the failure of Silicon Valley Bank have caused disruptions of global financial markets and resulted in increased volatility in the trading price of our common stock. In addition, industry factors may materially harm the market price of our common stock. Nasdaq, and the market for biotechnology companies in particular, have historically experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of the particular companies affected. The trading prices and valuations of these stocks, and of ours, may not be predictable. A loss of investor confidence in the market for biotechnology or pharmaceutical stocks or the stocks of other companies that investors perceive to be similar to us, the opportunities in the biotechnology and pharmaceutical market or the stock market in general, could depress our stock price regardless of our business, prospects, financial conditions or results of operations.

Provisions in our certificate of incorporation, bylaws, convertible notes documents, call spread hedge transaction documents 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, chairperson 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.

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In 2023, we completed a \$575 million offering of 1.75% Notes and used \$488.2 million of the net proceeds from the issuance of the 1.75% Notes to repurchase \$504.4 million of our 0.125% Notes. In 2021, we completed a \$632.5 million offering of 0% Notes and used a portion of the net proceeds from the issuance of the 0% Notes to repurchase \$247.9 million of our 1% Notes for \$257.0 million. In 2019, we entered into privately negotiated exchange and/or subscription agreements with certain new investors and certain holders of our existing 1% Notes to exchange \$375.6 million of our 1% Notes for \$439.3 million of our 0.125% Notes, and to issue \$109.5 million of our 0.125% Notes. Additionally, in connection with the pricing of our 0% Notes and 0.125% Notes, we entered into call spread transactions in which we purchased note hedges and sold warrants. Terminating or unwinding the call spread transactions could require us to make substantial payments to the counterparties under those agreements or may increase our stock price. The costs or any increase in stock price that may arise from terminating or unwinding such agreements could make an acquisition of our company significantly more expensive to the purchaser.

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.

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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 28.2 million shares of our common stock upon conversion of our 1.75% Notes, 0% Notes and 0.125% Notes. In connection with the issuance of the 0% Notes and 0.125% Notes, we entered into certain call spread transactions covering 10.9 million shares and 6.6 million shares, respectively, that we expect will offset the dilution to holders of common stock upon any conversion of those notes. In addition, of the shares reserved, 6.1 million shares are reserved for issuance upon conversion of 0.125% Notes that we have repurchased and are currently held by us in treasury (and thus would not be dilutive). As a result, to the extent we elect to convert the 0.125% Notes held by us in treasury, we expect we would receive up to 6.1 million shares upon settlement of related convertible note hedges (without any additional dilution caused by the conversion of the 0.125% Notes held in treasury). However, the anti-dilutive effect of the convertible note hedges is offset by certain warrant transactions we entered into in connection with the issuance of the 0% Notes and the 0.125% Notes. The addition of any of these shares into the public market may have an adverse effect on the price of our securities.

In addition, pursuant to the call spread transactions we entered into in connection with the pricing of our 0% Notes and 0.125% Notes, the counterparties are likely to modify their hedge positions from time to time at or prior to the conversion or maturity of the notes by purchasing and selling shares of our common stock, other of our securities, or other instruments, including over-the-counter derivative instruments, that they may wish to use in connection with such hedging, which may have a negative effect on the conversion value of those notes and an adverse impact on the trading price of our common stock. The call spread transactions are expected generally to reduce potential dilution to holders of our common stock upon any conversion of our 0% Notes or 0.125% Notes or offset any cash payments we are required to make in excess of the principal amount of the converted 0% Notes or 0.125% Notes, as the case may be. However, the warrant transactions could separately have a dilutive effect to the extent that the market value per share of our common stock exceeds the applicable strike price of the warrants.

Negative conditions in the global credit markets and financial services and other industries may adversely affect our business, financial condition or stock price.

The global credit and financial markets have experienced extreme volatility and disruptions recently, including as a result of the COVID-19 pandemic, ongoing conflicts in Eastern Europe and the Middle East, and the failure of Silicon Valley Bank. These disruptions can result in severely diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates and uncertainty about economic stability. There can be no assurance that further deterioration in credit and financial markets and confidence in economic conditions will not occur. If the current equity and credit markets deteriorate, it may make any necessary debt or equity financing more difficult, more costly and more dilutive. Failure to secure any necessary financing in a timely manner and on favorable terms could have a material adverse effect on our operations, growth plans, financial performance or stock price. In addition, 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.

A variety of risks associated with operating our business and marketing our medicines internationally could adversely affect our business. In addition to our U.S. operations, we are commercializing TEGSEDI in the EU, Canada, Latin America and certain Caribbean countries, and WAYLIVRA in the EU, Latin America and certain Caribbean countries. We face risks associated with our international operations, including possible unfavorable regulatory, pricing and reimbursement, political, tax and labor conditions, which could harm our business. Because we have international operations, we are subject to numerous risks associated with international business activities, including:

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

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

Risks related to compliance with laws

Our operations are subject to extensive legal and regulatory requirements affecting the health care industry.

Our operations are subject to extensive legal and regulatory requirements affecting the health care industry, including federal and state anti-kickback laws, false claims laws, transparency laws, such as the federal Sunshine Act, and health information privacy and security laws, which are subject to change at any time. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. Penalties for violations of applicable healthcare laws and regulations may include significant civil, criminal and administrative penalties, damages, disgorgement, fines, imprisonment, exclusion of products from government funded healthcare programs, such as Medicare and Medicaid, and additional reporting requirements and oversight if we enter into a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws. In addition, violations may also result in reputational harm, diminished profits and future earnings.

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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 for pollution liability in amounts and types that we consider commercially reasonable, the coverage or coverage limits of our insurance policies may not be adequate. If our losses exceed our insurance coverage, our financial condition would be adversely affected.

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 control systems 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. In July 2010, the Dodd-Frank Wall Street Reform and Protection Act, or the Dodd-Frank Act, was enacted, and in August 2022, the SEC adopted additional rules and regulations under the Dodd-Frank Act related to "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 has and may in the future lead to additional compliance costs and impact the manner in which we operate our business.

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Risks related to taxes

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 the Code, we can carry forward 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 current U.S. federal income tax law, U.S. federal NOLs generated in taxable years beginning after December 31, 2017 may be carried forward indefinitely, but the deductibility of such U.S. federal NOLs is limited to 80 percent of taxable income. It is uncertain if and to what extent various states will conform to current U.S. federal income tax law, and there may be periods during which states suspend or otherwise limit the use of NOLs for state income tax purposes.

In addition, under Sections 382 and 383 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 percentage-point cumulative change, by value, in its equity ownership over a three-year period, the corporation's ability to use its pre-change NOL 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 NOL carryforwards or other tax attributes is materially limited, it would harm our future operating results by effectively increasing our future tax obligations. As a result of our merger with Akcea Therapeutics, Inc. in 2020, or the Akcea Merger, we are subject to the separate return limitation year, or SRLY, rules. Under the SRLY rules, our utilization of Akcea's pre-merger NOL and tax credit carryforwards is limited to the amount of income that Akcea contributes to our consolidated taxable income. The Akcea pre-merger tax attributes cannot be used to offset any of the income that Ionis contributes to our consolidated taxable income. In addition, at the state level, there may be periods during which the use of NOLs is suspended or otherwise limited, which could accelerate or permanently increase state taxes owed.

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Our future taxable income could be impacted by changes in tax laws, regulations and treaties.

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 foreign income taxes, sales taxes in the U.S., withholding taxes and transaction taxes in foreign jurisdictions. Significant In 2021, the Organization for Economic Cooperation and Development, or OECD, announced an Inclusive Framework on Base Erosion and Profit Shifting including Pillar Two Model Rules defining a global minimum tax rate of 15% on a country-by-country basis for multinational corporations with annual consolidated revenue above €750 million. The ultimate impact from changes in legislation of countries in which we operate remains uncertain and such changes could have a material impact on our future effective tax rate. In addition, 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.

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.

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ITEM 5. OTHER INFORMATION

Trading Plans

During the quarter ended **March 31, 2024** June 30, 2024, our Section 16 officers and directors adopted or terminated contracts, instructions or written plans for the purchase or sale of our securities as noted in the table below.

* Contract, instruction or written plan intended to satisfy the affirmative defense conditions of Rule 10b5-1(c) under the Exchange Act.

** "Non-Rule 10b5-1 trading arrangement" as defined in item 408(c) of Regulation S-K under the Exchange Act.

Action	Date	Trading Arrangement		Total Shares to Be Sold	Expiration Date
		Rule 10b5-1*	Non-Rule 10b5-1**		

B. Lynne Parshall	Brett P. Monia	Termination	January 3, June 26, 2024	X	122,638	54,442	Upon the execution of all instructions provided in the plan
Board Member	Chief Executive Officer						
Joseph Klein, III	Richard S. Geary	Adoption	January 3, April 8, 2024	X	82,000		The earlier to occur of (i) December 31, 2025, and (ii) Upon the execution of all instructions provided in the plan
Board Member	EVP, Chief Development Officer						
Joseph Baroldi	EVP, Chief Business Officer	Adoption	January 5, 2024	X	40,000		The earlier to occur of (i) March 31, 2025, and (ii) Upon the execution of all instructions provided in the plan
Eugene Schneider	EVP, Chief Clinical Development and Operations Officer	Adoption	January 12, 2024	X	40,633	241,732	The earlier to occur of (i) July 29, 2025, and (ii) Upon the execution of all instructions provided in the plan
Elizabeth Hougen	EVP, Finance & Chief Financial Officer	Adoption	January 12, 2024	X	178,200		The earlier to occur of (i) October 11, 2025, and (ii) Upon the execution of all instructions provided in the plan
Patrick O'Neil	Chief Legal Officer & General Counsel	Termination	February 14, 2024	X	170,830		Upon the execution of all instructions provided in the plan
B. Lynne Parshall	Board Member	Adoption	February 21, 2024	X	145,568		The earlier to occur of (i) June 30, 2025, and (ii) Upon the execution of all instructions provided in the plan
Patrick O'Neil	Chief Legal Officer & General Counsel	Adoption	February 21, 2024	X	252,747		The earlier to occur of (i) May 31, 7, 2025, and (ii) Upon the execution of all instructions provided in the plan

ITEM 6. EXHIBITS
EXHIBITS

a. Exhibits

Exhibit Number	Description of Document
10.1	Advisory Services Second Amendment dated as of June 11, 2024 to the Amended and Restated Lease Agreement dated as of August 21, 2023 by and between the Registrant and Lots 21 and 22 Owner (DE) LLC, a Delaware limited liability company.
10.2	Amended and Restated License Agreement by and between the Registrant and Onaiza Cadoret-Manier Otsuka Pharmaceutical Co., Ltd. dated March 15, 2024 June 18, 2024. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
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 March 31, 2024 June 30, 2024, 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).

* 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.

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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/ BRETT P. MONIA Brett P. Monia, Ph.D.	Director and Chief Executive Officer (Principal executive officer)	May 7, August 1, 2024
/s/ ELIZABETH L. HOUGEN Elizabeth L. Hougen	Executive Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	May 7, August 1, 2024

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Exhibit 10.1

SECOND AMENDMENT TO AMENDED AND RESTATED LEASE

This SECOND AMENDMENT TO AMENDED AND RESTATED LEASE ("Amendment") is made as of June 11, 2024 (the "Effective Date"), by and between LOTS 21 & 22 OWNER (DE) LLC, a Delaware limited liability company ("Landlord"), and IONIS PHARMACEUTICALS, INC., a Delaware corporation ("Tenant").

RECITALS:

A. Landlord and Tenant are parties to that certain Amended and Restated Lease Agreement dated as of August 21, 2023, as amended by that certain First Amendment to Amended and Restated Lease dated as of November 6, 2023 (together, the "Lease"), pursuant to which Tenant leases from Landlord certain Premises that include certain Land, a Building under construction containing approximately 164,757 rentable square feet in the aggregate, and certain other improvements, all as more particularly described in the Lease.

C. Tenant desires to commence the construction of its Tenant Improvements earlier than originally anticipated and Landlord and Tenant have agreed to modify the scope of work necessary for Delivery Condition to occur for the purposes of facilitating the same.

D. The parties desire to amend the Lease in order to amend, among other things, the definition of Delivery Condition and certain matters related thereto.

D. Capitalized terms not defined herein have the meanings given to such terms in the Lease.

WITNESSETH:

NOW, THEREFORE, in consideration of the above Recitals and other good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, the parties agree as follows:

The Lease is hereby amended as follows:

1. Delivery Condition. Schedule 7 to Exhibit B to the Lease is hereby deleted and replaced in its entirety by Schedule 7 attached to this Amendment.

2. Estimated Calculation Notice. Section 2.1.2 of the Lease is hereby amended by deleting the words "one hundred eighty (180)" in the first line thereof and inserting the words "two hundred seventy (270)" in their place.

3. Delivery Date. Within Section 3.1 of the Work Letter, Exhibit B to the Lease, the definition of Delivery Date is hereby deleted and replaced in its entirety with the following:

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EXHIBIT 10.1 "As used herein, the "Delivery Date" means the date that is the earlier to occur of (x) the date (i) the Landlord's Construction Work is in the condition required by Schedule 7 (the "Delivery Condition"), and (ii) Landlord has provided Tenant with reasonably continuous and uninterrupted access to the Project for the construction of Tenant Improvements, subject to the reasonable requirements necessary for, and established by, Landlord's General Contractor to allow it to achieve Substantial Completion, complete the Punchlist Items and exercise any of its other rights or

obligations under this Work Letter and the Lease within the time periods set forth herein, and (y) sixty (60) days after the date that Tenant enters any portion of the Premises for the commencement of substantial work in connection with the Tenant Improvements; provided, however, in no event shall minor work such as the MEP deck inserts/hangers or other minor work that is installed early in the interest of efficiency be considered the commencement of the Tenant Improvements, and in no event shall the Delivery Date be any earlier than November 6, 2024."

4. Construction of the Tenant Improvements and LCW by Tenant; Coordination. Section 6.4(a) of the Work Letter, Exhibit B to the Lease, is hereby amended by deleting within the third paragraph the words "the first day of the 18th month" and inserting the words "the first day of the 21st month" in their place.

IONIS PHARMACEUTICALS, INC. 5. Successors and Assigns. Subject to the provisions of Article 5 of the Lease, the provisions of the Lease, as affected by this Amendment, shall be binding upon and inure to the benefit of the heirs, successors, executors, administrators, and assigns of Landlord and Tenant.

ADVISORY SERVICES AGREEMENT

(6. Tenant Improvement Allowance; Funding of TI by LL. The last sentence of the first paragraph of Section 10.2(a) of the Work Letter, Exhibit B to the Lease, is hereby amended and restated in its entirety as follows:

"Landlord shall have no obligation to make any disbursements of TI Allowance not properly requisitioned by Tenant by the date that is one year following the Commencement Date and Tenant shall have no further right to any undisbursed TI Allowance thereafter; provided that the portion of the TI Allowance not requisitioned by Tenant with respect to the Day 1 Space may be requisitioned by Tenant for the Day 2 Space by the date that is 21 months following the Commencement Date, and, thereafter, Tenant shall have no further right to any undisbursed TI Allowance."

7. Submission. The submission of this Amendment to Tenant or a summary of some or all of its provisions for examination does not constitute a reservation of or option to amend the Lease as set forth herein until fully executed by Tenant and Landlord. Landlord represents that this Amendment has been approved by the holder of any mortgage or deed of trust covering the Land having the right to approve this Amendment.

8. Authority. Tenant warrants and represents that (a) Tenant is duly organized, validly existing and in good standing under the laws of the jurisdiction in which such entity was organized; (b) Tenant has duly executed and delivered this Amendment; (c) the execution, delivery and performance by Tenant of this Amendment (i) are within the powers of Tenant, (ii) have been duly authorized by all requisite action (subject to the immediately following paragraph), (iii) will not violate any provision of law or any order of any court or agency of government, or any agreement or other instrument to which Tenant is a party or by which it or any of its property is bound, and (iv) will not result in the imposition of any lien or charge on any of Tenant's property, except by the provisions of this Amendment; and (d) this Amendment is a valid and binding obligation of Tenant in accordance with its terms.

SUMMARY PAGE Page 2nd

Landlord warrants and represents that (a) Landlord is duly organized, validly existing and in good standing under the laws of the jurisdiction in which such entity was organized; (b) Landlord has duly executed and delivered this Amendment; (c) the execution, delivery and performance by Landlord of this Amendment (i) are within the powers of Landlord, (ii) have been duly authorized on behalf of Landlord by all requisite action and (iii) will not violate any provision of law or any order of any court or agency of government, or any agreement or other instrument to which Landlord is a party or by which it or any of its property is bound; and (d) this Amendment is a valid and binding obligation of Landlord in accordance with its terms.

9. No Other Modifications. Except as modified in this Amendment, all other terms and conditions of the Lease shall remain unchanged and in full force and effect. As amended by this Amendment, the Lease represents the entire agreement between the parties with respect to the matters set forth herein. To the extent of a conflict between the terms of the Lease and this Amendment, this Amendment shall prevail.

10. Counterparts. This Amendment may be executed in 2 or more counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument. Counterparts may be delivered via facsimile, electronic mail (including pdf or any electronic signature process complying with the U.S. federal ESIGN Act of 2000) or other transmission method and any counterpart so delivered shall be deemed to have been duly and validly delivered and be valid and effective for all purposes. Electronic signatures shall be deemed original signatures for purposes of this Amendment and all matters related thereto, with such electronic signatures having the same legal effect as original signatures.

[SIGNATURES ON FOLLOWING PAGES]

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IN WITNESS WHEREOF, the parties hereto have duly executed this Amendment on the day and year first above written.

LANDLORD:

**LOTS 21 & 22 OWNER (DE) LLC, a Delaware
limited liability company**

By: /s/Tycho Suter
Name: Tycho Suter
Title: Vice President

By: /s/Kristen Binck
Name: Kristen Binck
Title: Vice President

TENANT:

IONIS PHARMACEUTICALS, INC., a
Delaware corporation

By: /s/Beth Hougen
Name: Beth Hougen
Title: CFO

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SCHEDULE 7

DELIVERY CONDITION

1. **Date** The following is not required for the achievement of **Advisory Services Agreement**: Delivery Condition but Landlord shall continue diligently and continuously, subject to Sections 7 and 12 of the Work Letter, following Delivery Condition, to use good faith, diligent efforts to prosecute the same, estimated for completion by February 21, 2025: the Building becomes "dried in" meaning that it is a "water tight shell", whether by permanent or temporary measures, in a manner that Landlord reasonably determines in good faith, based on the input of General Contractor, will not interfere with the progress of the Tenant Improvements in any material way due to the condition of the Building exterior.
2. **(As part of Tenant's schematic document submission to Landlord for the Tenant Improvements, Tenant shall identify any locations (not to exceed a reasonable number) where Tenant desires to place deck inserts on each floor of the Premises to accommodate Tenant's internal staircases or similar, customary items consistent with comparable first-class buildings used for life sciences purposes. Landlord shall cooperate and collaborate with Tenant to allow for the installation of such approved deck inserts, if any, prior to the occurrence of Delivery Condition, subject to agreeing with Tenant on the minimum amount of Tenant Delay resulting from the same and the other terms and conditions of the Work Letter.**
3. Tenant shall have safe and reasonably efficient access to the work site.
4. Installation of floors should be sufficiently complete to allow layout to begin of floor surfaces, column lines, control lines or (to the extent applicable) Trimble reference points. Any stored material for Landlord's Construction Work (including turnover attic stock) must be located outside of the building (on site), or in an area or areas on each applicable floor designated by the General Contractor that permit the orderly progress of Tenant Improvements.
5. Site access is available, as reasonably designated by the General Contractor, for efficient material delivery and Building loading.
6. Site access is available for the Tenant Improvement contractor and subcontractor's construction trailer (if applicable) and laydown space in a location reasonably designated by the General Contractor.
7. Temporary electrical infrastructure is available to the Premises and Building, with sufficient capacity to power small tools, temporary lighting, and equipment to provide temporary ventilation/heating to perform the Tenant Improvements using normal means of power use.

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8. The following is not required for the achievement of Delivery Condition but Landlord shall continue diligently and continuously, subject to Sections 7 and 12 of the Work Letter, following Delivery Condition, to use good faith, diligent efforts to prosecute the same, for completion by April 23rd, 2025: Tenant's Contractor has ability to terminate electrical wires in electrical switchgear and distribution boards installed as part of the Landlord's Construction Work.
9. Tenant's contractor is able to use fire stairs to travel to and from the street level and between each Tenant floor by either permanent or temporary means. Use of stairs subject to coordination with Landlord's completion of finishes and inspections of the stairs.

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CONFIDENTIAL

Execution Version

Exhibit 10.2

Certain portions of this exhibit, marked by [***], have been excluded because they are both not material and are the type that the registrant treats as private or confidential.

AMENDED AND RESTATED LICENSE AGREEMENT

BY AND BETWEEN

IONIS PHARMACEUTICALS, INC.

AND

OTSUKA PHARMACEUTICAL CO., LTD.

Dated June 18, 2024

CONFIDENTIAL

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AMENDED AND RESTATED LICENSE AGREEMENT

This **AMENDED AND RESTATED LICENSE AGREEMENT** (this “**Agreement**”) is made and entered into as of June 18, 2024 (the “**Restatement Date**”) between **IONIS PHARMACEUTICALS, Inc.**, a Delaware corporation, having its principal place of business at 2855 Gazelle Court, Carlsbad CA 92010 USA (“**Ionis**”), and **OTSUKA PHARMACEUTICAL Co., Ltd.**, a company organized and existing under the laws of Japan, having a place of business at 2-9, Kanda Tsukasa-machi, Chiyoda-ku, Tokyo 101-8535, Japan (“**Otsuka**”). Ionis and Otsuka may be referred to in this Agreement individually as a “**Party**” and collectively as the “**Parties**.” Capitalized terms used in this Agreement, whether used in the singular or the plural, have the meaning set forth in APPENDIX 1 (Definitions). All attached appendices and schedules are a part of this Agreement.

RECITALS

WHEREAS, Ionis possesses certain Patent Rights, Know-How, technology and expertise with respect to research, development, and manufacturing of drugs for the treatment of HAE, and has regulatory and commercial capabilities in the Ionis Territory;

WHEREAS, Otsuka (itself and through its Affiliates) has expertise in the development and commercialization of biopharmaceutical products and has regulatory, development, and commercial capabilities in the Otsuka Territory;

WHEREAS, Ionis and Otsuka entered into that certain License Agreement, dated as of December 15, 2023 (the “**Original Effective Date**” and such License Agreement, the “**Original Agreement**”) for the Development and Commercialization of the Licensed Products in the Europe Territory, as set forth in, and subject to the terms of, the Original Agreement;

WHEREAS, the Original Agreement will continue to govern the Parties’ rights and obligations during the Original Agreement Term; and

WHEREAS, the Parties desire to amend and restate the Original Agreement from and after the Restatement Date in order to, among other things, expand Otsuka’s rights to Develop and Commercialize the Licensed Products in the Asia Territory in addition to the Europe Territory, as set forth in, and subject

to the terms of, this Agreement.

NOW THEREFORE, the Parties agree as follows:

ARTICLE 1

OVERVIEW

1.1 Development and Commercialization. As of the Restatement Date, Ionis is Developing a Licensed Product in ongoing Clinical Trials in both the Europe Territory and the Ionis Territory (such studies, as further described and defined in [Section 4.2.1](#) (Cross-Territory Clinical Development Plan)). Under this Agreement, the Parties intend (a) that Ionis will continue to conduct the Ongoing Cross-Territory Studies in accordance with the Cross-Territory Clinical Development Plan, at [***] and (b) to share the costs of all Future Cross-Territory Studies included in the Cross-Territory Clinical Development Plan as of the Original Effective Date and any additional Cross-Territory Clinical Studies included in any updated version of the Cross-Territory Clinical Development Plan approved by the [**], in each case, in accordance with the [**]. In addition, the Parties intend for Ionis to Commercialize the Licensed Products in the Ionis Territory and Otsuka to Commercialize the Licensed Products in the Otsuka Territory, which Commercialization activities will be consistent with the global commercialization and global medical affairs strategy (as further described in [Article 6](#) (Commercialization and Medical Affairs)).

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1.2 Governance. The Parties have agreed to form a Europe joint steering committee and an Asia joint steering committee to oversee and coordinate the Development, Manufacturing, and Commercialization activities with respect to the Licensed Products under this Agreement in the Europe Territory and Asia Territory, respectively, and an executive committee to resolve matters that are subject to approval, but are not unanimously agreed, by such joint steering committees or other Subcommittees.

1.3 Purpose. The purpose of this [Article 1](#) (Overview) is to provide a high-level overview of the roles, responsibilities, rights, and obligations of each Party under this Agreement, and therefore, this [Article 1](#) (Overview) is qualified in its entirety by the more detailed provisions of this Agreement set forth below.

ARTICLE 2

LICENSES

2.1 License Grants to Otsuka. Subject to the terms of this Agreement (including Ionis' retained rights set forth in [Section 2.5](#) (No Other Rights and Retained Rights; Negative Covenant)), Ionis hereby grants to Otsuka:

2.1.1 an exclusive, royalty-bearing license, with the right to grant sublicenses solely in accordance with [Section 2.3.1\(a\)](#) (Rights of Otsuka to Grant Sublicenses), under the Ionis Technology and the Unitary Product Trademarks, in each case, to (a) Develop the Licensed Products in the Field in the Otsuka Territory in accordance with the Otsuka Territory-Specific Development Plans solely for Commercialization and for the conduct of Medical Affairs for such Licensed Products in the Field in the Otsuka Territory and (b) Commercialize and conduct Medical Affairs for the Licensed Products in the Field in the Otsuka Territory. For clarity, the license grants under this [Section 2.1.1](#) (License Grants to Otsuka) do not include the right to Manufacture the Licensed Products.

2.1.2 a non-exclusive, royalty-bearing license, with the right to grant sublicenses solely in accordance with [Section 2.3.1\(b\)](#) (Rights of Otsuka to Grant Sublicenses), under the Ionis Technology and the Unitary Product Trademarks solely to (a) Package and Label the Licensed Products in the Field in the Territory and (b) Manufacture the Licensed Products in the Field in the Territory from and after the time Otsuka provides a Manufacturing Handover Notice, in each case (a) and (b), solely for Commercialization and for the conduct of Medical Affairs for such Licensed Products in the Field in the Otsuka Territory.

2.2 License Grant to Ionis. Subject to the terms of this Agreement, including Otsuka's retained rights set forth in [Section 2.5](#) (No Other Rights and Retained Rights; Negative Covenants), Otsuka hereby grants to Ionis an exclusive, royalty-free, fully-paid, perpetual license, with the right to grant sublicenses through multiple tiers, under the Otsuka Technology solely to (a) Develop the Licensed Products in the Ionis Territory and the Otsuka Territory; *provided* that, unless this Agreement has been terminated, any such Development in the Otsuka Territory will be conducted solely in accordance with the Cross-Territory Clinical Development Plan and the Non-Clinical HAE Development Plans, (b) Manufacture the Licensed Products worldwide in accordance with this Agreement, and (c) Commercialize the Licensed Products in the Ionis Territory in accordance with this Agreement and, subject to [Section 14.9.5](#) (Sublicenses), worldwide following any termination of this Agreement.

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2.3 Sublicensing and Subcontracting Terms.

2.3.1 Rights of Otsuka to Grant Sublicenses.

(a) Subject to the terms of this Agreement, Otsuka will have the right to grant sublicenses of the rights granted under [Section 2.1.1](#) (License Grants to Otsuka) (i) [***], and (ii) [***].

(b) Subject to the terms of this Agreement, Otsuka will have the right to grant sublicenses of the rights granted under [Section 2.1.2](#) (License Grants to Otsuka) (i) [***], and (ii) [***].

2.3.2 Right to Subcontract. Each Party may engage one or more Third Party subcontractors to perform services in furtherance of the performance of its obligations or exercise of its rights under this Agreement, including any Third Party contract manufacturer, contract research organization, contract sales organization, wholesaler or distributor (including a distributor that is engaged to conduct promotional activities with respect to the Licensed Products on such Party's behalf and under such Party's control) ("Subcontractors"); *provided* that (a) neither Party will engage any such Subcontractor that has been Debarred/Excluded; and (b) no engagement of any such Subcontractors will relieve the engaging Party of its obligations under this Agreement or any liability hereunder.

2.3.3 March 15, 2024 Sublicense and Subcontract Agreements. Each agreement pursuant to which a sublicense is granted to a Sublicensee by Otsuka pursuant to this [Section 2.3](#) (Sublicensing and Subcontracting Terms), each agreement pursuant to which a sublicense is granted to a Sublicensee by Ionis of the rights granted to it under [Section 2.2](#) (License Grant to Ionis), and each agreement pursuant to which a Party engages any Subcontractor, in each case after the Restatement Date and during the Term, will (a) be subject and subordinate to this Agreement, (b) be consistent with the terms of this Agreement, (c) include obligations of confidentiality and non-use applicable to the Confidential Information of the other Party that are at least as stringent as those set forth in [Article 12](#) (Confidentiality), and (d) include terms that are consistent with the intellectual property provisions set forth in this Agreement. As soon as reasonably practicable after execution of any sublicense agreement with a Sublicensee after the Restatement Date, [***]. In addition, [***].

2.3.4 **Responsibility for Sublicensees and Subcontractors.** Notwithstanding any sublicense, the sublicensing or subcontracting Party will remain primarily liable to the other Party for the performance of all of its obligations under, and such Party's compliance with all provisions of, this Agreement. Each Party agrees that it will be fully responsible and liable for any breach of the terms of this Agreement by any of its Sublicensees or Subcontractors to the same extent as if such Party itself has committed any such breach.

2.4 **Collaboration Technology Enabling License.** Subject to the terms and conditions of this Agreement (and without limiting the licenses granted to Otsuka under Section 2.1 (License Grants to Otsuka)), Otsuka hereby grants Ionis a fully-paid, royalty-free, irrevocable, worldwide, non-exclusive, sublicensable (through multiple tiers) license under any Otsuka Collaboration Know-How and Otsuka Collaboration Patent Rights (excluding any Product-Specific Patents) to Exploit products that include an oligonucleotide as an active pharmaceutical ingredient (other than a Licensed Product); *provided* that Ionis may only grant a sublicense under the rights granted in this Section 2.4 (Collaboration Technology Enabling License) if such sublicense includes the grant of a license under Know-How or Patent Rights Controlled by Ionis or its Affiliates to Exploit such products that include an oligonucleotide as an active pharmaceutical ingredient (other than a Licensed Product).

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2.5 No Other Rights and Retained Rights; Negative Covenant.

2.5.1 **No Other Rights and Retained Rights.** Nothing in this Agreement will be interpreted to grant a Party any rights under any intellectual property rights owned or Controlled by the other Party, including Ionis Technology or Otsuka Technology, in each case, that are not expressly granted herein, whether by implication, estoppel, or otherwise. Otsuka will not practice the Ionis Technology other than as expressly licensed and permitted under this Agreement and Ionis will not practice the Otsuka Technology other than as expressly licensed and permitted under this Agreement. Any rights not expressly granted to a Party by the other Party under this Agreement are hereby retained by such other Party. Without limiting the foregoing, (a) Ionis hereby expressly retains the right to perform (i) Development activities for the Licensed Products worldwide in accordance with the Cross-Territory Clinical Development Plan and the Non-Clinical HAE Development Plans, (ii) Manufacturing activities worldwide, and (iii) Ionis' other obligations under this Agreement, and (b) Otsuka hereby expressly retains the right to perform Development activities for the Licensed Products in the Field in the Otsuka Territory in accordance with the Otsuka Territory-Specific Development Plans solely for Commercialization and for the conduct of Medical Affairs for such Licensed Products in the Field in the Otsuka Territory and to Manufacture the Licensed Products in the Field in the Territory solely for Commercialization and for the conduct of Medical Affairs for such Licensed Products in the Field in the Otsuka Territory, in each case, in accordance with this Agreement.

2.5.2 **Negative Covenant.** Ionis shall not, and shall cause its Affiliates to not, grant or convey any right to any Third Party (pursuant to a license grant, collaboration or services agreement, option grant, or otherwise) that would be in conflict with, limit the scope of, or otherwise adversely affect the licenses granted to Otsuka pursuant to Section 2.1 (License Grants to Otsuka).

2.6 Existing Third-Party IP Agreements.

2.6.1 **Compliance.** Otsuka acknowledges and agrees that (a) the rights and licenses granted to Otsuka under this Agreement are subject to the applicable terms of all Existing Third-Party IP Agreements with respect to the Ionis Technology that is being sublicensed thereunder to Otsuka, (b) Ionis' ability to comply with its obligations, and grant rights and licenses to Otsuka, under this Agreement are limited by any and all requirements and restrictions imposed on Ionis under the Existing Third-Party IP Agreements with respect to the Ionis Technology that is being sublicensed to Otsuka by Ionis under such Existing Third-Party IP Agreements, and (c) Ionis will not be required to take any action or inaction pursuant to this Agreement that would cause Ionis to be in breach of any Existing Third-Party IP Agreement or to grant any rights to Otsuka hereunder that are in violation of, or inconsistent with, any Existing Third-Party IP Agreement. Otsuka will abide by the applicable terms of the Existing Third-Party IP Agreements, and, subject to [***], the applicable terms of any amendments, in each case, to the extent such terms are disclosed in the copies of the Existing Third-Party IP Agreements, and amendments thereto, that are provided or made available to Otsuka.

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2.6.2 **Existing Third-Party IP Amendments.** During the Term, Ionis will promptly furnish Otsuka with copies of any amendment to any Existing Third-Party IP Agreement to the extent related to any of the rights sublicensed to Otsuka hereunder, from which copies Ionis may redact confidential or commercially sensitive information or other information that is not relevant to the rights sublicensed to Otsuka pursuant to the applicable Existing Third-Party IP Agreement. During the Term, Ionis shall: (a) [***]; (b) [***]; (c) [***]; and (d) [***]. Notwithstanding any provision to the contrary in this Agreement, as between the Parties, [***] shall be solely responsible for the payment of all license fees, royalties, milestone payments, and other payment obligations under all Existing Third-Party IP Agreements.

2.7 New Third-Party IP Agreements.

2.7.1 **Identification of New In-License Agreements.** If either Party intends to obtain Control of any Patent Rights or Know-How from a Third Party (whether by acquisition or license) that such Party believes are [***] to Exploit the Licensed Compound or a Licensed Product (other than in connection with a Change of Control of a Party or as a result of the acquisition by a Party of a Third Party by merger, acquisition, or similar transaction or series of related transactions) (such Patent Rights and Know-How, "**Identified Rights**"), then such Party will notify the other Party of the Identified Rights.

2.7.2 Potential In-Licenses.

(a) Acquisition of Potential In-Licenses.

(i) [***] that [***] in the Exploitation of a Licensed Product in [***] Territory, whether by license or acquisition, (each agreement to license or acquire such Identified Rights, a "**Potential In-License**") in accordance with this Section 2.7.2 (Potential In-Licenses). If [***] after the Restatement Date, then [***] will [***]. If [***] pursuant to this Section 2.7.2(a) (Acquisition of Potential In-Licenses), then [***] with respect to [***] to Exploit the Licensed Products. [***] such Potential In-License will [***]. [***]. If the Identified Rights to be licensed or acquired under a Potential In-License would constitute Ionis Core Technology or Ionis Manufacturing and Analytical Technology if such Identified Rights were Controlled by Ionis (any such Identified Rights, "**Core or Manufacturing Identified Rights**") then, [***], [***] will have the first right to enter into such Potential In-License (a "**Core or Manufacturing Potential In-License**") in accordance with Section 2.7.2(c)(i) ([***] Potential In-Licenses).

(ii) If either Party [***] and if the [***], then [***]. At either Party's request if [***] in accordance with this Section 2.7.2(a)(ii) (Acquisition of Potential In-Licenses), the Parties will [***]. If [***], then the Potential In-License [***] for all purposes of this Agreement. If [***], then Ionis will [***]. If Ionis [***] pursuant to this Section 2.7.2(a)(ii) (Acquisition of Potential In-Licenses) and Ionis [***] in accordance with this Section 2.7.2(a)(ii) (Acquisition of Potential In-Licenses), then [***]. If Ionis [***], then Otsuka will [***] in accordance with the terms of this Section 2.7.2(a)(ii) (Acquisition of Potential In-Licenses) and Otsuka will [***].

- (b) **Collaboration In-Licenses.** For any Potential In-License that [***] in accordance with Section 2.7.2(a) (Acquisition of Potential In-Licenses), and for [***], (i) such Potential In-License will [***], (ii) the Party [***] will [***], to the extent set forth in Section 2.7.2(a)(ii) (Acquisition of Potential In-Licenses), (iii) the Patent Rights or Know-How in-licensed under such [***], and (iv) (A) each Party will [***], and (B) the Parties will [***]. The Party that [***] will [***] pursuant to this Section 2.7.2(b) (Collaboration In-Licenses), and such other Party will [***].
- (c) **[***] Potential In-Licenses.**
 - (i) If the [***] a Potential In-License [***], then (A) such Potential In-License [***], (B) subject to Section 2.7.2(c)(i) ([***] Potential In-Licenses), the Patent Rights and Know-How in-licensed under such Potential In-License [***], (C) except as set forth in clause (D) of this Section 2.7.2(c)(i) ([***] Potential In-Licenses), Ionis will [***] and, subject to Section 2.7.2(c)(ii) ([***] Potential In-Licenses), will [***]; provided that if such Potential In-License [***], then [***], and Ionis [***] in accordance with Section 2.7.2(c)(ii) ([***] Potential In-Licenses), then Otsuka [***], and (D) if such Potential In-License (1) was [***] pursuant to Section 2.7.2(a) (Acquisition of Potential In-Licenses), (2) was not [***], and (3) is not [***], then [***] in accordance with this Agreement [***], and the terms of this Section 2.7.2 (Potential In-Licenses) [***]. If Ionis [***] in accordance with Section 2.7.2(a) (Acquisition of Potential In-Licenses), then Otsuka [***]. If Ionis [***], then Otsuka [***] in accordance with this Section 2.7.2(c)(i) ([***] Potential In-Licenses) and Otsuka will [***].
 - (ii) If Ionis [***], then Ionis [***]. If Ionis [***] in accordance with Section 2.7.2(c)(i) ([***] Potential In-Licenses), then Ionis will [***]. Ionis may [***]. Within [***], Otsuka will [***]. If Otsuka [***] in accordance with this Section 2.7.2(c)(ii) ([***] Potential In-Licenses), then such [***] and Section 2.7.2(b) (Collaboration In-Licenses) will apply, *mutatis mutandis*. If Otsuka [***] in accordance with this Section 2.7.2(c)(ii) ([***] Potential In-Licenses), then Otsuka [***].

2.8 Right of First Negotiation for Follow-On Products.

2.8.1 **ROFN Exercise.** If (a) during the period from the Original Effective Date until the [***] (such period, the "**Europe ROFN Period**"), Ionis intends to grant rights to a Third Party that include the right to Commercialize [***] designed to bind to the RNA encoding PKK for the treatment of HAE (any such compound, a "**Follow-On Product**") in the Europe Territory or (b) during the period from the Restatement Date until the [***] (such period, the "**Asia ROFN Period**", provided that [***] Ionis intends to grant rights to a Third Party that include the right to Commercialize a Follow-On Product in the Asia Territory, then, in each case ((a) or (b)) Ionis will provide to Otsuka (i) notice of whether Ionis intends to grant Commercialization rights to such proposed Follow-On Product in the Europe Territory, Asia Territory or both (such applicable countries within the Europe Territory or the Asia Territory, the "**ROFN Territory**"; provided that the ROFN Territory will not include any countries within the Europe Territory if the Europe ROFN Period has expired or any countries within the Asia Territory if the Asia ROFN Period has expired) and the proposed scope of Commercialization rights that Ionis proposes to grant, and (ii) an information package containing, to the extent such information is in Ionis' or its Affiliate's Control: (A) summaries of [***], (B) information about [***], (C) a summary of [***], and (D) [***] related to the Follow-On Product to the extent necessary or reasonably useful for Otsuka to evaluate whether to obtain rights with respect to Follow-On Product ("**Effective ROFN Notice and Package**"). Promptly thereafter, Ionis will provide a high-level presentation to the JSCs (at a joint meeting), if during the Europe ROFN Period, or to the Asia JSC, if during the Asia ROFN Period after expiration of the Europe ROFN Period, relating to the Follow-On Product and the rights Ionis proposes to grant. Otsuka will have an exclusive right, exercisable no later than [***] after receipt of a ROFN Notice and Package from Ionis containing all information set forth in the foregoing clauses ((A) through (D)) to the extent such information is in Ionis' or its Affiliate's Control, to notify Ionis in writing as to whether Otsuka desires to negotiate for such rights to Commercialize such Follow-On Product in the applicable ROFN Territory (a "**ROFN Exercise Notice**"). During such [***], Ionis will [***].

2.8.2 **Negotiation.** If Otsuka provides a ROFN Exercise Notice to Ionis within such [***], then the Parties will negotiate in good faith for [***] from the date of Ionis' receipt of the ROFN Exercise Notice, or such longer period as may be agreed upon in writing by the Parties (the "**ROFN Negotiation Period**") the terms of a definitive agreement (or amendment to this Agreement) pursuant to which Ionis would grant to Otsuka the rights to Commercialize (and, as agreed by the Parties, to otherwise Exploit) such Follow-On Product in the applicable ROFN Territory. Neither Party will have any obligation to enter into any agreement or amendment to this Agreement granting rights to Otsuka to Commercialize or otherwise Exploit such Follow-On Product in the applicable ROFN Territory. If the ROFN Negotiation Period expires before the Parties have entered into an agreement or amendment to this Agreement with respect to Otsuka's Commercialization or other Exploitation of such Follow-On Product in the applicable ROFN Territory, and if such ROFN Negotiation Period [***] in such ROFN Territory, then Ionis will have the right to negotiate and enter into an agreement with any Third Party with respect to a grant of rights to Exploit such Follow-On Product in such ROFN Territory [***]. If Ionis does not grant rights to a Third Party that include the right to Commercialize such Follow-On Product in the applicable ROFN Territory [***], then the terms of this Section 2.8 (Right of First Negotiation for Follow-On Products) will [***]. If the [***] in such ROFN Territory expires before the Parties have entered into an agreement or amendment to this Agreement with respect to Otsuka's Commercialization or other Exploitation of such Follow-On Product in such ROFN Territory then Ionis will have no further obligation to negotiate with Otsuka with respect to any grant of such rights to Otsuka and will be free to negotiate and enter into an agreement with any Third Party with respect to a grant of rights to Exploit such Follow-On Product in such ROFN Territory.

2.8.3 **Follow-On Product Activities.** If Ionis enters into an agreement with a Third Party granting any rights to Exploit a Follow-On Product, then all Development, Commercialization, and Medical Affairs activities related to such Follow-On Product ("**Follow-On Product Activities**") will be subject to the following: (a) [***] related to such Follow-On Product; and (b) Ionis and its Affiliates shall conduct the Follow-On Product Activities independently of the activities under this Agreement and [***].

ARTICLE 3 TECHNOLOGY TRANSFER

3.1 Initial Know-How Transfer. At a time period to be agreed upon by the Parties after the Restatement Date, Ionis will provide and transfer, and in any event will initiate such transfer within [***] after the Restatement Date, to Otsuka copies of the Ionis Know-How (other than Ionis Manufacturing and Analytical Know-How, the transfer of which will be conducted pursuant to Section 7.4 (Manufacturing Technology Transfer)) that (a) exists on the Restatement Date, (b) was not previously provided to Otsuka, and (c) is [***] to Develop, Commercialize or conduct Packaging and Labeling or Medical Affairs for a Licensed Product (such transfer, the "**Initial Know-How Transfer**"). Ionis may make such Ionis Know-How available in such reasonable form as maintained by Ionis. In addition to the Initial Know-How Transfer, upon Otsuka's reasonable request during the Term, Ionis will provide and transfer to Otsuka copies of or otherwise make available to Otsuka all Ionis Know-How (other than Ionis Manufacturing and Analytical Know-How) not previously provided to Otsuka hereunder to the extent such Ionis Know-How is [***] to Develop, Commercialize or conduct Packaging and Labeling or Medical Affairs for a Licensed Product, including in accordance with Section 4.7 (Data Transfer), Section 5.6 (Cooperation), Section 6.1.2 (Commercialization in the Otsuka Territory), Section 6.2 (Commercialization and Medical Affairs Reporting), and Section 7.1.1 (Ionis Manufacturing) (the "**Continuing Know-How Transfer**," and together with the Initial Know-How Transfer, the "**Technology Transfer**").

Name of Advisor: Onaiza Cadoret-Manier (hereinafter **Technology Transfer Costs**). Ionis will conduct the Technology Transfer, and will provide consultation and assistance with [***] to provide support set forth in Section 7.1.1 (Ionis Manufacturing) (any such consultation, assistance, or support provided by [***]). Ionis will [***] in connection with the Initial Know-How Transfer, including, for clarity, [***]. In addition, Ionis will [***] in providing Requested Assistance to Otsuka in connection with such Continuing Know-How Transfer; *provided that*, with respect to Requested Assistance related to [***] until [***] and, thereafter, [***]. After [***]. At all times, (a) Otsuka will [***]. Ionis may [***] following [***]. Ionis shall [***]. Notwithstanding the foregoing, [***]. For clarity, the terms of this Section 3.2 (Technology Transfer Costs) shall not apply with respect to [***] and, for clarity, the terms of this Section 3.2 (Technology Transfer Costs) shall not apply to [***]. Notwithstanding any provision to the contrary, Ionis' obligations to conduct the Technology Transfer and provide Requested Assistance will not require Ionis to conduct any additional Clinical Trials or generate any additional data or information that is not expressly contemplated by the Cross-Territory Clinical Development Plan or the Non-Clinical HAE Development Plans. Notwithstanding any provision to the contrary in this Section 3.2 (Technology Transfer Costs), if Ionis provides to Otsuka any Requested Assistance or Continuing Know-How Transfer, in each case, related to the Europe Territory, then to the extent such Requested Assistance or Continuing Know-How Transfer is applicable to the Asia Territory and to the extent feasible, Otsuka will seek such support or assistance from Otsuka's Affiliates rather than requesting additional Requested Assistance or a Continuing Know-How Transfer from Ionis.

3.2 **Development Diligence Obligations.** Ionis will be responsible for conducting the activities under the Cross-Territory Clinical Development Plan (other than with respect to Clinical Trial sites in Japan, if applicable) and both of the Non-Clinical HAE Development Plans (other than with respect to any activities allocated to Otsuka under the Non-Clinical Asia HAE Development Plan) and will use Commercially Reasonable Efforts to carry out such activities. For clarity, Ionis shall not conduct any [***]. Otsuka will be responsible for conducting the activities under the Europe Territory-Specific Development Plan, the Asia Territory-Specific Development Plan, and solely to the extent any activities are allocated to Otsuka under the Non-Clinical Asia HAE Development Plan, the Non-Clinical Asia HAE Development Plan, [***]. Notwithstanding the foregoing, if, as provided in Section 4.4.1(c)(ii) (Shared Development Costs), the Parties agree to update the Cross-Territory Clinical Development Plan (including the Shared Development Budget) to include [***], then Otsuka will [***]. Each Party will conduct all Development activities for which it is responsible under this Agreement in a good scientific manner, in accordance with GLP and GCP, as applicable, and in compliance with Professional Requirements and Applicable Law.

4.2 Development Plans.

4.2.1 Cross-Territory Clinical Development Plan. The current development plan for the clinical Development activities for both the Europe Territory and the Ionis Territory is set forth on SCHEDULE 4.2.1 (such development plan as it may be modified in accordance with the terms and conditions of this Agreement, the "**Advisor Cross-Territory Clinical Development Plan**"). The current Cross-Territory Clinical Development Plan includes (and any updates to the Cross-Territory Clinical Development Plan will at all times include) all Clinical Trials that are intended to support obtaining or maintaining Regulatory Approval for any Licensed Product in both the Europe Territory and the Ionis Territory (and Japan, if the Parties agree to include Clinical Trial sites in Japan for any Cross-Territory Clinical Study as provided in Section 4.4.1(c)(ii) (Shared Development Costs)) (any such Clinical Trials, "**Cross-Territory Clinical Studies**"), including (a) all Cross-Territory Clinical Studies that were ongoing as of the Original Effective Date (the "**Ongoing Cross-Territory Studies**"), (b) all Post-Approval Mandatory Studies that are (i) required to support maintaining Regulatory Approval for any Licensed Product in both the Europe Territory and the Ionis Territory and (ii) designed to meet the requirements of the EMA for maintaining Regulatory Approval of the Licensed Product in the Europe Territory (collectively ((i) and (ii)), "**Post-Approval Cross-Territory Mandatory Studies**"), and (c) all future Cross-Territory Clinical Studies for [***]. From time to time during the Term, either Party may submit to the Europe JSC any proposed update to the Cross-Territory Clinical Development Plan to include additional Cross-Territory Clinical Studies, including the study designs for such additional Cross-Territory Clinical Studies. In addition, each Party shall submit to the Europe JSC (or other designated Subcommittee) reasonably in advance proposed updates to the Cross-Territory Clinical Development Plan to take into account changed circumstances, such as cessation of any Cross-Territory Clinical Study, or the need to amend any Cross-Territory Clinical Study, including amendments in response to Regulatory Authority requirements, for safety reasons or otherwise. The Europe JSC will review, discuss, and determine whether to approve each update to the Cross-Territory Clinical Development Plan. Once reviewed and approved by the Europe JSC (or the Executive Committee, if the Europe JSC cannot agree), each update to the Cross-Territory Clinical Development Plan will automatically become effective and supersede the previous Cross-Territory Clinical Development Plan, as of the date of such approval by the Europe JSC (or Executive Committee).

Scope of 4.2.2 AsNon-Clinical HAE Development Plans.

Advisory Services:

(a) **Europe Territory.** The current development plan for all CMC Development and non-clinical Development, in each case, required to obtain and maintain Regulatory Approval for the Licensed Product for the treatment of HAE in the Europe Territory is set forth on SCHEDULE 4.2.2 (such development plan, as it may be modified in accordance with the terms and conditions of this Agreement, the "**Non-Clinical Europe HAE Development Plan**"). From time to time during the Term, either Party may submit to the Europe JSC any proposed update to the Non-Clinical Europe HAE Development Plan to include additional CMC Development or non-clinical Development activities required to obtain or maintain Regulatory Approval for the Licensed Product for the treatment of HAE in the Europe Territory. In addition, each Party shall submit to the Europe JSC reasonably in advance proposed updates to take into account changed circumstances or the need to amend any CMC Development or non-clinical Development activities for the Licensed Product for the treatment of HAE in the Europe Territory. The Europe JSC will review, discuss, and determine whether to approve each update to the Non-Clinical Europe HAE Development Plan. Once reviewed and approved by the Europe JSC (or the Executive Committee, if the Europe JSC cannot agree), each update to the Non-Clinical Europe HAE Development Plan will automatically become effective and supersede the previous Non-Clinical Europe HAE Development Plan as of the date of such approval by the Europe JSC (or Executive Committee).

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(b) **Asia Territory.** If any CMC Development or non-clinical Development is required by a Regulatory Authority in the Asia Territory to obtain and maintain Regulatory Approval for the Licensed Product for the treatment of HAE in the Asia Territory and such Development activities are not set forth in the Non-Clinical Europe HAE Development Plan (such activities, "**Asia-Specific Non-Clinical HAE Development Activities**"), then Otsuka may prepare and submit to the Asia JSC a written plan pursuant to which such Asia-Specific Non-Clinical HAE Development Activities will be conducted (such development plan, as it may be updated in accordance with the terms and conditions of this Agreement, the "**Non-Clinical Asia HAE Development Plan**"). The Asia JSC will review, discuss, and determine whether to approve the Non-Clinical Asia HAE Development Plan. From time to time during the Term, either Party may submit to the Asia JSC any proposed update to the Non-Clinical Asia HAE Development Plan to include additional Asia-Specific Non-Clinical HAE Development Activities and the Asia JSC will review, discuss, and determine whether to approve such update to the Non-Clinical Asia HAE Development Plan. Once reviewed and approved by the Asia JSC (or the Executive Committee, if the Asia JSC cannot agree), the initial Non-Clinical Asia HAE Development Plan and each update thereto will automatically become effective and supersede the previous Non-Clinical Asia HAE Development Plan as of the date of such approval by the Asia JSC (or Executive Committee).

4.3 Otsuka Territory-Specific Development Plans.

4.3.1 **Europe Territory-Specific Development Plan.** Unless otherwise mutually agreed by Advisor the Parties, within [**], then Otsuka will prepare and [onis] CEO submit to the Europe JSC a plan setting forth all Development activities that are intended to support obtaining or maintaining Regulatory Approval for the Licensed Products solely in the Europe Territory other than the activities set forth in the Non-Clinical Europe HAE Development Plan (the "**Europe Territory-Specific Development Plan**"). If such plan is submitted by separate scopes Otsuka, then the Europe JSC will review, discuss, and determine whether to approve the Europe Territory-Specific Development Plan. Notwithstanding the foregoing or anything to the contrary in this Agreement, the Europe Territory-Specific Development Plan (if submitted by Otsuka) will at all times include Development activities that are (i) necessary to obtain and maintain Regulatory Approval for at least one Licensed Product in [**] consistent with Otsuka's obligations under Section 4.1 (Development Diligence Obligations) and (ii) not included in the Cross-Territory Clinical Development Plan or the Non-Clinical Europe HAE Development Plan. For clarity, if no Development activities are necessary to obtain or maintain Regulatory Approval for at least one Licensed Product in [**], other than the Development activities set forth in the Cross-Territory Clinical Development Plan or the Non-Clinical Europe HAE Development Plan, then Otsuka shall not be obligated to prepare or submit to the Europe JSC a Europe Territory-Specific Development Plan for the HAE indication.

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4.3.2 **Asia Territory-Specific Development Plan.** Within [**] following the Restatement Date, Otsuka will prepare and submit to the Asia JSC a plan setting forth all Development activities that are intended to support obtaining or maintaining Regulatory Approval for the Licensed Products solely in the Major Asian Countries, other than the activities set forth in the Non-Clinical Europe HAE Development Plan or, if applicable, the activities set forth in the Non-Clinical Asia HAE Development Plan (the "**Asia Territory-Specific Development Plan**," and together with the Europe Territory-Specific Development Plan (if prepared by Otsuka), the "**Otsuka Territory-Specific Development Plans**"). The Asia JSC will review, discuss, and determine whether to approve the Asia Territory-Specific Development Plan. Notwithstanding the foregoing or anything to the contrary in this Agreement, the Asia Territory-Specific Development Plan will at all times include Development activities that are (a) necessary to obtain and maintain Regulatory Approval [**] consistent with Otsuka's obligations under Section 4.1 (Development Diligence Obligations) and (b) not included in the Cross-Territory Clinical Development Plan or the Non-Clinical HAE Development Plans.

4.3.3 **Consistency with Cross-Territory Clinical Development Plan.** The Europe Territory-Specific Development Plan and the Asia Territory-Specific Development Plan will each, at all times during the Term, be consistent with the then-current Cross-Territory Clinical Development Plan, except to the extent such inconsistency is (a) necessary to conform with any written requirement from any Regulatory Authority or with any Applicable Law (including compliance requirements) in the Europe Territory or the Asia Territory, as applicable, or (b) approved by the applicable JSC (or the Executive Committee, if the applicable JSC cannot agree) (in each case by unanimous Party Vote).

4.3.4 **Updates.** At least [**] during the Term (and more frequently as may be necessary), Otsuka will prepare an update to the Asia Territory-Specific Development Plan and, if applicable, the Europe Territory-Specific Development Plan, to amend or include additional Development activities to be conducted during the [**] Calendar Year that are intended to support obtaining or maintaining Regulatory Approval for the Licensed Products solely in the Europe Territory or Asia Territory, as applicable, other than the activities set forth in the Non-Clinical HAE Development Plans (or otherwise update the Development activities under the applicable Otsuka Territory-Specific Development Plan). The applicable JSC will review, discuss, and determine whether to approve each update to the Europe Territory-Specific Development Plan or the Asia Territory-Specific Development Plan. Once approved by the applicable JSC (or the Executive Committee, if the applicable JSC cannot agree), the Europe Territory-Specific Development Plan and each update thereto or the Asia Territory-Specific Development Plan and each update thereto will automatically become effective and, in the case of work, an update, supersede the previous Europe Territory-Specific Development Plan or Asia Territory-Specific Development Plan, as applicable, as of the date of such approval.

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Duration An initial term beginning on (and including) your last day **Development Costs**.

of
Advisory
Services
(the
"Advisory
Period"):

4.4

4.4.1 Overview.

(a) **Ionis Costs.** Ionis will be [***] responsible for all costs and expenses incurred in connection with the performance of employment the [***]. In addition, Ionis will be [***] responsible for all costs and expenses incurred in connection with the performance of all activities under the [***].

(b) **Otsuka Costs.** Otsuka will be [***] responsible for all costs and expenses incurred in connection with the performance of all activities under the [***]. In addition, Otsuka will reimburse Ionis (for [***]).

(c) **"Start Date" Shared Development Costs.**

(i) Subject to Section 4.4.1(c)(i) (Shared Development Costs), with respect to (A) all Post-Approval Cross-Territory Mandatory Studies for the treatment of HAE that are included in the Cross-Territory Clinical Development Plan as of the Original Effective Date and ending on January 10, 2025 (the "**Scheduled End Date**") (B) any other Post-Approval Cross-Territory Mandatory Studies for the treatment of HAE or any Future Cross-Territory Studies, in each case ((A) and (B)) unless terminated, that are added to the Cross-Territory Clinical Development Plan in accordance with Section 8.4.2.1 (Cross-Territory Clinical Development Plan), the Parties will share, [***], in each case, in accordance with the Cross-Territory Clinical Development Plan and Shared Development Budget (such costs, "**Shared Cross-Territory Development Costs**") in accordance with the terms of Exhibit A below Section 4.4.3 (Shared Cross-Territory Development Costs).

(ii) As if (A) the Parties agree to update the Cross-Territory Clinical Development Plan (including the Shared Development Budget) to include Clinical Trial sites in Japan for any Cross-Territory Clinical Study and (B) the PMDA agrees in advance that such Cross-Territory Clinical Study (including the Clinical Trial sites in Japan) will be sufficient to obtain Regulatory Approval in Japan for use of the Licensed Product without the need for additional Japan-only Clinical Trials, then [***]; provided that, if a Cross-Territory Clinical Study has been initiated as of or after the Original Effective Date and is subsequently amended to include Clinical Trial sites in Japan, then at the time the Parties agree to include Clinical Trial sites in Japan in such Cross-Territory Clinical Study, Ionis will provide to Otsuka a written report of the [***] (the "**Ionis Incurred Development Costs**"). Such written report shall include [***]. Ionis will provide an invoice to Otsuka for [***] of the Ionis Incurred Development Costs, and Otsuka will pay such amount [***] after receipt of such invoice [***]; provided that, if Otsuka disputes any invoiced amount, then Otsuka will pay the undisputed invoiced amount [***] and will pay any disputed amounts [***] following resolution of the dispute and determination that such amounts are owed; and provided, further that Otsuka shall have the right to [***].

Consideration for
Advisory Services:

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4.4.2 Shared Development Budget; Cost Overruns.

(a) **Shared Development Budget.** The current budget for the Shared Cross-Territory Development Costs (such budget as it may be modified in accordance with the terms and conditions of this Agreement, the "**Shared Development Budget**") for the Post-Approval Cross-Territory Mandatory Studies that are included in the Cross-Territory Clinical Development Plan as of the Restatement Date is set forth on SCHEDULE A ATTACHED HERETO. 4.4.2 (Shared Development Budget). With respect to each other Post-Approval Cross-Territory Mandatory Study for the treatment of HAE and each Future Cross-Territory Study that is subject to cost sharing by the Parties in accordance with Section 4.4.1(c) (Shared Development Costs), including any Cross-Territory Clinical Study that the Parties agree will include Clinical Trial sites in Japan, the Europe JSC (or the Executive Committee if the Europe JSC cannot agree) will develop, discuss, and determine whether to approve an update to the Shared Development Budget at the time the Europe JSC (or Executive Committee) reviews, discusses, and determines whether to approve the update to the Cross-Territory Clinical Development Plan applicable to such additional Cross-Territory Clinical Study. Any update to the Shared Development Budget will at all times include a detailed written budget for the performance of all Future Cross-Territory Studies and any additional Post-Approval Cross-Territory Mandatory Studies for the treatment of HAE, in each case, that are included in the Cross-Territory Clinical Development Plan (as updated). From time to time during the Term, either Party may submit to the Europe JSC any proposed update to the Shared Development Budget, including in connection with any update to the Cross-Territory Clinical Development Plan or to address a potential Cost Overrun. The Europe JSC will review, discuss, and determine whether to approve each update to the Shared Development Budget. Once reviewed and approved by the Europe JSC (or the Executive Committee if the Europe JSC cannot agree), each update to the Shared Development Budget will automatically become effective and supersede the previous Shared Development Budget, as of the date of such approval by the Europe JSC (or Executive Committee).

(b) **Advisor commitsCost Overruns.** Ionis (and Otsuka, if the Parties agree to include Clinical Trial sites in Japan in any Cross-Territory Clinical Study as provided in Section 4.4.1(c)(ii) (Shared Development Costs)) [***] for a given Calendar Year [***] for such Calendar Year. Ionis (and Otsuka, if applicable) will notify the Europe JSC (or any other designated Subcommittee) without undue delay if it reasonably anticipates that the Shared Cross-Territory Development Costs incurred by the applicable Party are reasonably likely to exceed the applicable budgeted amounts under the then-current Shared Development Budget by more than [***] (a "**Cost Overrun**"). Ionis (and Otsuka, if applicable) will include [***] and, to the extent reasonably possible, will [***]. Thereafter, the Europe JSC (or other designated Subcommittee) shall promptly hold an average ad-hoc meeting to evaluate whether there are mitigation measures to prevent the Cost Overrun, and if not, the Europe JSC (or other designated Subcommittee) will discuss what steps to take to address such Cost Overrun, including updating the Shared Development Budget or the Cross-Territory Clinical Development Plan, as applicable. If the Europe JSC (or the Executive Committee if the Europe JSC cannot agree) does not approve an update to the Shared Development Budget to reflect the anticipated Cost Overrun, then [***] and, to the extent [***]. For clarity, [***].

Time Provided
by Advisor:

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4.4.3 Shared Cross-Territory Development Costs. The Parties will share, at the [***], all Shared Cross-Territory Development Costs incurred by or on behalf of ten hours Ionis or its Affiliates and by or on behalf of Otsuka or its Affiliates (if the Parties agree to include Clinical Trial sites in Japan in any Cross-Territory Clinical Study as provided in Section 4.4.1(c)(ii) (Shared Development Costs)), in accordance with the Cross-Territory Clinical Development Plan and the amount budgeted therefor in the Shared Development Budget, plus [***] ("Eligible Cross-Territory Development Costs"). No later than [***] after the end of each Calendar Quarter, Ionis will deliver to Otsuka a written report specifying in reasonable detail the Eligible Cross-Territory Development Costs incurred by or on behalf of Ionis during such Calendar Quarter, together with reasonable supporting documentation, and if Clinical Trial sites in Japan are included in any Cross-Territory Clinical Study, Otsuka will deliver to Ionis a written report specifying in reasonable detail the Eligible Cross-Territory Development Costs incurred by or on behalf of Otsuka or its Affiliates during such Calendar Quarter, together with reasonable supporting documentation. Promptly thereafter, Ionis will submit to Otsuka an invoice (and, if there has been any change to a Payment Form previously submitted, or if a previously submitted Payment Form has expired, an updated Payment Form) for Otsuka's unpaid share (at the [***]) of such Eligible Cross-Territory Development Costs (i.e., [***]) or, if applicable, Ionis will submit to Otsuka a statement of Ionis' unpaid share (at the [***]) of such Eligible Cross-Territory Development Costs. No later than [***] after Otsuka's receipt of such invoice (and updated Payment Form, if applicable) for such Calendar Quarter, Otsuka will make a balancing payment to Ionis equal to Otsuka's unpaid share of the total Eligible Cross-Territory Development Costs to effect the [***] for such Eligible Cross-Territory Development Costs (or, if applicable, no later than [***] after Ionis' submission of a statement to Otsuka, Ionis will make a balancing payment to Otsuka equal to Ionis' unpaid share of the total Eligible Cross-Territory Development Costs to effect the [***] for such Eligible Cross-Territory Development Costs); *provided* that, if Otsuka disputes any invoiced amount, then Otsuka will pay the undisputed invoiced amount within such [***] and will pay any disputed amounts within [***] following resolution of the dispute and determination that such amounts are owed.

4.4.4 Future Cross-Territory Studies for [*].**

(a) **Shared Costs.** At any time during the Term, either Party may propose that the Parties clinically Develop a Licensed Product [***]. Such Party will submit a proposal to the Europe JSC setting forth the proposed clinical Development activities in the Europe Territory, Japan, or the Ionis Territory for such [***] and a timeline and budget for such activities (a [***]). The Europe JSC (or the Executive Committee if the Europe JSC cannot agree) will review, discuss, and determine whether to approve such [***], either as proposed or as may be revised by agreement of the Europe JSC (or Executive Committee), within [***] of the submission thereof. If the Europe JSC (or Executive Committee) approves such [***], as proposed or as revised per week through September 30, 2024 the agreement of the Parties, then (i) the Europe JSC (or Executive Committee) will approve an update to the Cross-Territory Clinical Development Plan in accordance with Section 4.2.1 (Cross-Territory Clinical Development Plan) and thereafter to the Shared Development Budget in accordance with Section 4.4.2(a) (Shared Development Budget) to include any Future Cross-Territory Studies in the Europe Territory, Japan, or the Ionis Territory (as applicable) for such [***] and (ii) the Parties will share the cost of any Eligible Cross-Territory Development Costs incurred in connection with the performance of such Future Cross-Territory Studies in accordance with Section 4.4.3 (Shared Cross-Territory Development Costs).

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(b) **[***] by Ionis.** If the Europe JSC (or the Executive Committee if the Europe JSC cannot agree) does not approve a [***] for a given [***] or does not approve an updated Cross-Territory Clinical Development Plan in accordance with Section 4.2.1 (Cross-Territory Clinical Development Plan) or Shared Development Budget in accordance with Section 4.4.2(a) (Shared Development Budget) to include the Future Cross-Territory Studies for such [***], then (i) Ionis will have the right, but not the obligation, to proceed with the Development of such [***] in the Territory as requested contemplated by such [***] with such modifications as Ionis deems appropriate [***] ("Ionis [***]") and such Development will be conducted outside the Cross-Territory Clinical Development Plan; and (ii) notwithstanding the licenses, rights of reference, and other rights granted to Otsuka under this Agreement, Otsuka will not have any license or rights to use any Ionis [***] (including any right of reference to use such Ionis [***] contained in the related Regulatory Submissions by Ionis and notwithstanding the inclusion of any such data in the Ionis Technology) in support of any Regulatory Submissions or Regulatory Approval for the Licensed Product in the Europe Territory or in the Commercialization of such Licensed Product in the Europe Territory, unless and until [***], *provided* that Otsuka may use safety data in connection with such Ionis [***] solely to satisfy any safety-related reporting obligations to Regulatory Authorities related to Licensed Products in the Europe Territory without [***]. For clarity, Ionis [***]. For further clarity, the terms of clause (ii) in this Section 4.4.4(b) ([***] by Ionis) do not apply with respect to exceed an average of five hours per week. [***].

(c) **In addition Otsuka Opt-In.** If Ionis conducts any Ionis [***] pursuant to Section 4.4.4(b) ([***] by Ionis), then Ionis shall provide Development reports to Otsuka related to such compensation, Ionis Pharmaceuticals, Inc. [***] in accordance with Section 4.5 (Development Reports), and Otsuka shall have the right, [***] to opt-in with respect to such Ionis [***] in accordance with this Section 4.4.4(c) (Otsuka Opt-In). Upon Otsuka's written request, Ionis shall provide to Otsuka a written report of the Internal Costs and External Costs, in each case, incurred directly by or on behalf of Ionis or its Affiliates as of the date of such written request in the performance of such Ionis [***] (the "Ionis [***] Costs"). Such written report shall include supporting documentation of the External Costs included within the Ionis [***] Costs. Otsuka shall have the right, exercisable during the [***] period after receipt of such report, to provide notice to Ionis that Otsuka wishes to share the costs of such Ionis [***] ("Opt-In Notice"). Following the receipt of an Opt-In Notice, Ionis shall provide an invoice to Otsuka for [***] of such Ionis [***] ("Opt-In Fee") as follows: [***]. Otsuka shall pay the Opt-In Fee within [***] after receipt of such invoice and supporting documentation; *provided* that, if Otsuka disputes any invoiced amount, then Otsuka will reimburse Advisor for pay the undisputed invoiced amount within such [***] and will pay any disputed amounts within [***] following resolution of the dispute and determination that such amounts are owed. Following Otsuka's payment of the Opt-In Fee, (A) the Ionis approved travel [***] shall be deemed a Future Cross-Territory Study and other out-of-pocket costs will be added to the Cross-Territory Clinical Development Plan, (B) the Parties will share [***] all Internal Costs reasonably incurred and External Costs incurred, in each case, directly by or on behalf of Ionis or its Affiliates in the course performance of performing Advisory Services the Ionis [***] from the date on which Ionis provides a written report of the Ionis [***] Costs, (C) the applicable Ionis [***] shall be included within Ionis Know-How and subject to the licenses in Section 2.1 (License Grants to Otsuka), and (D) the Ionis [***] included in related Regulatory Submissions will be subject to Otsuka's right of use and right of reference provided in Section 5.9 (Right of Reference).

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(d) **Otsuka Use in the Asia Territory.** For clarity, if Ionis Develops the Licensed Product in a [***] in accordance with Section 4.4.4(b) ([***] by Ionis), then (i) Otsuka will have the right, at Otsuka's [***], to Develop, seek Regulatory Approval for, and otherwise Exploit the Licensed Product in such [***] in the Asia Territory in accordance with this Agreement, (ii) the applicable Ionis [***] shall be included within Ionis Know-How and subject to the licenses in Section 2.1 (License Grants to Otsuka) solely to the extent such licenses relate to the Asia Territory, and (iii) the Ionis [***] included in related Regulatory Submissions will be subject to Otsuka's right of use and right of reference provided in Section 5.9 (Right of Reference) solely in the Asia Territory, in each case, regardless of whether Otsuka has opted in to Ionis [***] in accordance with Section 4.4.4(c) (Otsuka Opt-In). For further clarity, if the Parties agree (through the Europe JSC or the Executive Committee) on a [***] that includes Clinical Trial sites in Japan, the last sentence of Section 4.4.4(a) (Shared Costs) shall apply and Otsuka will share the applicable Eligible Cross-Territory Development Costs in accordance with Section 4.4.3 (Shared Cross-Territory Development Costs).

4.5 Development Reports. At each meeting of the Europe JSC or Asia JSC, as applicable, Ionis and Otsuka will each provide (a) the Europe JSC with (i) a written summary of the activities conducted by or on behalf of such Party under the Cross-Territory Clinical Development Plan, and with respect to Ionis, [***], in each case ((a) and (b)), since the last Europe JSC meeting or Asia JSC meeting, as applicable, including patient enrollment, the ongoing status, and material results of all Clinical Trials for the Licensed Products conducted by or on behalf of such Party. Each Party will also promptly provide written notice to the other Party and keep the other Party reasonably informed, (A) through the Europe JSC or Alliance Managers, of (i) any significant Development events under the Cross-Territory Clinical Development Plan, and with respect to Ionis, any additional Development activities conducted by or on behalf of Ionis or any of its Affiliates for the Licensed Product that are not set forth in the Cross-Territory Clinical Development Plan or the Non-Clinical HAE Development Plans, and (ii) any significant Development events under the Non-Clinical Europe HAE Development Plan or the Europe Territory-Specific Development Plan and (B) through the Asia JSC or Alliance Managers, of any significant Development events under the Non-Clinical Asia HAE Development Plan and Asia Territory-Specific Development Plan, in each case ((A) and (B)), that [***] the Development activities of the other Party under this Agreement.

Advisor agrees to provide Ionis with Advisory Services on the terms described above and according to the additional terms attached hereto as Exhibit A.

Advisor	Ionis Pharmaceuticals, Inc.
By (Signature):	
4.6	/s/ Onaiza Cadoret-Manier
Date:	February 27, 2024
Printed Name:	Onaiza Cadoret-Manier
Title:	Individual
Address:	Provided Separately
Telephone:	Provided Separately
Fax:	Provided Separately
e-mail:	Provided Separately
Social Security or Employer Tax ID Number to be provided separately via W-9 form or foreign equivalent.	

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EXHIBIT A

TERMS OF ADVISORY AGREEMENT

1. Engagement of Services; Transition to Advisor

Advisor is retained to perform certain services during the Advisory Period, as needed **Development Records; Cooperation.** Each Party and its Affiliates will maintain written or electronic records, in sufficient detail, in a good scientific manner, in accordance with Applicable Law (including GLP, GCP, and GMP, as applicable), and appropriate for regulatory and patent purposes, and requested by Ionis, which services will be more specifically described in separate scopes of work ("**Advisory Services**"). Advisor will perform such Advisory Services to the best of Advisor's talent and ability.

It is the intent of the parties that Advisor seamlessly and without interruption of service transition from being an executive level employee of Ionis to a strategic advisor for Ionis in accordance with this Agreement.

2. Compensation

As full and complete compensation for Advisory Services and for the discharge of all of Advisor's obligations hereunder, Ionis will pay Advisor at the rate set forth on Schedule A attached hereto. Advisor will invoice Ionis on a quarterly basis for Advisor fees and reimbursable expenses, and Ionis, upon its approval, will pay all undisputed fees and expenses within 30 days after Ionis' receipt of the invoice.

3. Independent Contractor

Advisor is an independent contractor and not an employee of Ionis. Advisor has no authority to obligate Ionis by contract or otherwise. Taxes will be the sole responsibility of Advisor.

4. Additional Activities

(a) Advisor agrees that during are complete and accurate and reflect all Development work performed and results achieved, in each case, by or on behalf of such Party and its Affiliates under, as applicable, the Advisory Period Cross-Territory Clinical Development Plan, the Non-Clinical HAE Development Plans, and the Otsuka Territory-Specific Development Plans, and with respect to Ionis, [***]. Each Party shall retain such records for one year thereafter, Advisor at least three years after the end of the Term or for such longer period as may be required by Applicable Law. The Parties will not attempt cooperate with each other to induce any employee or employees of Ionis to terminate their employment with, or otherwise cease their relationship with Ionis. achieve the Development objectives contemplated herein in a timely, accurate, and responsive manner. Without limiting the foregoing, [***].

(b) Advisor acknowledges that Ionis has developed, through an extensive acquisition process, valuable information regarding actual or prospective partners, licensors, licensees, clients, customers and accounts of Ionis ("Trade Secret Information"). Advisor acknowledges that Advisor's use of such Trade Secret Information after the termination of the Advisory Period would cause Ionis irreparable harm. Therefore, Advisor also agrees that Advisor will not utilize any Trade Secret Information to solicit the business relationship or patronage of any of the actual or prospective partners, licensors, licensees, clients, customers or accounts of Ionis.

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(c) 4.7 **Data Transfer.** Upon Otsuka's reasonable request, Ionis shall provide to Otsuka, [***] notwithstanding the terms of Section 3.2 (Technology Transfer Costs), true and complete copies of all written, graphic or electronic embodiments of non-clinical data and clinical data generated by or on behalf of Ionis or any of its Affiliates in connection with the Development of Licensed Products, including all draft and final protocols and final study reports and raw data, in each case, to the extent such data is (a) Controlled by Ionis or its Affiliates and (b) [***] to Exploit a Licensed Product. In addition, and without limiting the foregoing, promptly following the Restatement Date, Ionis shall provide to Otsuka, [***] notwithstanding the terms of Section 3.2 (Technology Transfer Costs), electronic datasets from all Clinical Trials of the Licensed Products, in either the Clinical Data Interchange Standards Consortium (CDISC) standards format or in legacy format (as requested by Otsuka), together with related documents, for use in obtaining Regulatory Approvals of the Licensed Products in the Asia Territory. [***].

ARTICLE 5 REGULATORY AFFAIRS

5.1 **Regulatory Responsible Party.** Ionis will be the Regulatory Responsible Party for the Licensed Products in the Ionis Territory. Otsuka will be the Regulatory Responsible Party for the Licensed Products in the Otsuka Territory, *provided that*, Ionis shall have the right to conduct regulatory activities in the Otsuka Territory, including interacting with Regulatory Authorities, solely with respect to (a) the Development activities for the Licensed Products in the Europe Territory for which Ionis is responsible under the Cross-Territory Clinical Development Plan and the Development activities in the Europe Territory and, if applicable, the Asia Territory under the Non-Clinical HAE Development Plans and (b) the Manufacturing activities for the Licensed Products for which Ionis is responsible in accordance with Article 7 (Manufacturing), in each case subject to the remainder of this Article 5 (Regulatory Affairs) ("Ionis Regulatory Activities"). Subject to the obligations in this Article 5 (Regulatory Affairs), the Regulatory Responsible Party will be responsible for, and [***] all Regulatory Submissions, communications, and other dealings with the Regulatory Authorities relating to the Licensed Products in the applicable Territory, and for seeking and maintaining all Regulatory Approvals with respect to the Licensed Product in the applicable Territory. The restrictions Regulatory Responsible Party will not be required to delay any submission, correspondence, or communication with any Regulatory Authorities in a manner that affects such Regulatory Responsible Party's ability to comply with any Regulatory Authority requirement or deadline or Applicable Law in such jurisdiction. For clarity, Otsuka or its designee shall be the holder of all Regulatory Approvals for the Licensed Product in the Otsuka Territory and will own all Regulatory Submissions in the Otsuka Territory, and Ionis or its designee shall be the holder of all Regulatory Approvals for the Licensed Product in the Ionis Territory and will own all Regulatory Submissions in the Ionis Territory. Otsuka will only [***] and will not [***].

5.2 **Europe Regulatory Subcommittee.** The Parties have established a Subcommittee of the Europe JSC to (a) oversee the preparation and submission of any MAA for a Licensed Product in the Europe Territory and (b) coordinate the regulatory responsibilities between the Parties in the Europe Territory, which allocation will be consistent with this Article 5 (Regulatory Affairs) (such Subcommittee, the "Europe Regulatory Subcommittee"). The Europe Regulatory Subcommittee will review and comment on any proposed MAA application for a Licensed Product in the Europe Territory sufficiently in advance of the filing or submission thereof by Otsuka, and Otsuka will [***] any comments received from the Europe Regulatory Subcommittee. The Europe Regulatory Subcommittee will meet as often as necessary to carry out the activities described in this Section 5.2 (Europe Regulatory Subcommittee) and the terms of Section 8.3 (Subcommittees) will apply to the Europe Regulatory Subcommittee.

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5.3 **Correspondences with Regulatory Authorities.** Otsuka shall be solely responsible for communications with Regulatory Authorities in the Otsuka Territory regarding the Licensed Product and in no event will [***] regarding the Licensed Product in the Otsuka Territory, except in connection with [***], and subject to the remainder of this Section 5.3 (Correspondences with Regulatory Authorities). Ionis will [***]. In addition, Ionis will [***]. Furthermore, upon Otsuka's reasonable request and at [***], Ionis will [***]. The Regulatory Responsible Party will provide the other Party with (a) copies of any material written correspondence submitted to or received from (i) with respect to Otsuka, the EMA, PMDA, or any other Regulatory Authority in the Europe Territory or [***], and (ii) with respect to Ionis, the FDA or any other Regulatory Authority in the U.S., and (b) summaries of any material oral communications with such Regulatory Authority in clause (a), in each case ((a) and (b)), relating to Regulatory Submissions in support of Development of the Licensed Products in such jurisdiction or country, reasonably promptly after receipt or delivery by such Regulatory Responsible Party of such correspondence or communication, as the case may be (but in any event, no later than [***] after receipt or delivery).

5.4 **Regulatory Meetings.** Ionis will [***] meetings pertaining to Regulatory Submissions for the Licensed Products relating to the Ionis Regulatory Activities [***] in the Otsuka Territory to the extent not prohibited by Applicable Law or the applicable Regulatory Authority. At Otsuka's request, Ionis will [***]. With respect to all other meetings with any Regulatory Authority in the Europe Territory or [***] in support of Development of the Licensed Products, (a) Ionis will have the right, but not the obligation, [***] to attend such meetings [***] and (b) at Otsuka's reasonable request, Ionis will [***] and Otsuka will [***]. Further, Ionis will [***], unless Ionis reasonably believes that [***], and will not [***] except as (i) required by Applicable Law, (ii) permitted pursuant to Section 12.4.1(b) (Permitted Circumstances) or Section 12.4.1(c) (Permitted Circumstances), or (iii) authorized by Otsuka in writing. For clarity, the terms of this Section 5.4 (Regulatory Meetings) will apply solely with respect to any meetings with any Regulatory Authority in the Europe Territory or [***] in support of Development of the Licensed Products and do not apply to any other meetings with Regulatory Authorities in the Otsuka Territory, including any meetings pertaining to [***].

5.5 Regulatory Submissions. Each Party (the “*Filing Party*”) will provide the other Party with a copy of [***] (including, [***]) that the Filing Party intends to file with or submit to any Regulatory Authority in support of Development in the Otsuka Territory for the other Party’s review and comment sufficiently in advance of the Filing Party’s filing or submission thereof; *provided* that, as it relates to the Asia Territory, Otsuka (a) will [***], (b) will [***], and (c) will [***]. The Filing Party will [***] any reasonable comments received from the other Party into such Regulatory Submissions. In addition and notwithstanding Section 3.2 (Technology Transfer Costs), Ionis will provide to Otsuka, [***].

5.6 Cooperation. The Parties will cooperate with each other to achieve the regulatory objectives contemplated herein in a timely, accurate, and responsive manner. Without limiting the foregoing or the terms of Section 5.5 (Regulatory Submissions), at Otsuka’s reasonable request, Ionis will [***] of the Licensed Products in the Otsuka Territory or for obtaining and maintaining Regulatory Approval of the Licensed Products in the Otsuka Territory. Without limiting the foregoing, if requested by any Regulatory Authority in the Asia Territory or [***] for obtaining Regulatory Approvals in the Asia Territory, Ionis will provide to Otsuka (to the extent not prohibited by confidentiality obligations to a Third Party) or directly to the applicable Regulatory Authority (to the extent confidentiality obligations to a Third Party prohibit disclosure to Otsuka but permit disclosure to such Regulatory Authority) reports and other documents related to other antisense oligonucleotide compounds or products (other than the Licensed Products) being developed by Ionis or any of its Affiliates or Third Party licensees. If Otsuka receives any inquiry from a Regulatory Authority in the Otsuka Territory pertaining to any activities for which Ionis is responsible hereunder (including Cross-Territory Clinical Studies, non-clinical or CMC Development or Manufacturing (prior to the applicable Manufacturing Handover Date)), then notwithstanding Section 3.2 (Technology Transfer Costs), upon Otsuka’s request, Ionis will, [***]. In addition, upon Otsuka’s reasonable request, Ionis shall provide [***] in the Otsuka Territory (“**Regulatory Support**”). With respect to the Asia Territory, Regulatory Support includes, and [***] Ionis shall provide, [***]. Ionis will provide all Regulatory Support [***] (i) with respect to Regulatory Support related to the Europe Territory, until [***] and (ii) with respect to Regulatory Support related to the Asia Territory, until [***]. Thereafter, (A) [***], Ionis will [***], and [***], Ionis will [***] and (B) [***], Ionis will [***], and [***], Ionis will [***]. At all times, Otsuka will [***]. Ionis may [***] for such (1) [***], and (2) [***] and, in each case ((1) and (2)), [***] (and, with respect to [***]) therefor [***]. [***]. For clarity, if Otsuka requests Regulatory Support in connection with [***], Ionis shall provide such Regulatory Support [***], and Otsuka [***]. Notwithstanding any provision to the contrary, this Section 5.6 (Cooperation) will not require Ionis to conduct any additional Clinical Trials or generate any additional data or information that is not expressly contemplated by the Cross-Territory Clinical Development Plan or Non-Clinical HAE Development Plans.

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5.7 Cost of Regulatory Activities. Except to the extent specified otherwise in this Article 5 (Regulatory Affairs), each Party will be responsible for all costs and expenses incurred in connection with its activities under this Article 5 (Regulatory Affairs), including the preparation or maintenance of Regulatory Submissions and Regulatory Approvals with respect to the Licensed Products for which it is responsible, including any filing fees and, with respect to Ionis, including all costs and expenses of Ionis Regulatory Activities and all costs and expenses related to the ASMF (if filed) and other regulatory affairs related to Manufacturing of Licensed Products, which in each case will be borne solely by Ionis.

5.8 No Harmful Actions. If [***], then such first Party will have the right to bring such matter to the attention of the JSCs at a joint meeting (or the applicable JSC if such matter pertains only to the Europe Territory or the Asia Territory) and the Parties will discuss in good faith to resolve such concern. Without limiting the foregoing and notwithstanding any provision to the contrary in this Agreement, Otsuka will not [***].

5.9 Right of Reference. Subject to the rules of the relevant Regulatory Authority and the terms of this Agreement, including Section 4.4.4(b) ([***] by Ionis), each Party hereby grants to the other Party a “Right of Reference,” as that term is defined in 21 C.F.R. § 314.3(b) (or any successor rule or analogous Applicable Law recognized outside of the United States) to, and a right to copy, access, and otherwise use, all information and data relating to the Licensed Products in any Regulatory Submission or Regulatory Approval Controlled by the grantor Party during the Term (including, with respect to the grant to Otsuka, a right of reference to Ionis’ Drug Master File and ASMF, if filed), solely for the other Party’s or its Affiliates’ use in the Development or Commercialization of the Licensed Products in the other Party’s Territory in accordance with this Agreement. All such information and data contained in any such Regulatory Submissions or Regulatory Approvals will be considered Confidential Information of the grantor Party and subject to the terms of Article 12 (Confidentiality). If requested by the grantee Party, the grantor Party will provide a signed statement to this effect in accordance with 21 C.F.R. § 314.50(g)(3) (or any successor rule or analogous Applicable Law outside of the United States) to give effect to the intent of this Section 5.9 (Right of Reference).

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5.10 Pharmacovigilance; Safety Information. Each Party will cooperate with the other Party, at no cost to the other Party (notwithstanding Section 3.2 (Technology Transfer Costs)), with regard to the reporting and handling of safety information involving the Licensed Products in accordance with Applicable Law, regulatory requirements, and regulations on pharmacovigilance and clinical safety. Otsuka will be responsible for all processing of information related to any adverse events for the Licensed Products in the Otsuka Territory and Ionis will be responsible for all processing of information related to any adverse events for the Licensed Products in the Ionis Territory, in each case, including any information regarding such adverse events that is received from a Third Party. Each Party will provide to the other Party in a timely manner the relevant safety information it receives (either directly or indirectly) related to the Licensed Products. At an appropriate time as agreed upon by the Parties following the Restatement Date, but in any event prior to the [***], the Parties will negotiate in good faith and enter into a Pharmacovigilance Agreement related to the Licensed Products, which will define the pharmacovigilance responsibilities of the Parties and include safety data exchange procedures governing the exchange of information affecting the class and products (e.g., Serious Adverse Events, emerging safety issues) to enable each Party to comply with all of its legal and regulatory obligations related to such Licensed Product. Prior to the execution of the Pharmacovigilance Agreement, each Party will have the right, upon reasonable notice to the other Party, to [***]. Ionis will own and maintain the global safety database for the Licensed Products at [***], *provided* that at Otsuka’s reasonable request, Ionis will run queries of such global safety database and will provide copies of the data contained in such global safety database to the extent necessary or reasonably useful to the Development and Commercialization of the Licensed Product in the Otsuka Territory. As part of the negotiation of the Pharmacovigilance Agreement, the Parties will [***], taking into account that Ionis will own and maintain the global safety database, and the Parties’ determination of such matter will be set forth in the Pharmacovigilance Agreement. Subject to compliance with Applicable Law, each Party hereby agrees to comply with its respective obligations under the Pharmacovigilance Agreement as the Parties may agree to modify it from time to time, and to cause its (sub)licensees to comply with such obligations. If there is a conflict between the terms and conditions of this Agreement and any terms and conditions of the Pharmacovigilance Agreement, then the terms and conditions of the Pharmacovigilance Agreement will govern with respect to any pharmacovigilance matters and this Agreement will govern with respect to any other matters.

5.11 Pharmacovigilance Subcommittee. As of the Restatement Date, the Parties have established a joint pharmacovigilance subcommittee (the “**PV Subcommittee**”) that will be a Subcommittee of the Executive Committee. In addition to any other matters that the Executive Committee or JSCs may delegate to the PV Subcommittee, the PV Subcommittee shall provide a forum for the Parties to discuss, share information, and escalate and attempt to resolve safety issues regarding the Licensed Product, and any other pharmacovigilance matters, worldwide. The PV Subcommittee will meet as often as necessary to carry out such activities, and the terms of Section 8.3 (Subcommittees) will apply to the PV Subcommittee.

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5.12 Ionis Internal Oligonucleotide Safety Database.

5.12.1 Ionis maintains an internal database that includes information regarding the tolerability of its drug compounds, individually and as a class, including information discovered during non-clinical and clinical Development (the “**Ionis Internal Oligonucleotide Safety Database**”). To maximize understanding of the safety profile and pharmacokinetics of Ionis’ compounds, (a) Ionis will have the right to use any safety-related information provided by Otsuka pursuant to the Pharmacovigilance Agreement or this Section 5.12 (Ionis Internal Oligonucleotide Safety Database) to maintain the Ionis Internal Oligonucleotide Safety Database and (b) Otsuka will cooperate, at no cost to Ionis, with Ionis’ reasonable requests in connection with populating the Ionis Internal Oligonucleotide Safety Database, including by providing Ionis with reasonably requested safety-related supporting data and answering any follow-up questions reasonably requested by Ionis or its Affiliates in connection with any information provided under the Pharmacovigilance Agreement, in each case to the extent such data and answers are reasonably available to Otsuka. In addition, with respect to Clinical Trials of the Licensed Products conducted by or on behalf of Otsuka pursuant to the Otsuka Territory-Specific Development Plans, Otsuka will provide Ionis with copies of annual safety updates filed with each IND and the safety sections of any final Clinical Trial reports within [***] following the date such information is filed, as applicable. All such information disclosed by Otsuka to Ionis will be Otsuka Confidential Information; *provided, however*, that so long as Ionis does not disclose the identity of a Licensed Product or Otsuka’s identity, Ionis may disclose any such Otsuka Confidential Information to (i) Ionis’ other partners if such information is regarding class generic properties of oligonucleotides, (ii) any Third Party that contributes to the populating of the Ionis Internal Oligonucleotide Safety Database, or (iii) any Regulatory Authority. Otsuka will also cause its Affiliates and Sublicensees to comply with this Section 5.12 (Ionis Internal Oligonucleotide Safety Database).

5.12.2 From time to time, Ionis utilizes the information in the Ionis Internal Oligonucleotide Safety Database to conduct analyses to keep Ionis and its partners informed regarding class generic properties of oligonucleotides, including with respect to safety. As such, if and when Ionis identifies safety or other related issues that may be relevant to a Licensed Product (including any potential class-related toxicity), Ionis will promptly inform Otsuka of such issues and provide the data supporting Ionis’ conclusions.

5.13 Recall, Withdrawal, or Field Alerts.

5.13.1 **Notification and Determination.** Each Party will notify the other Party immediately, and promptly confirm such notice in writing, if it obtains information indicating that any Licensed Product may be subject to a recall (whether voluntary or mandated), corrective action, or similar regulatory action by any Governmental Authority or Regulatory Authority (a “**Remedial Action**”). The Parties will assist each other in gathering and evaluating such information as is necessary to determine the necessity of conducting a Remedial Action with respect to the applicable Territory, and otherwise reasonably cooperate with each other with respect to such Remedial Action or potential Remedial Action. Ionis will have sole discretion and final decision-making authority with respect to, and control over, any Remedial Action in the Ionis Territory, including any decision to commence such Remedial Action in the Ionis Territory. Otsuka will have sole discretion and final decision-making authority with respect to, and control over, any Remedial Action in the Otsuka Territory, including any decision to commence such Remedial Action in the Otsuka Territory; *provided that* if Ionis notifies Otsuka of [***] that Ionis reasonably believes could give rise to a Remedial Action in the Otsuka Territory (or applicable Region), then Otsuka will initiate such Remedial Action in accordance with Ionis’ request and at [***].

5.13.2 **Cost Allocation.** Except as otherwise set forth in Section 5.13.1 (Notification and Determination), all costs directly associated with implementing a Remedial Action with respect to a Licensed Product will be allocated between Ionis and Otsuka as follows:

(a) If, and to the extent, that the Remedial Action arises as a result of [***], then [***] will bear all such costs and expenses; and

(b) in all other cases, Ionis will be responsible for such costs and expenses for such Licensed Product in the Ionis Territory and Otsuka will be responsible for such costs and expenses for such Licensed Product in the Otsuka Territory.

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ARTICLE 6
COMMERCIALIZATION AND MEDICAL AFFAIRS

6.1 Commercialization Responsibilities for Licensed Product.

6.1.1 **Commercialization in the Ionis Territory.** Subject to the last sentence of Section 6.4.1 (Global Brand Strategy and American Commercialization Operating Plan) and the last sentence of Section 6.6.1 (Global Medical Affairs Strategy and American Medical Affairs Operating Plan), and without limiting Ionis’ obligations under this Article 6 (Commercialization and Medical Affairs), Ionis and its Affiliates will have [***] with respect to the Commercialization of the Licensed Products in the Ionis Territory, including, if applicable, [***].

6.1.2 **Commercialization in the Otsuka Territory.** Subject to the terms and conditions of this Agreement, and without limiting Otsuka’s obligations under this Article 6 (Commercialization and Medical Affairs), Otsuka and its Affiliates will have [***] with respect to the Commercialization of the Licensed Products in the Otsuka Territory, including [***]. Upon Otsuka’s reasonable request, Ionis shall [***], including [***], and Ionis will [***].

6.1.3 **Coordination of Commercialization Activities.** The Parties will coordinate global Commercialization activities with respect to Commercialization of the Licensed Products in each Party’s Territory through the JSCs, as further set forth in Section 8.2 (Joint Steering Committees) and this Article 6 (Commercialization and Medical Affairs).

6.2 Commercialization and Medical Affairs Reporting. At each Europe JSC meeting following the first Regulatory Approval for a Licensed Product in the Europe Territory and at each Asia JSC meeting following the first Regulatory Approval for a Licensed Product in [***], Otsuka will provide to the applicable JSC a high-level summary (which may be in the form of a slide presentation) of the material Commercialization and Medical Affairs activities conducted by Otsuka or its Affiliates or Sublicensees for the Licensed Products in the Europe Territory or [***], as applicable, during the period since the last applicable JSC meeting and the material Commercialization and Medical Affairs activities expected to be conducted by Otsuka or its Affiliates, or Sublicensees in the Europe Territory or [***], as applicable, for the Licensed Products during the period from the date of such update until the next applicable JSC meeting, and shall answer any reasonable questions asked by Ionis to enable Ionis to assess Otsuka's compliance with its Commercialization diligence obligations set forth in [Section 6.5](#) (Otsuka Commercialization Diligence Obligations). In addition, no later than [***], Otsuka will provide to the Europe JSC or the Asia JSC, as applicable, a report of the forecasted Net Sales anticipated to be generated by Otsuka or its Affiliates, licensees, or Sublicensees in the Europe Territory or [***], as applicable, during the upcoming Calendar Year, which forecast will be broken down on a country-by-country basis. At each Europe JSC meeting following the first Regulatory Approval for a Licensed Product in the Ionis Territory, Ionis will provide to the Europe JSC a high-level summary (which may be in the form of a slide presentation) of the material Commercialization and Medical Affairs activities conducted by Ionis or its Affiliates for the Licensed Products in the Ionis Territory during the period since the last Europe JSC meeting and the material Commercialization and Medical Affairs activities expected to be conducted by Ionis or its Affiliates in the Ionis Territory for the Licensed Products during the period from the date of such update until the next Europe JSC meeting. Without limiting the foregoing, at Otsuka's reasonable request, Ionis will provide to Otsuka, [***], all information relating to the [***]. In addition, Otsuka will [***].

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6.3 Pricing. All decisions for the Licensed Products related to list price, targeted net pricing, sales-weighted average discounts and rebates, pricing strategy (including the approach to pricing with different types of accounts and plans, including types of discounts and rebates), and modifications to any of the foregoing, will be made by (a) Ionis in the Ionis Territory and (b) Otsuka in the Otsuka Territory; *provided* that, [***].

6.4 Brand Strategy and Operating Plans.

6.4.1 Global Brand Strategy and American Commercialization Operating Plan. Prior to the Restatement Date, Ionis developed and [***], a global brand strategy for the Commercialization of the Licensed Products throughout the Territory (the "**Global Brand Strategy**") and an operating plan with respect to Commercialization activities in the U.S. (the "**American Commercialization Operating Plan**"). The Global Brand Strategy and the American Commercialization Operating Plan shall at all times conform to applicable Professional Requirements and Applicable Law (including compliance requirements). Ionis, through the Europe JSC, will update the Global Brand Strategy and the American Commercialization Operating Plan [***]. In addition, [***], either Party may propose material updates or modifications to the Global Brand Strategy and Ionis may propose material updates to the American Commercialization Operating Plan to [***]. No update or modification to the Global Brand Strategy or to the American Commercialization Operating Plan will be effective unless and until [***]. Once [***], such updated version of the Global Brand Strategy or the American Commercialization Operating Plan will automatically become effective and replace the then-prior version of the Global Brand Strategy or the American Commercialization Operating Plan, as applicable. The Global Brand Strategy will include, in reasonable detail, the Trademarks to be used by the Parties or its Affiliates or its or their Sublicensees for the Commercialization of Licensed Product, trade dress, positioning, market access strategy, and marketing strategic imperatives, objectives and messaging with respect to the Licensed Products. At Otsuka's reasonable request, Ionis will provide to Otsuka, [***]. Ionis will, [***], lead and conduct all Commercialization activities for the Licensed Products in the Ionis Territory [***].

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6.4.2 Otsuka Territory Brand Strategy and Commercialization Operating Plans. Within [***] after the date [***] approves the initial Global Brand Strategy and the initial American Commercialization Operating Plan, Otsuka will prepare and submit to [***] a brand strategy for the Commercialization of the Licensed Products in the Europe Territory (the "**Europe Territory Brand Strategy**") and an operating plan with respect to the Commercialization of the Licensed Products in the Europe Territory (the "**Europe Territory Commercialization Operating Plan**"). If Otsuka's brand strategy for the Commercialization of the Licensed Products in any country in the Asia Territory will be materially inconsistent with the Global Brand Strategy, then, [***], Otsuka will prepare and submit to [***] a brand strategy for the Commercialization of the Licensed Products in such country in the Asia Territory (the "**Asia Territory Brand Strategy**," and together with the Europe Territory Brand Strategy, the "**Otsuka Territory Brand Strategy**"). For clarity, Otsuka shall not be required to prepare or submit to [***] any brand strategy with respect to the Commercialization of the Licensed Products in any country in the Asia Territory unless such strategy for such country is materially inconsistent with the Global Brand Strategy. [***], Otsuka will prepare and submit to [***] an operating plan with respect to the Commercialization of the Licensed Products in [***] (each such plan for [***], the "**Asia Territory Commercialization Operating Plan**," and together with the Europe Territory Commercialization Operating Plan, the "**Otsuka Territory Commercialization Operating Plans**"). [***] will review, discuss, and determine whether to approve the initial Europe Territory Brand Strategy and the initial Europe Territory Commercialization Operating Plan and [***] will review, discuss, and determine whether to approve each initial Asia Territory Brand Strategy (if any) and each initial Asia Territory Commercialization Operating Plan. Each Otsuka Territory Brand Strategy will, at all times during the Term, be consistent with the then-current Global Brand Strategy, except to the extent such inconsistency is (i) necessary to (A) conform with any written requirement from any Regulatory Authority or with any Applicable Law or Professional Requirements in the Europe Territory or the Asia Territory, as applicable, or (B) avoid infringement of a Third Party Trademark in the Europe Territory or Asia Territory, as applicable, or (ii) approved by the applicable JSC or Executive Committee (by unanimous Party Vote). On [***] during the Term (and more frequently as may be necessary), Otsuka will prepare an update to each Otsuka Territory Brand Strategy and each Otsuka Territory Commercialization Operating Plan. [***] will review, discuss, and determine whether to approve each update to the Europe Territory Brand Strategy and each update to the Europe Territory Commercialization Operating Plan and [***] will review, discuss, and determine whether to approve each update to each Asia Territory Brand Strategy and each update to each Asia Territory Commercialization Operating Plan. Once approved by [***], the applicable Otsuka Territory Brand Strategy and the applicable Otsuka Territory Commercialization Operating Plan will automatically become effective and, in the case of an update, will supersede the applicable previous Otsuka Territory Brand Strategy and the applicable previous Otsuka Territory Commercialization Operating Plan as of the date of such approval by [***]. Otsuka will, at its cost and expense, lead and conduct all Commercialization activities in the Otsuka Territory [***].

6.5 Otsuka Commercialization Diligence Obligations. On a country-by-country basis in the Otsuka Territory, following [***], Otsuka will use Commercially Reasonable Efforts to obtain Reimbursement Approval for and otherwise Commercialize such Licensed Product in such country.

6.6 Medical Affairs Plans.

6.6.1 **Global Medical Affairs Strategy and American Medical Affairs Operating Plan.** Prior to the Restatement Date, Ionis developed and [***], a plan for the global Medical Affairs activities for the Licensed Products throughout the Territory (the “**Global Medical Affairs Strategy**”) and an operating plan with respect to Medical Affairs activities in the U.S. (the “**American Medical Affairs Operating Plan**”). The Global Medical Affairs Strategy and the American Medical Affairs Operating Plan shall at all times conform to applicable Professional Requirements and Applicable Law (including compliance requirements) with adjustments with respect to the Global Medical Affairs Strategy as necessary to comply with local Applicable Law and Professional Requirements in the Otsuka Territory. Ionis, through the Europe JSC, will update the Global Medical Affairs Strategy and the American Commercialization Operating Plan on [***] basis. In addition, between [***] updates, either Party may propose material updates or modifications to the Global Medical Affairs Strategy and Ionis may propose material updates or modifications to the American Medical Affairs Operating Plan [***]. No update or modification to the Global Medical Affairs Strategy or the American Medical Affairs Operating Plan will be effective unless and until approved by [***]. Once approved by [***], such updated version of the Global Medical Affairs Strategy or the American Medical Affairs Operating Plan will become effective and replace the then-prior version of the Global Medical Affairs Strategy or American Medical Affairs Operating Plan. Ionis will, at its cost and expense, lead and conduct all Medical Affairs activities for the Licensed Products in the Ionis Territory [***].

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6.6.2 **Otsuka Territory Medical Affairs Plans.** Within [***] after the date [***] approves the initial Global Medical Affairs Strategy and the initial American Medical Affairs Operating Plan, Otsuka will prepare and submit to [***] a plan for the Medical Affairs activities for the Licensed Products in the Europe Territory (such plan, the “**Europe Territory Medical Affairs Plan**”). [***], Otsuka will prepare and submit to [***] a plan for the Medical Affairs activities for the Licensed Products in [***] (each such plan for [***], the “**Asia Territory Medical Affairs Plan**,” and together with the Europe Territory Medical Affairs Plan, the “**Otsuka Territory Medical Affairs Plans**”). [***] will review, discuss, and determine whether to approve the initial Europe Territory Medical Affairs Plan and [***] will review, discuss, and determine whether to approve the initial Asia Territory Medical Affairs Plan. Each Otsuka Territory Medical Affairs Plan will, at all times during the Term, be consistent with the then-current Global Medical Affairs Strategy, except to the extent such inconsistency is (i) necessary to conform with any written requirement from any Regulatory Authority or with any Applicable Law or Professional Requirements in the Europe Territory or the Asia Territory, as applicable, or (ii) approved by the applicable JSC or Executive Committee (by unanimous Party Vote). On [***] during the Term (and more frequently as may be necessary), Otsuka will prepare an update to each Otsuka Territory Medical Affairs Plan. [***] will review, discuss, and determine whether to approve each update to the Europe Territory Medical Affairs Plan and [***] will review, discuss, and determine whether to approve each update to the Asia Territory Medical Affairs Plan. Once approved by [***], the applicable Otsuka Territory Medical Affairs Plan will automatically become effective and, in the case of an update, supersede the previous Otsuka Territory Medical Affairs Plan as of the date of such approval by [***]. Otsuka will, at its cost and expense, lead and conduct all Medical Affairs activities in the Otsuka Territory [***].

6.7 **Standards of Conduct; Compliance.** Each Party will perform, or will ensure that each of its Affiliates, Sublicensees, and Subcontractors perform, all Commercialization and Medical Affairs activities in a professional and ethical business manner and in compliance with Applicable Law and applicable Professional Requirements.

6.8 **Product Materials.** Each Party will, at its cost and expense, be responsible for preparing, developing, producing, or otherwise obtaining, and utilizing promotional materials, training materials, medical education materials, Packaging and Labeling, and all other literature or other information related to the Licensed Products (“**Product Materials**”) to support its Commercialization and Medical Affairs activities in such Party’s Territory, which Product Materials will at all times [***]. From time to time, and in any event upon Otsuka’s request, Ionis will share with Otsuka samples of Product Materials Controlled by Ionis and which are used by Ionis, its Affiliates, or licensees in connection with the Commercialization of or conduct of Medical Affairs activities for the Licensed Products. From time to time, and in any event upon Ionis’ request, Otsuka will share with Ionis samples of Product Materials Controlled by Otsuka and which are used by Otsuka, its Affiliates or sublicensees in connection with the Commercialization of or conduct of Medical Affairs activities the Licensed Products in the Otsuka Territory.

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6.9 **Diversion.** Neither Party nor its Affiliates will, and each Party will take reasonable measures to ensure that its Sublicensees, licensees, and Subcontractors do not, either directly or to such Party’s knowledge, intentionally indirectly, promote, market, distribute, import, sell, or have sold any Licensed Product to any Third Party or to any address or Internet Protocol address or the like outside of such Party’s Territory including via the Internet or mail order. Notwithstanding any provision to the contrary set forth in this Agreement, [***]. As applicable, (i) in the case of Otsuka, in any country or jurisdiction outside of the Otsuka Territory, and (ii) in the case of Ionis, in any country or jurisdiction outside of the Ionis Territory:

- 6.9.1 such Party and its Affiliates will not engage, nor permit its Sublicensees, licensees, and Subcontractors to engage, in any advertising or promotional activities relating to any Licensed Product for use directed primarily to customers or other buyers or users of the Licensed Products located in any such country or jurisdiction;
- 6.9.2 such Party and its Affiliates will not solicit orders of the Licensed Products from any prospective purchaser located in any such country or jurisdiction;
- 6.9.3 such Party and its Affiliates will not, and will take reasonable measures to cause its Sublicensees, licensees and Subcontractors to not, deliver or tender (or cause to be delivered or tendered) any Licensed Product to Third Parties for use in such country or jurisdiction; and
- 6.9.4 if either Party or its Affiliates, Sublicensees, or licensees receive any order for any Licensed Product from a prospective purchaser located in any such country or jurisdiction, then such Party will immediately refer that order to the other Party or its designee and will not accept any such orders.

ARTICLE 7

MANUFACTURING

7.1 **Responsibility.**

7.1.1 **Ionis Manufacturing.**

- (a) **Ionis Territory.** Ionis will have sole control over and decision-making authority with respect to, at its cost and expense, the Manufacture of (i) all supplies of the Licensed Products required for Ionis’ activities under the Cross-Territory Clinical Development Plan and the Non-Clinical HAE Development Plans, and for all Development activities in the Ionis Territory and (ii) all supplies of the Licensed Products for Commercialization purposes in the Ionis Territory.
- (b) **Europe Territory.** Subject to the remainder of this Section 4 are considered 7.1.1(b) (Europe Territory) and Section 7.1.2 (Otsuka Manufacturing), in accordance with the Supply Agreements and Quality Agreements, Ionis will Manufacture and supply Otsuka with all Licensed Product that is necessary for Otsuka to (i) [***] and (ii) [***].

(c) **Asia Territory.** Subject to the remainder of this Section 7.1.1(c) (Asia Territory) and Section 7.1.2 (Otsuka Manufacturing), in accordance with the Supply Agreements and Quality Agreements, Ionis will Manufacture and supply Otsuka with all Licensed Product that is necessary for Otsuka to (i) [***] and (ii) [***]. Notwithstanding the foregoing, on a country-by-country basis in the Asia Territory, (A) if required by Applicable Law, any Regulatory Authority or the conditions and requirements of Regulatory Approvals in such country in the Asia Territory, Ionis will [***], or (B) if mutually agreed by the parties Parties (such agreement not to be unreasonably withheld, conditioned or delayed), Ionis will [***], provided that, in each case ((A) and (B)), [***]. Notwithstanding any provision to the contrary in this Agreement, Ionis will [***].

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(d) **Support.** Upon Otsuka's reasonable request prior to the applicable Manufacturing Handover Date, Ionis will provide (or will use commercially reasonable efforts to cause its CMOs to provide) to Otsuka (i) [***], (ii) [***], and (iii) [***], in each case ((i) – (iii)), to the extent [***]. Ionis will provide all such Requested Assistance to Otsuka in accordance with the terms of Section 3.2 (Technology Transfer Costs) and will provide such data and information to Otsuka [***]. For clarity, and notwithstanding anything to the contrary herein, Ionis will provide to the Qualified Person for the Licensed Products in the Europe Territory, [***], Manufacturing audit or inspection reports as required under EU GMP, Annex 16, section 2.2 for the purposes of protecting batch certification in the Europe Territory.

7.1.2 Otsuka Manufacturing. [***], Otsuka will have the right to assume responsibility for Manufacturing (a) all supplies of the Licensed Products required for Otsuka's activities under the Otsuka Territory-Specific Development Plans in [***] the Otsuka Territory and (b) all supplies of the Licensed Products for Commercialization purposes in [***] the Otsuka Territory, in each case, upon written notice to Ionis at any time after the earliest of (i) [***], (ii) [***], and (iii) [***] (such notice [***], the "Manufacturing Handover Notice" [***]). If Otsuka provides Ionis with a Manufacturing Handover Notice [***], then Ionis' business. However, obligations to Manufacture and supply Otsuka in accordance with Section 7.1.1 (Ionis Manufacturing) will terminate [***], following the completion of all activities under the Manufacturing Technology Transfer Agreement in accordance with Section 7.4 (Manufacturing Technology Transfer) [***], and the initiation of actual Manufacturing of the Licensed Products to be sold by or on behalf of Otsuka [***] at Otsuka's or its designee's manufacturing facility (such date [***], the "Manufacturing Handover Date" [***]).

7.2 Supply and Quality Agreements; Manufacturing Costs.

7.2.1 Clinical Supply Agreement. Unless otherwise agreed by the Parties, within a timeframe following the Restatement Date to be agreed by the Parties, the Parties will negotiate in good faith and enter into a supply agreement on reasonable and customary terms for the supply of Licensed Products by Ionis to Otsuka for clinical use (the "Clinical Supply Agreement"), which agreement (together with the related Quality Agreement) will govern the terms and conditions of the Manufacture and supply of the Licensed Products for Development purposes in the Otsuka Territory. Otsuka will pay a supply price to Ionis under the Clinical Supply Agreement equal to [***].

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7.2.2 Commercial Supply Agreement. Within a timeframe following the Restatement Date to be agreed by the Parties, the Parties will negotiate in good faith and enter into a commercial supply agreement on reasonable and customary terms for the commercial-grade supply of Licensed Products by Ionis to Otsuka (the "Commercial Supply Agreement" and together with the Clinical Supply Agreement, the "Supply Agreements"), which agreement (together with the related Quality Agreement) will govern the terms and conditions of the Manufacture and supply of the Licensed Products for Commercialization purposes in the Otsuka Territory. Otsuka will pay a supply price to Ionis under the Commercial Supply Agreement equal to [***]. The Commercial Supply Agreement shall allow Otsuka to order, and Ionis to supply, a portion of a batch as the minimum order quantity, as further detailed in such Commercial Supply Agreement; provided that [***].

7.2.3 Quality Agreements. The Parties will negotiate in good faith and enter into one or more quality technical agreements pertaining to clinical and commercial supply of Licensed Products to Otsuka (each, a "Quality Agreement") containing reasonable and customary terms and conditions regarding quality assurance, quality control, compliance with GMP, GDP and GCP (as applicable), specifications, change control procedures, and provisions relating to audits and inspections. If Otsuka is required by Regulatory Authority or Applicable Law in any country in the Asia Territory to enter into a Quality Agreement directly with a CMO that Manufactures Licensed Product (including drug substance (API) and bright stock or finished Licensed Product) for Commercialization in such country, then the Parties will [***]. If there are terms or conditions that are required to be in a quality agreement by Applicable Law or a Regulatory Authority in the Asia Territory but that are inconsistent with an existing quality agreement between Ionis and its CMO, Ionis will [***].

7.2.4 Manufacturing Cost Increases. If the Manufacturing Costs, whether for clinical or commercial supplies of Licensed Product, are reasonably anticipated to increase, on a per unit basis, such that the [***], then Ionis will provide prompt written notice to Otsuka of such increase. If such increase is anticipated to result in [***], on a per unit basis, then [***]. If such increase is anticipated to result in [***] on a per unit basis, then [***].

7.2.5 Capital Expenditures. Ionis [***]. In addition, if any CMO requests or requires [***], then Ionis will notify Otsuka and the Parties will [***].

7.2.6 [***]. If the reasonable allocation of [***], then [***].

7.3 Audits and Inspections.

7.3.1 By Otsuka. Prior to execution of the first Quality Agreement, Otsuka shall be entitled to conduct [***]. In addition, if Ionis elects to inspect or audit any facilities of its CMOs with respect to the Manufacture of Licensed Products for the Otsuka Territory, Ionis shall notify Otsuka of such restriction inspection or audit and, [***]. In addition, to the extent permitted under Ionis' agreement with the applicable CMO and subject to any conditions set forth in such agreement with respect to any inspection or audit (e.g., an obligation to enter into a confidentiality agreement with the applicable CMO), Ionis shall [***]. If Otsuka identifies the need to perform a "for cause" audit of such facilities to address quality or compliance issues related to any Licensed Product Manufactured for the Otsuka Territory (including to address any notice from a Governmental Authority in the Otsuka Territory of noncompliance with Applicable Laws), as well as in connection with the preparation of Regulatory Submissions for the Otsuka Territory and in response to Regulatory Authority requirements in the Otsuka Territory, then Otsuka shall notify Ionis and if Ionis agrees with Otsuka's determination that a "for cause" audit is found needed, Ionis will schedule and conduct such audit and Otsuka will [***], in each case, to the extent permitted pursuant to the applicable agreement with the applicable CMO.

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7.3.2 **By Governmental Authority.** If any Governmental Authority carries out or gives notice of its intention to carry out any inspection or audit of any of Ionis' CMOs in relation to Manufacture of Licensed Products for the Otsuka Territory and Ionis is aware of such upcoming inspection or audit, then Ionis shall promptly notify Otsuka thereof and Ionis shall, to the extent permitted by its agreement with the applicable CMO and the applicable Governmental Authority, [***]. Following receipt by Ionis of the inspection results or audit observations of the Governmental Authority from such inspection or audit (a redacted copy of which Ionis will promptly provide to Otsuka to the extent it relates to Licensed Products Manufactured for the Otsuka Territory), Ionis will (a) prepare any appropriate responses and (b) provide a court copy of competent jurisdiction such responses to Otsuka [***] in advance of the date such responses are due, to the extent such responses pertain to the Manufacture of Licensed Products for the Otsuka Territory, and Ionis shall [***], in each case ((a) and (b)), to the extent permitted under Ionis' agreement with such CMOs and subject to any conditions set forth in the applicable agreement with such CMOs with respect to any inspection or audit (e.g., an obligation to enter into a confidentiality agreement with the applicable CMO).

7.3.3 **CMO Agreements.** Ionis shall [***].

7.4 **Manufacturing Technology Transfer.** At Otsuka's request any time after Otsuka provides a Manufacturing Handover Notice [***], Ionis will make available to Otsuka all Ionis Manufacturing and Analytical Know-How and materials (the "**Manufacturing Technology Transfer**") for [***]. Otsuka will (a) use Ionis Manufacturing and Analytical Know-How and materials provided by Ionis in connection with the Manufacturing Technology Transfer only in the fulfillment of obligations or exercise of rights under this Agreement, and (b) not transfer such Ionis Manufacturing and Analytical Know-How or materials or deliver the same to any Third Party, without Ionis' prior written consent. For purposes of a Manufacturing Technology Transfer, the Parties together with Ionis' CMO (subject to the next sentence) will enter into a manufacturing technology transfer agreement, which will also provide for reasonable technical assistance and support by Ionis and Ionis' CMOs as reasonably requested by Otsuka to enable Otsuka or its Affiliates, or if agreed by Ionis, a Third Party manufacturer (other than Ionis' CMOs), to Manufacture the Licensed Products (a, "**Manufacturing Technology Transfer Agreement**"). Ionis will use reasonable efforts to [***]. If Ionis agrees to transfer Ionis Manufacturing and Analytical Know-How to a Third Party manufacturer other than Ionis' CMOs, such transfer shall be carried out pursuant to a direct license between Ionis and such Third Party manufacturer. If Otsuka [***]. Otsuka will [***]. Accordingly, Ionis may [***]. Otsuka will [***].

ARTICLE 8 GOVERNANCE

8.1 Executive Committee.

8.1.1 **Formation and Purpose of the Executive Committee.** Promptly, but not more than [***] after the Restatement Date, Ionis and Otsuka will establish an executive committee ("Executive Committee"), which will have the responsibilities set forth in this [Section 8.1](#) (Executive Committee). The Executive Committee will dissolve upon the expiration of the Term.

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8.1.2 **Membership.** The Executive Committee will be composed of an equal number of representatives from each Party who have the appropriate and direct knowledge and expertise and requisite decision-making authority; provided that at least one representative from each Party will be an Executive Officer of such Party. Any such representative who serves on the Executive Committee may also serve on one or more other committees under this Agreement. Each Party may replace any of its representatives on the Executive Committee and appoint a person to fill the vacancy arising from each such replacement. A Party that replaces a representative will notify the other Party at least [***] prior to the next scheduled meeting of the Executive Committee. Ionis will designate one of its Executive Committee members as one of the co-chairpersons of the Executive Committee and Otsuka will designate one of its members as the other co-chairperson of the Executive Committee (each, an "**Executive Committee Co-Chairperson**"). The Executive Committee Co-Chairpersons or their designees, in collaboration with the Alliance Managers, will be responsible for calling meetings, preparing and circulating an agenda and related information in advance of each meeting, and preparing and issuing minutes of each meeting within [***] thereafter. Such minutes will not be finalized until the Executive Committee Co-Chairpersons or their designees have had [***] to review and confirm the accuracy of such minutes.

8.1.3 **Meetings.** The Executive Committee will hold meetings [***]. The Executive Committee may meet in person or by means of teleconference, Internet conference, video conference, or other similar communication method. Each Party will be responsible for all of its own costs and expenses of participating in any JSC meeting.

8.1.4 **Meeting Agendas.** Unless agreed otherwise by the Parties, the Parties will jointly prepare the agenda for each Executive Committee meeting, facilitated by the Alliance Managers working closely with the Executive Committee Co-Chairpersons and, as appropriate, other Executive Committee members and Subcommittee Co-Chairpersons, at least [***] in advance of each meeting of the Executive Committee, and each Party will provide the other Party with all relevant materials to be unenforceable because it extends for too long presented at each Executive Committee meeting at least [***] in advance of each meeting of the Executive Committee; provided that under exigent circumstances requiring Executive Committee input, the agenda may be prepared or presentation materials may be provided within a shorter period of time in advance of a meeting, with the approval of the Executive Committee Co-Chairpersons. Either Party may propose that there not be a specific agenda for a particular meeting, so long as the other Party consents to the later addition or over too great modification of agenda items or the absence of a range specific agenda for such Executive Committee meeting.

8.1.5 **Specific Responsibilities of activities or in too broad a geographic area, if the Executive Committee.** The responsibilities of the Executive Committee will be interpreted to extend only over the maximum period of time, range of activities or geographic areas as to which it may be enforceable. to:

5. Confidential Information

- (a) Ionis possesses confidential information that has been created, discovered, developed by, establish and delegate specifically defined duties to any Subcommittees, as described in [Section 8.3.1](#) (Formation; Authority);
- (b) attempt to resolve any disputes or otherwise become known to Ionis (including, without limitation, information created, discovered, developed or made known by Advisor disagreements arising from matters within the Advisory Services) jurisdiction of the Europe JSC, the Asia JSC, the PV Subcommittee or any other Subcommittee established by the Executive Committee; and
- (c) perform such other functions as appropriate to further the purposes of this Agreement as determined by the Parties.

8.2 Joint Steering Committees.

8.2.1 Formation and Purposes of the Joint Steering Committees. As of the Restatement Date, the Parties have established a Joint Steering Committee for the Europe Territory, which will have the responsibilities set forth in this [Section 8.2](#) (Joint Steering Committees) ("Europe JSC"). Promptly, but not more than [***] after the Restatement Date, Ionis and Otsuka will establish a Joint Steering Committee for the Asia Territory, which will have the responsibilities set forth in this [Section 8.2](#) (Joint Steering Committees) (the "Asia JSC," and together with the Europe JSC, the "JSCs").

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8.2.2 Membership. As of the Restatement Date, the Europe JSC is, and each of the JSCs will be throughout the Term, composed of an equal number of representatives from each Party who have the appropriate and direct knowledge and expertise and requisite decision-making authority. Any such representative who serves on the JSCs may also serve on one or more other committees under this Agreement. Additional terms relating to the JSCs, including terms relating to JSC meetings and meeting agendas, are set forth in [Section 8.3.2](#) (Subcommittee Leadership and Meetings).

8.2.3 Specific Responsibilities of the Europe JSC. The Europe JSC will have the following responsibilities:

- (a) manage the overall strategic alignment between the Parties under this Agreement and maintain the relationship between the Parties;
- (b) oversee, review, monitor, and coordinate, and, where specified in this [Section 8.2.3](#) (Specific Responsibilities of the Europe JSC), approve the Parties' Development, Manufacturing, Medical Affairs, and Commercialization activities under this Agreement for the Licensed Products in the Territory (excluding the Asia Territory to the extent within the responsibilities of the Asia JSC);
- (c) review, discuss, and determine whether to [***];
- (d) review, discuss, and determine (at a joint meeting with the Asia JSC) whether [***];
- (e) review, discuss, and determine whether [***];
- (f) review, discuss, and determine whether [***];
- (g) review, discuss and determine whether [***];
- (h) review, discuss, and determine whether to approve any updates to the Shared Development Budget, as described in [Section 4.4.2\(a\)](#) (Shared Development Budget);
- (i) **All** review, discuss, and determine whether to approve [***] and the Shared Development Budget, as described in [Section 4.4.4\(a\)](#) (Shared Costs);
- (j) share information related to, and review and discuss activities and progress of each Party (A) in connection with the Development of Licensed Products in the Europe Territory and Ionis Territory and (B) under the Cross-Territory Clinical Development Plan, including through updates from each Party of the status of Development for the Licensed Products in each such Territory, as described in [Section 4.5](#) (Development Reports);

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- (k) share information **is** hereinafter related to, and review and discuss activities and progress under the Europe Territory-Specific Development Plan, and the Non-Clinical Europe HAE Development Plan, as described in [Section 4.5](#) (Development Reports);
- (l) review and discuss any matters related to the Development of the Licensed Products applicable to the Europe Territory referred to the Europe JSC by either Party's representatives, including matters related to the Development of the Licensed Products applicable to both the Europe Territory and the Asia Territory that are referred to a joint meeting of the Europe JSC and the Asia JSC by either Party's representatives;
- (m) discuss any concerns raised by either Party regarding any action that the other Party is taking or intends to take with respect to a Licensed Product that is [***], as described in [Section 5.8](#) (No Harmful Actions);
- (n) discuss [***];
- (o) review, discuss, and determine whether to approve [***];
- (p) review, discuss, and determine whether to approve [***];
- (q) review, discuss, and determine whether to approve [***];
- (r) review, discuss and determine whether to approve [***];
- (s) review and discuss any matters related to the Commercialization of the Licensed Products applicable to the Europe Territory that are referred to the Europe JSC by either Party's representatives, including matters related to the Commercialization of the Licensed Products applicable to both the Europe Territory and the Asia Territory that are referred to a joint meeting of the Europe JSC and the Asia JSC by either Party's representatives;
- (t) establish and delegate specifically defined duties to any Subcommittees, as described in [Section 8.3.1](#) (Formation; Authority);
- (u) review, discuss and determine whether to approve [***];
- (v) discuss the inclusion of Ionis' logo, name, and housemark on the packaging for the Licensed Products in the Europe Territory, as described in [Section 10.10.6](#) (Housemarks);
- (w) attempt to resolve any disputes or disagreements arising from matters within the jurisdiction of the Europe Regulatory Subcommittee or any other Subcommittee established by the Europe JSC; and
- (x) perform such other functions as appropriate to further the purposes of this Agreement as determined by the Parties.

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8.2.4 Specific Responsibilities of the Asia JSC. The Asia JSC will have the following responsibilities:

- (a) oversee, review, monitor, and coordinate, and, where specified in this [Section 8.2.4](#) (Specific Responsibilities of the Asia JSC), approve the Parties' Development, Manufacturing, Medical Affairs, and Commercialization activities under this Agreement for the Licensed Products in the Asia Territory;
- (b) review, discuss, and determine whether to [***];

- (c) review, discuss, and determine (at a joint meeting with the Europe JSC) whether [***];
- (d) review, discuss, and determine whether [***];
- (e) review, discuss and determine whether [***];
- (f) share information related to, and review and discuss activities and progress under the Asia Territory-Specific Development Plan and the Non-Clinical Asia HAE Development Plan, as described in Section 4.5 (Development Reports);
- (g) review and discuss any matters related to the Development of the Licensed Products applicable to the Asia Territory that are referred to the Asia JSC by either Party's representatives, including matters related to the Development of the Licensed Products applicable to both the Europe Territory and the Asia Territory that are referred to a joint meeting of the Europe JSC and the Asia JSC by either Party's representatives;
- (h) discuss any concerns raised by either Party regarding any action that the other Party is taking or intends to take with respect to a Licensed Product that is [***], as described in Section 5.8 (No Harmful Actions);
- (i) review, discuss, and determine whether to [***];
- (j) review, discuss and determine whether to [***];
- (k) review and discuss any matters related to the Commercialization of the Licensed Products applicable to the Asia Territory that are referred to the Asia JSC by either Party's representatives, including matters related to the Commercialization of the Licensed Products applicable to both the Europe Territory and the Asia Territory that are referred to a joint meeting of the Europe JSC and the Asia JSC by either Party's representatives;
- (l) establish and delegate specifically defined duties to any Subcommittees, as described in Section 8.3.1 (Formation; Authority);
- (m) review, discuss and determine whether to [***];
- (n) discuss the inclusion of Ionis' logo, name, and housemark on the packaging for the Licensed Products in the Asia Territory, as described in Section 10.10.6 (Housemarks);
- (o) attempt to resolve any disputes or disagreements arising from matters within the jurisdiction of any Subcommittee established by the Asia JSC; and
- (p) perform such other functions as appropriate to further the purposes of this Agreement as determined by the Parties.

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8.3 Subcommittees.

8.3.1 Formation; Authority. In addition to the Europe Regulatory Subcommittee, the PV Subcommittee, and each JSC, the Executive Committee and the JSCs (each, an "**Confidential Information Establishing Committee**") may establish and delegate specifically defined duties to operational committees or *ad hoc* subcommittees, on an "as needed" basis to oversee particular projects or activities (any such operational committees and subcommittees, including the Europe Regulatory Subcommittee, the PV Subcommittee, and each JSC, a "**Subcommittee**"). Both of the JSCs and the PV Subcommittee are Subcommittees of the Executive Committee and the Europe Regulatory Subcommittee is a Subcommittee of the Europe JSC. Any representative who serves on any Subcommittee under this Agreement may also serve on one or more other committees under this Agreement. Subject to Section 8.2 (Joint Steering Committees), each Subcommittee will be constituted and will operate as the applicable Establishing Committee determines. Each Subcommittee and its activities (other than the JSCs and their activities) will be subject to the oversight of, and will report to, the applicable Establishing Committee. Each Establishing Committee or its co-chairpersons, in each case as mutually agreed, may delegate to a Subcommittee any responsibilities of such Establishing Committee set forth in Section 8.1 (Executive Committee) or Section 8.2 (Joint Steering Committees), and, in such case, any agreement reached by unanimous Party Vote of the applicable Subcommittee with respect to such delegated responsibilities will be deemed to be approved by the applicable Establishing Committee (to the extent such approval is required hereunder). Each Establishing Committee or its co-chairpersons acting together may also reallocate any responsibility of a Subcommittee to any other Subcommittee. No Subcommittee's authority may exceed that specified for the applicable Establishing Committee in this Article 8 (Governance). Any disagreement between the representatives of the Parties on a Subcommittee will be referred to the applicable Establishing Committee for resolution in accordance with Section 8.5 (Decision-Making).

8.3.2 Subcommittee Leadership and Meetings. By way Ionis will designate a co-chairperson of illustration, but each Subcommittee and Otsuka will designate a co-chairperson of each Subcommittee, each of whom will be a Party's representative who is a member of such Subcommittee (each, a "**Subcommittee Co-Chairperson**"). The Subcommittee Co-Chairpersons or their designees, in collaboration with the Alliance Managers, will be responsible for calling meetings, preparing and circulating an agenda in advance of each meeting, and preparing and issuing minutes of each meeting promptly thereafter; *provided* that, as it relates to the JSC meetings, (a) the agenda will be prepared at least [***] in advance of such meeting, (b) each Party will provide the other Party with all relevant materials to be presented at such JSC meeting at least [***] in advance of such meeting, in each case, unless there are exigent circumstances requiring JSC input, in which case, the agenda may be prepared or presentation materials may be provided within a shorter period of time in advance of such JSC meeting, with the approval of the Subcommittee Co-Chairpersons of the applicable JSC, and (c) minutes of such JSC meeting will be issued within [***] thereafter. Such minutes will not limitation, be finalized until (i) as it relates to the JSC meetings, the Subcommittee Co-Chairpersons or their designees have had [***] to review and confirm the accuracy of such minutes, or (ii) as it relates to any Subcommittee meeting other than the JSC meetings, all Subcommittee members have had [***] to review and confirm the accuracy of such minutes. Each Party may replace its representatives and Subcommittee Co-Chairpersons on each such Subcommittee at any time upon written notice to the other Party; *provided* that, if such replacement relates to a JSC, then such Party making such replacement will notify the other Party at least [***] prior to the next scheduled meeting of the applicable JSC. The Alliance Manager of each Party (or his or her designee) will attend each meeting of each Subcommittee as a non-voting participant. Each Subcommittee will hold meetings at such times as it elects to do so, and at such locations as the Parties may agree upon or by means of teleconference, Internet conference, video conference, or other similar communication method; *provided* that, each JSC will meet no less frequently than quarterly prior to receipt of Regulatory Approval for the first Licensed Product in the Europe Territory or the Asia Territory, as applicable, and thereafter no less frequently than [***], in each case, unless otherwise agreed by the Parties. Each Party will be responsible for all of its own expenses of participating in any Subcommittee meeting.

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8.4 Additional Participants. Employees of a Party or any of its Affiliates involved in the Exploitation of the Licensed Products may attend meetings of the Executive Committee, a JSC, or any other Subcommittee as non-voting participants. In addition, with the prior consent of each Party, consultants, representatives, or advisors involved in the same activities and under written obligations of confidentiality and non-use applicable to the Confidential Information **includes**: (A) inventions, developments, designs, improvements, trade secrets, ideas, formulas, source of each Party that are at least as stringent as those set forth in Article 12 (Confidentiality) may attend meetings of the Executive Committee, a JSC or any other Subcommittee as non-voting observers.

8.5 Decision-Making.

8.5.1 General Decision-Making Process. Each Party's representatives on the Executive Committee, each JSC, and object codes, programs, each other works Subcommittee will, collectively, have one vote (the "**Party Vote**") on all matters brought before such committee for a decision by consensus. The Executive Committee, each JSC, and each other Subcommittee will make decisions as to matters within its jurisdiction by unanimous Party Vote, which may be reflected in the minutes of authorship, organisms, plasmids, expression vectors, know-how, processes, cell lines, discoveries, techniques, data the committee meeting or by an action by written consent signed by the Executive Committee Co-Chairpersons or the Subcommittee Co-Chairpersons, as applicable, or their designees identified in writing. Except as otherwise expressly set forth in this Agreement, the phrase "determine," "designate," "approve," or "determine whether to approve" by the Executive Committee, either JSC or any other Subcommittee and documentation systems (hereinafter collectively similar phrases used in this Agreement will mean approval in accordance with this Section 8.5 (Decision-Making) or Section 8.6 (Resolution of Committee Disputes), including the escalation and tie-breaking provisions herein. For the avoidance of doubt, matters that are specified in Section 8.2.3 (Specific Responsibilities of the Europe JSC) or Section 8.2.4 (Specific Responsibilities of the Asia JSC) to be reviewed and discussed (as opposed to reviewed, discussed, and approved) do not require any agreement or decision by either Party and are not subject to the voting and decision-making procedures set forth in this Section 8.5 (Decision-Making) or Section 8.6 (Resolution of Committee Disputes).

8.5.2 Decisions of the Subcommittees. If any Subcommittee cannot reach unanimous agreement using good faith efforts on any matter within their respective scope of authority within [***] of the meeting at which such matter was discussed, then a Party may refer such matter to the applicable Establishing Committee for resolution in accordance with Section 8.5.3 (Decisions of Establishing Committees).

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8.5.3 Decisions of Establishing Committees. If any Subcommittee established by a JSC is unable to reach a consensus decision on a matter within the scope of such Subcommittee's authority in accordance with Section 8.5.2 (Decisions of the Subcommittees), then, at either Party's request, each Party will submit in writing its respective positions with respect to such unresolved matter to the applicable JSC and if such JSC, after the use of good faith efforts, including reasonable discussion and good faith consideration of each Party's view on a particular matter, is unable to resolve such matter within a period of [***] after each Party submits in writing its respective position with respect to such matter, then either Party may refer such matter to the Executive Committee. If a JSC or other Subcommittee established by the Executive Committee is unable to reach a consensus decision on a matter within the scope of such JSC's or other Subcommittee's authority in accordance with Section 8.5.2 (Decisions of the Subcommittees) or a JSC is unable to reach a consensus decision on a Subcommittee-related matter submitted to such JSC pursuant to the first sentence of this Section 8.5.3 (Decisions of Establishing Committees), then, [***].

8.6 Resolution of Committee Disputes.

8.6.1 Final Decision-Making Authority. For any matter referred to as "the Executive Committee in accordance with Section 8.5.3 (Decisions of Establishing Committees), if the Executive Committee is unable to reach a consensus decision on such matter, then, with respect to any matter set forth in clauses (b) and (c) of this Section 8.6.1 (Final Decision-Making Authority), the applicable Executive Committee Co-Chairperson appointed by the Party with final decision-making authority over such matter will make a final decision on such matter in accordance with this Section 8.6.1 (Final Decision-Making Authority) and subject to Section 8.6.2 (Limitations on Decision Making). Any matter set forth in clause (a) of this Section 8.6.1 (Final Decision-Making Authority) shall be subject to the mutual agreement of both Parties and, unless and until such mutual agreement is reached (by consensus decision of the applicable JSC or Executive Committee), the status quo will be maintained.

(a) **Inventions No Change; Status Quo**. Neither Party's Executive Committee Co-Chairperson will have final decision-making authority with respect to the final resolution of any disagreement related to: (i) [***]; (ii) [***]; (iii) [***]; (iv) [***]; (v) [***]; (vi) [***]; (vii) [***]; (viii) [***]; and (B) information regarding plans for research, development, new products, clinical data, pre-clinical product data, clinical trial patient data, marketing and selling, business plans, budgets and unpublished financial statements, licenses, prices and costs, as well as information regarding the skills and compensation of employees of Ionis. (ix) [***].

(b) **Ionis Final Decision-Making Authority.** The Executive Committee Co-Chairperson for Ionis will have final decision-making authority over (i) [***], (ii) [***], (iii) [***], (iv) [***], (v) [***], and (vi) [***]. Notwithstanding the foregoing, [***].

(c) **Otsuka Final Decision-Making Authority.** The Executive Committee Co-Chairperson for Otsuka will have final decision making authority over (i) [***], (ii) [***], (iii) [***], (iv) [***], (v) [***], and (v) [***].

8.6.2 Limitations on Decision Making. Notwithstanding anything to the contrary set forth in this Agreement, without the other Party's prior written consent, no decision of the Executive Committee, either JSC, any other Subcommittee, or a Party's Executive Committee Co-Chairperson (in the exercise of a Party's decision-making authority on any such matters), in each case may, without the other Party's prior written consent, (a) be likely to [***], (b) impose any requirements that the other Party take or decline to take any action that a Party reasonably believes would result in a violation of any Applicable Law, the requirements of any Regulatory Authority, or any agreement with any Third Party (including any Collaboration In-License) or the infringement or misappropriation of intellectual property rights of any Third Party, or (c) conflict with, amend, interpret, modify, or waive compliance under this Agreement.

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8.7 Day-to-Day Responsibilities. Each Party will: (a) be responsible for day-to-day implementation and conduct of the activities hereunder for which it has or is otherwise assigned responsibility under this Agreement, *provided* that such implementation is consistent with the express terms of this Agreement or the decisions of the Executive Committee, either JSC, or any other Subcommittee, in each case, within the scope of its authority as provided herein; and (b) provide the other Party with information about material events related to the progress of such activities, as may be reasonably requested by the other Party from time to time.

8.8 Alliance Managers. As of the Restatement Date, each of the Parties has appointed a representative of such Party to act as its alliance manager under this Agreement for the Europe Territory and, within [***] after the Restatement Date, each Party will appoint a representative to act as its alliance manager under this Agreement for the Asia Territory (each, an “**Alliance Manager**”). The role of the Alliance Managers is to act as a single point of contact between the Parties to ensure a successful relationship under this Agreement. All of the Alliance Managers will attend all Executive Committee meetings and joint meetings of the JSCs, the Alliance Managers for each Region shall attend the applicable JSC meetings, and the Alliance Managers or their respective designees will attend all other Subcommittee meetings and will support the Executive Committee Co-Chairpersons and any Subcommittee Co-Chairpersons in the discharge of their responsibilities. Alliance Managers will be non-voting participants in all Executive Committee and Subcommittee meetings, but an Alliance Manager may bring any matter to the attention of the Executive Committee or any Subcommittee if such Alliance Manager reasonably believes that such matter warrants such attention. Each Party may change its designated Alliance Manager(s) at any time upon written notice to the other Party. Any Alliance Manager may designate a substitute to temporarily perform the functions of that Alliance Manager by written notice to the other Party. Each Alliance Manager, with respect to each Region, or all Alliance Managers with respect to the Territory, will also: (a) be the point of first referral in all matters of conflict resolution; (b) provide a single point of communication for seeking consensus between the Parties regarding key strategy and plan issues; (c) identify and bring disputes to the attention of the JSCs or Executive Committee in a timely manner; (d) plan and coordinate cooperative efforts and internal and external communications; and (e) take responsibility for ensuring that governance activities, such as the conduct of required Executive Committee and any Subcommittee meetings and production of meeting minutes, occur as set forth in this Agreement, and that the relevant action items resulting from such meetings are appropriately carried out or otherwise addressed.

ARTICLE 9 PAYMENTS

9.1 Upfront Payment. The Parties acknowledge that, in connection with the execution of the Original Agreement, Otsuka paid to Ionis \$65,000,000. Following the Restatement Date, within [***], Otsuka will pay to Ionis, by wire transfer of immediately available funds, a non-refundable, non-creditable upfront payment of \$20,000,000 (the “**Restatement Upfront Payment**”).

9.2 Milestone Payments.

9.2.1 Regulatory Milestones. Subject to Section 9.2.1(a) (Europe Territory Regulatory Milestone Adjustment), after the first achievement of each regulatory milestone event set forth in Table 9.2.1 below by Otsuka or its Affiliates or Sublicensees for the first Licensed Product, Otsuka will pay to Ionis the corresponding regulatory milestone payment set forth in Table 9.2.1 (the regulatory milestone events set forth in Table 9.2.1, the “**Regulatory Milestone Events**” and the regulatory milestone payments set forth in Table 9.2.1, the “**Regulatory Milestone Payments**”).

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Table 9.2.1 – Regulatory Milestones

Regulatory Milestone Event	Regulatory Milestone Payment (in U.S. Dollars)
1. [***]	\$[***]
2. [***]	\$[***]
3. [***]	\$[***]
4. [***]	(a) \$[***] or (b) \$[***]
5. [***]	\$[***]

(ii) (a) All Europe Territory Regulatory Milestone Adjustment. If any [***], then the Regulatory Milestone Payments for the Europe Territory [***].

(b) Notice and Payment. Otsuka will notify Ionis in writing of the achievement of each Regulatory Milestone Event within [***] after achievement of such Regulatory Milestone Event by Otsuka or its Affiliates or within [***] after Otsuka’s receipt of notification of such achievement by its Sublicensees. However, in no event will a failure or delay by Otsuka to deliver such notice of achievement of a Regulatory Milestone Event relieve Otsuka of its obligation to pay Ionis the corresponding Regulatory Milestone Payment for achievement of such Regulatory Milestone Event. Following receipt of such notice, Ionis will send Otsuka an invoice (and, if there has been any change to a Payment Form previously submitted, or if a previously submitted Payment Form has expired, then an updated Payment Form) for the applicable Regulatory Milestone Payment, and Otsuka shall pay such Regulatory Milestone Payment within [***] after receipt of such invoice (and Payment Forms, if applicable). Each Regulatory Milestone Payment is payable only once, regardless of the number of times the corresponding Regulatory Milestone Event is achieved. If Otsuka or its Affiliates or Sublicensees achieve all of the Regulatory Milestone Events, then the Regulatory Milestone Payments payable by Otsuka under this Section 9.2.1 (Regulatory Milestones) will not exceed \$[***].

9.2.2 Sales Milestones. After each sales milestone event set forth in Table 9.2.2 below is achieved by Otsuka or its Affiliates or Sublicensees for the Licensed Products in the Europe Territory or the Asia Territory, as applicable, Otsuka will pay to Ionis the corresponding sales milestone payment, as set forth below (the sales milestone events set forth in Table 9.2.2, the “**Sales Milestone Events**” and the sales milestone payments set forth in Table 9.2.2, the “**Sales Milestone Payments**”).

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Table 9.2.1 – Regulatory Milestones

Regulatory Milestone Event	Regulatory Milestone Payment (in U.S. Dollars)
1. [***]	\$[***]

2. [***]	\$[***]
3. [***]	\$[***]
4. [***]	(a) \$[***] or (b) \$[***]
5. [***]	\$[***]

(a) **Notice and Payment.** Otsuka will notify Ionis in writing of the achievement of each Sales Milestone Event no later than (i) [***] or (ii) [***]. However, in no event will a failure or delay by Otsuka to deliver such notice of achievement of a Sales Milestone Event relieve Otsuka of its obligation to pay Ionis the corresponding Sales Milestone Payment for achievement of such Sale Milestone Event. Following receipt of such notice, Ionis will send Otsuka an invoice (and, if there has been any change to a Payment Form previously submitted, or if a previously submitted Payment Form has expired, then an updated Payment Form) for the applicable Sales Milestone Payment, and Otsuka shall pay such Sales Milestone Payment within [***] after receipt of such invoice (and Payment Forms, if applicable). If more than one of the Sales Milestone Events is achieved for the first time in a given Calendar Quarter during the Term, then Otsuka will pay to Ionis a separate Sales Milestone Payment with respect to each such Sales Milestone Event. Each Sales Milestone Payment is payable only once, regardless of the number of times the corresponding Sales Milestone Event is achieved. If Otsuka or its Affiliates or Sublicensees achieve all of the Sales Milestone Events, then the Sales Milestone Payments payable by Otsuka under this [Section 9.2.2](#) (Sales Milestones) will not exceed \$[***].

9.3 Royalties.

9.3.1 **Royalty Payments During the Initial Royalty Term.** Subject to the provisions of [Section 9.3.2](#) (Royalty Reductions), Otsuka will pay to Ionis royalties based on the Net Sales of a Licensed Product by Otsuka and its Affiliates and Sublicensees in the Otsuka Territory at the rates set forth in Table 9.3.1 below (the "*Initial Royalties*"), on a Licensed Product-by-Licensed Product and country-by-country basis, commencing on the first sale of such Licensed Product that results in Net Sales of such Licensed Product in such country and ending on the latest to occur of (a) the [***] anniversary of the First Commercial Sale of such Licensed Product in such country, (b) the expiration of the last Valid Claim in the [***] that Cover such Licensed Product in such country [***], and (c) loss of Regulatory Exclusivity of such Licensed Product in such country (the "*Initial Royalty Term*").

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Table 9.3.1- Royalty Rates for the Licensed Products

Calendar Year Net Sales of all Licensed Products in the Europe Territory or the Applicable Country or Jurisdiction in the Asia Territory	Royalty Rate
Europe Territory	
Portion of annual Net Sales of all Licensed Products in the Europe Territory that is [***]	[***]%
Portion of annual Net Sales of all Licensed Products in the Europe Territory that is greater than [***]	[***]%
Portion of annual Net Sales of all Licensed Products in the Europe Territory that is [***]	[***]%
[***]	
Portion of annual Net Sales of all Licensed Products in [***] that is [***]	[***]%
Portion of annual Net Sales of all Licensed Products in [***] that is [***]	[***]%
Portion of annual Net Sales of all Licensed Products in [***] that is [***]	[***]%
Portion of annual Net Sales of all Licensed Products in [***] that is [***]	[***]%
[***]	
Portion of annual Net Sales of all Licensed Products in [***] that is [***]	[***]%
Portion of annual Net Sales of all Licensed Products in [***] that is [***]	[***]%
Portion of annual Net Sales of all Licensed Products in [***] that is [***]	[***]%
Portion of annual Net Sales of all Licensed Products in [***] that is [***]	[***]%
Portion of annual Net Sales of all Licensed Products in [***] that is [***]	[***]%

By way of example only, if Otsuka receives [***] in Net Sales of all Licensed Products during a given Calendar Year in the Europe Territory, then Otsuka would owe Ionis a royalty of [***] (as converted into U.S. Dollars in accordance with [Section 9.8](#) (Method of Payment; Exchange Rate)).

9.3.2 Royalty Reductions.

(a) **Generic Approval.** On a country-by-country and Licensed Product-by-Licensed Product basis, if at any time during the Initial Royalty Term a Generic Product receives Regulatory Approval in a country in the Otsuka Territory, then, subject to [Section 9.3.2\(e\)](#) (Royalty Reductions Floor), the royalty rates set forth in Table 9.3.1 will be reduced by [***] for such Licensed Product in such country.

(b) **Third Party Payments.** Subject to [Section 9.3.2\(e\)](#) (Royalty Reductions Floor), Otsuka may credit [***] of [***] in a country in the Otsuka Territory in a Calendar Quarter during the Royalty Term against the Royalties due and payable by Otsuka to Ionis on the Net Sales for such Licensed Product in such country in such Calendar Quarter; *provided* that the terms of this [Section 9.3.2\(b\)](#) (Third Party Payments) will not apply to any license agreement entered into without Ionis' prior written consent in violation of the terms of [Section 10.5.3](#) (Settlement). For clarity, Otsuka will not have the right to offset any Third Party Payments arising out of, or allocable to, the Manufacture of a Licensed Product.

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- (c) [***]. Subject to Section 9.3.2(e) (Royalty Reductions Floor), on a Licensed Product-by-Licensed Product and country-by-country basis, if during any Calendar Quarter during the Initial Royalty Term for such Licensed Product in such country, (i) [***], and (ii) [***], then, commencing [***]; *provided* that, if [***], then [***].
- (d) [***]. Subject to Section 9.3.2(e) (Royalty Reductions Floor), on a Licensed Product-by-Licensed Product and country-by-country basis, during the Initial Royalty Term for such Licensed Product in such country, if, [***].
- (e) **Royalty Reductions Floor.** In no event will the Royalties due to Ionis for a Licensed Product in a country in the Otsuka Territory [***] set forth in this Section 9.3.2 (Royalty Reductions). Notwithstanding the foregoing, [***].

9.3.3 Reduced Royalty Term. On a Licensed Product-by-Licensed Product, country-by-country and Region-by-Region basis in the Otsuka Territory, following expiration of the Initial Royalty Term for a Licensed Product in a given country in a Region, Otsuka will pay Ionis a [***] royalty on the Net Sales of such Licensed Product by Otsuka and its Affiliates and Sublicensees in such country (the "**Reduced Royalties**" and together with the Initial Royalties, the "**Royalties**") until the later of (a) [***], and (b) [***] (the "**Reduced Royalty Term**" and together with the Initial Royalty Term, the "**Royalty Term**"). For clarity, on a Licensed Product-by-Licensed Product and country-by-country basis, [***].

9.3.4 Royalty Payments and Reports.

- (a) [***]. Commencing with the Calendar Quarter during which the first sale of a Licensed Product is made that results in Net Sales anywhere in the Otsuka Territory, [***].
- (b) **Royalty Report.** Commencing with the Calendar Quarter during which the first sale of a Licensed Product is made that results in Net Sales anywhere in the Otsuka Territory, within [***] after the end of each Calendar Quarter, Otsuka will provide to Ionis a written report (each, a "**Royalty Report**") setting forth in reasonable detail: (i) the gross sales of the Licensed Products sold by Otsuka or its Affiliate or Sublicensee in each of the Europe Territory, [***] in such Calendar Quarter; (ii) the aggregate Net Sales of the Licensed Products sold by Otsuka or its Affiliates or Sublicensees in each of the Europe Territory, [***] in such Calendar Quarter; (iii) all deductions and reductions used to determine the Net Sales of the Licensed Products for such Calendar Quarter or the Royalties payable with respect to the Licensed Products for such Calendar Quarter, including any reduction pursuant to Section 9.3.2 (Royalty Reductions) (if applicable); (iv) the exchange rates used to calculate the Royalties payable in U.S. Dollars; (v) any withholding taxes required to be made from such Royalties; and (vi) the quantity and description of the Licensed Products sold by Otsuka or its Affiliate or Sublicensee in each of the Europe Territory, [***] during such Calendar Quarter comprising such Net Sales. The Parties will seek to resolve any questions or issues related to a Royalty Report within [***] following receipt by Ionis of each Royalty Report.
- (c) **Royalty Payments.** The information contained in each Royalty Report will be considered the Confidential Information of Otsuka. Following receipt of each Royalty Report, Ionis will [***] and, [***], Otsuka will pay the Royalties due hereunder for the Calendar Quarter covered by the applicable Royalty Report.

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9.4 Other Amounts Payable. With respect to any amounts owed under this Agreement by one Party to the other for which no other invoicing and payment procedure is specified hereunder, within [***] after the end of each Calendar Quarter, each Party will provide an invoice, together with reasonable supporting documentation, to the other Party for such amounts owed in respect of such Calendar Quarter. The owing Party will pay any undisputed invoiced amounts within [***] after the date of the invoice, and any disputed amounts owed by a Party will be paid within [***] following resolution of the dispute.

9.5 Financial Records and Audits. Each Party will, and will require its Sublicensees and Subcontractors to, maintain complete and accurate records in accordance with such Party's Accounting Standards in sufficient detail to permit the other Party to confirm the accuracy of any amounts payable under this Agreement for at least the preceding [***] (*provided* that, with respect to Internal Costs, such records may be based on estimates as long as the method of calculating such estimates is consistently applied), including (as applicable) any External Costs incurred in connection with the performance of the Asia-Specific Non-Clinical HAE Development Activities, Eligible Cross-Territory Development Costs, Milestone Payments, Royalties, and sales of the Licensed Products (including all calculations of Net Sales). Upon reasonable prior notice, each Party agrees to permit such records to be open during regular business hours for examination by an independent certified public accountant selected by the auditing Party and reasonably acceptable to the audited Party for the sole purpose of verifying the accuracy of the financial reports furnished by the audited Party pursuant to this Agreement or of any payments made, or required to be made, by the audited Party pursuant to this Agreement; *provided* that such independent accounting firm is subject to written obligations of confidentiality and non-use applicable to each Party's Confidential Information that are at least as stringent as those set forth in Article 12 (Confidentiality). Such audit will not be (a) performed more frequently than [***], or (b) repeated for any Calendar Year or with respect to the same set of records (in each case, except for cause). Such auditor will not disclose the audited Party's Confidential Information to the auditing Party or to any Third Party, except to the extent such disclosure is necessary to verify the accuracy of the financial reports furnished by the audited Party or the amount of payments by the audited Party under this Agreement. The audited Party will pay any amounts shown to be owed to the auditing Party but unpaid within [***] after the accountant's report, *plus* interest (as set forth in Section 9.11 (Late Payments; Disputed Payments)) from the original due date solely if the audited Party is responsible for the discrepancy. If such examination of records reveals any overpayment by Ionis, then Otsuka will reimburse Ionis for the amount overpaid within [***] after the accountant's report, *plus* interest (as set forth in Section 9.11 (Late Payments; Disputed Payments)) from the original due date [***]. If such examination of records reveals any overpayment by Otsuka, then [***]. The auditing Party will bear the full cost of such audit unless such audit reveals an underpayment by the audited Party of more than [***] of the amount actually due for the time period being audited, in which case the audited Party will reimburse the auditing Party for the reasonable audit fees for such examination.

9.6 No Refunds. Except as expressly provided herein, all payments under this Agreement will be irrevocable, non-refundable, and non-creditable.

9.7 Accounting Standards. If a Party changes its general accounting principles from its then-current Accounting Standard (e.g., from GAAP to IFRS) at any time during the Term, then at least [***] prior to adopting such change in principles, such Party will provide written notice to the other Party of such change. A Party may not change its general accounting principles to any accounting standard other than GAAP or IFRS without the prior written approval of the other Party.

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9.8 Method of Payment; Exchange Rate. All amounts to be paid pursuant to this Agreement will be made in U.S. Dollars and will be paid by wire transfer in immediately available funds to a bank account designated by the receiving Party. The rate of exchange to be used in computing the amount of currency equivalent in U.S. Dollars owed to a Party under this Agreement will be the sole property Selling Party's then-current standard exchange rate methodology employed for the translation of Ionis foreign currency sales into U.S. Dollars in accordance with its Accounting Standards and consistently applied during the period.

9.9 Blocked Payments. If by reason of Applicable Law in any country or jurisdiction, it becomes impossible or illegal for a Party to transfer, or have transferred on its behalf, payments owed the other Party hereunder, then such Party will promptly notify the other Party of the conditions preventing such transfer and Ionis will use reasonable efforts to deposit such payments in U.S. Dollars. If, after using reasonable efforts, such Party is not able to deposit such payments in U.S. Dollars, then such payments will be deposited in local currency in the relevant country to the credit of the other Party in a recognized banking institution designated by the other Party or, if none is designated by the other Party within [***], in a recognized banking institution selected by the transferring Party, as the case may be, and identified in a written notice given to the other Party.

9.10 Taxes.

9.10.1 Taxes on Income. Each Party will be solely responsible for the payment of any and all income Taxes levied on account of all payments it receives under this Agreement.

9.10.2 Withholding Tax. Any and all payments made pursuant to this Agreement will be paid without deduction or withholding for any Taxes, except as required by Applicable Law. To the extent a Party is required by Applicable Law to deduct or withhold Taxes on any payment to the other Party (the "Withheld Amount"), such Party will remit such Withheld Amount to the proper Governmental Authority in a timely manner and promptly transmit to the other Party an official Tax certificate or other evidence of any withholding sufficient to enable the other Party to claim available credits for such Withheld Amount. The withholding Party will have the right to deduct such Withheld Amount from payment due to the other Party. For the avoidance of doubt, to the extent such Withheld Amount is so withheld and remitted in accordance with this [Section 9.10.2 \(Withholding Tax\)](#), such Withheld Amount will be treated for all purposes of this Agreement as having been paid to the other Party.

9.10.3 Tax Cooperation. The Parties agree to cooperate with one another in accordance with Applicable Law and use reasonable efforts to [***] in respect of payments made by each Party to the other Party under this Agreement. Without limiting the generality of the foregoing, each Party will provide the other with any Tax forms and other information that may be reasonably necessary to [***] based on an applicable treaty or otherwise, including a properly completed Internal Revenue Service ("IRS") Form W-9 or appropriate IRS Form W-8, as applicable, before a payment is made. If any Tax form or other information a Party previously delivered expires or becomes obsolete or inaccurate in any respect, then such Party will provide the other Party with an updated version of such form or certification or promptly notify the other Party in writing of its assigns legal inability to do so. Each Party will provide the other Party with reasonable assistance to enable the recovery, as permitted by Applicable Law, of withholding Taxes or similar obligations resulting from payments made under this Agreement, such recovery to be for the benefit of the Party bearing such withholding Tax.

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9.10.4 Changes in Domicile. Notwithstanding any provision to the contrary in this Agreement, including [Section 9.10.2 \(Withholding Tax\)](#), if as a result of a Party assigning, transferring, or conveying rights under this Agreement to an Affiliate or changing its domicile, additional Taxes become due that would not otherwise have been due hereunder with respect to payments under this Agreement, then such Party will be responsible for all such additional withholding Taxes.

9.11 Late Payments; Disputed Payments. Any undisputed payments or portions thereof due hereunder that are not paid on or before the date such payments are due under this Agreement will bear interest from the due date until the date of payment at a per annum rate equal to the lesser of: (a) [***] percentage points above the prime rate as published by *The Wall Street Journal* or any successor thereto; or (b) the maximum rate permitted by Applicable Law. If a Party disputes an invoice or other payment obligation under this Agreement, then such Party will timely pay the undisputed amount of the invoice or other payment obligation, and the Parties will resolve such dispute in accordance with [Article 15 \(Dispute Resolution; Governing Law\)](#).

ARTICLE 10 INTELLECTUAL PROPERTY

10.1 Inventions.

10.1.1 Ownership of Background Intellectual Property. As between the Parties, and subject to the licenses granted under this Agreement, each Party retains all rights, title, and interests in and to all Patent Rights and Know-How that such Party owns or Controls as of the Original Effective Date or that it develops or otherwise acquires after the Original Effective Date outside the performance of the activities under the Original Agreement during the Original Agreement Term or under this Agreement.

10.1.2 Ownership of Arising Intellectual Property. As between the Parties, ownership of all Collaboration Know-How will be as follows:

- (a) Ionis will be the sole owner of any (i) Collaboration Know-How that is developed or invented solely by Representatives of Ionis or its Affiliates or its or their licensees (other than Otsuka), Sublicensees, or Subcontractors, or any Persons contractually required to assign or license such Collaboration Know-How to Ionis or any Affiliate of Ionis ("**Ionis Collaboration Know-How**"), and (ii) Patent Rights that Cover the Ionis Collaboration Know-How ("**Ionis Collaboration Patent Rights**"), and will retain all patents, copyrights of its rights thereto, subject to any rights or licenses expressly granted by Ionis to Otsuka under this Agreement.
- (b) Otsuka will be the sole owner of any (i) Collaboration Know-How that is developed or invented solely by Representatives of Otsuka or its Affiliates or its or their licensees (other than Ionis), Sublicensees, or Subcontractors, or any Persons contractually required to assign or license such Collaboration Know-How to Otsuka or any Affiliate of Otsuka ("**Otsuka Collaboration Know-How**"), and (ii) Patent Rights that Cover the Otsuka Collaboration Know-How ("**Otsuka Collaboration Patent Rights**"), and will retain all of its rights thereto, subject to any rights or licenses expressly granted by Otsuka to Ionis under this Agreement.
- (c) Each Party will own an equal, undivided share of all Joint Collaboration Technology.

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10.1.3 Disclosure; Inventorship.

- (a) **Invention Disclosure.** Each Party will promptly disclose to the other Party all Inventions within the Collaboration Know-How developed or invented during the Original Agreement Term or during the Term by or on behalf of such Party, in each case, as soon as practicable prior to an intended public disclosure of such Invention and prior to the filing of a patent application thereon. Each Party will also promptly respond to reasonable requests from the other Party for additional information relating thereto.

(b) **Inventions by a Party.** Inventorship for Inventions and discoveries (including Know-How) first invented or developed during the course of the performance of activities under the Original Agreement and this Agreement will be determined in accordance with United States Patent Laws for determining inventorship.

(c) **Joint Research Agreement under the Leahy-Smith America Invents Act.** If a Party intends to invoke its rights under 35 U.S.C. § 102(c) of the Leahy-Smith America Invents Act, then it will notify the other Party and neither Party will make an election under such provision when exercising its rights under this Article 10 (Intellectual Property) without the prior written consent of the other Party (such consent not to be unreasonably withheld, conditioned, or delayed), and the Parties will use reasonable efforts to cooperate and coordinate their activities with respect to any submissions, filings or other activities in support thereof. The Parties acknowledge and agree that the Original Agreement and this Agreement is a "joint research agreement" as defined in 35 U.S.C. § 100(h).

10.1.4 **Practice Under and Other Use of Joint Collaboration Technology.** Subject to the rights granted under and the restrictions set forth in this Agreement (including the licenses granted under Article 2 (Licenses)), each Party will be entitled to the free use and enjoyment of all Joint Collaboration Technology and neither Party will have any obligation to account to the other Party for profits, or to obtain any approval of the other Party to license, assign, or otherwise exploit any Joint Collaboration Technology by reason of joint ownership thereof. Each Party hereby waives any right it may have under the Applicable Law of any jurisdiction to require any such approval or accounting. To the extent any further consent is required to enable a Party to so license or exploit its interest in the Joint Collaboration Technology, the other Party will grant consent promptly upon request. Without limitation, each Party will cooperate with the other Party if the Parties determine to apply for U.S. or foreign patent protection for any Joint Collaboration Technology and will obtain the cooperation of the individual inventors of any such Joint Collaboration Technology.

10.1.5 **Representative Assignment.** Each Party and its Affiliates will, and will cause its licensees, Sublicensees and Subcontractors to, enter into an agreement or employment policy with each of its Representatives performing activities related to Development, Manufacture, or Commercialization of a Licensed Product that (a) compels prompt disclosure to such Party (or its Affiliate, licensee, Sublicensee or Subcontractor, as applicable) of all Collaboration Know-How and Collaboration Patent Rights discovered, developed, invented, or filed by such Representative during any performance of such Development, Manufacture or Commercialization activities; and (b) automatically assigns to such Party (or its Affiliate, licensee, Sublicensee or Subcontractor, as applicable) all rights, title, and interests in and to all Collaboration Know-How and Collaboration Patent Rights, and requires each Representative to execute all documents and take such other actions as may be necessary to effectuate such assignment (or, if such assignment is not feasible, provides for such Party's (or its Affiliate's, licensee's, Sublicensee's or Subcontractor's, as applicable) joint ownership of, or an irrevocable, royalty-free license to such Party (or its Affiliate, licensee, Sublicensee or Subcontractor, as applicable) under, all Collaboration Know-How and Collaboration Patent Rights, with the right to sublicense to the other Party as contemplated in this Agreement), provided that the foregoing will not apply with respect to improvements to background technology of a Subcontractor.

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10.2 Patent Prosecution.

10.2.1 Ionis Patent Rights and Joint Collaboration Patent Rights.

(a) **Right to Prosecute.** As between the Parties, Ionis will have the (i) first right, in its sole discretion, to control the Patent Prosecution of all Ionis Product-Specific Patents in the Otsuka Territory and all Joint Collaboration Patent Rights worldwide, and (ii) sole right, in its sole discretion, to control the Patent Prosecution of all (A) Ionis Product-Specific Patents in the Ionis Territory, and (B) Ionis Core Technology Patents and Ionis Manufacturing and Analytical Patents, in each case, worldwide (collectively, (i) and (ii)), the "Ionis Prosecuted Patent Rights"). Upon Ionis' request, Otsuka will obtain any necessary assignment documents for Ionis with respect to the Patent Prosecution of Ionis Prosecuted Patent Rights, will render all signatures that will be necessary for such patent filings, and will assist Ionis in all other reasonable ways that are necessary for the issuance of Ionis Prosecuted Patent Rights as well as for the Patent Prosecution of Ionis Prosecuted Patent Rights, and Ionis will reimburse Otsuka's reasonable External Costs incurred in connection therewith. Ionis will be responsible for [**] of the costs and expenses incurred with respect to the Patent Prosecution of all Ionis Product-Specific Patents, Ionis Core Technology Patents and Ionis Manufacturing and Analytical Patents throughout the world and for [**] of the costs and expenses incurred with respect to the Patent Prosecution of Joint Collaboration Patent Rights in the Ionis Territory. Otsuka will be responsible for [**] of the reasonable out-of-pocket costs incurred by or on behalf of Ionis with respect to the Patent Prosecution of the Joint Collaboration Patent Rights in the Otsuka Territory (including any maintenance fees owed to local patent offices for the Joint Collaboration Patent Rights in the Otsuka Territory), and Otsuka will reimburse Ionis for such costs within [**] after receiving an invoice with reasonable supporting documentation for such costs.

(b) **Review and Consult.** Ionis will consult with Otsuka and keep Otsuka reasonably informed regarding the Patent Prosecution of the Ionis Product-Specific Patents in the Otsuka Territory and the Patent Prosecution of the Joint Collaboration Patent Rights worldwide and will provide Otsuka with all substantive correspondence received from any patent authority in connection therewith no later than [**] after receipt thereof. In addition, Ionis will provide Otsuka with drafts of proposed substantive filings in the Otsuka Territory and correspondence to any patent authority in the Otsuka Territory in connection with the Patent Prosecution of the Ionis Product-Specific Patents and with drafts of proposed substantive filings in the Territory and correspondence to any patent authority in the Territory in connection with the Patent Prosecution of Joint Collaboration Patent Rights, in each case for Otsuka's review and comment at least [**] prior to the submission of such Confidential Information. At all times, both proposed filings and correspondence, which comments (if any) Otsuka must provide no later than [**] after receipt of the applicable filing or correspondence. Ionis will consider in good faith Otsuka's reasonable comments on the Patent Prosecution of the Ionis Product-Specific Patents in the Otsuka Territory and the Joint Collaboration Patent Rights in the Territory, but Ionis will have final decision-making authority regarding Patent Prosecution of such Patent Rights under this Section 10.2.1(b) (Review and Consult).

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(c) **Abandonment.** If, at any time during the term Term, Ionis decides to cease the Patent Prosecution of a particular Ionis Product-Specific Patent in the Otsuka Territory, or a particular Joint Collaboration Patent Right in the Territory, then Ionis will provide written notice to Otsuka of such decision at least [***] prior to the date that such applicable Patent Right will become abandoned. Unless such written notice includes a reasonable strategic reason for ceasing such Patent Prosecution (e.g., continuing such Patent Prosecution would adversely affect Ionis' Patent Prosecution or litigation strategy), Otsuka may, upon written notice to Ionis, assume the Patent Prosecution of any such Patent Right at Otsuka's sole cost and expense. Without limiting the foregoing, with respect to any such Joint Collaboration Patent Right abandoned by Ionis, Ionis shall assign, and hereby does assign, to Otsuka all of its rights, title and interests in and to such Joint Collaboration Patent Right, and upon such assignment, such Joint Collaboration Patent Right shall be deemed an Otsuka Patent Right for all purposes of this Agreement Agreement.

10.2.2 Otsuka Patent Rights.

(a) **Right to Prosecute.** As between the Parties, Otsuka will have the first right to control the Patent Prosecution of all Otsuka Patent Rights throughout the world. Otsuka will be responsible for [***] of the costs and for three years after its termination, Advisor expenses incurred with respect to the Patent Prosecution of such Patent Rights throughout the world.

(b) **Review and Consult.** Otsuka will consult with Ionis and keep in confidence and trust all Confidential Information Ionis reasonably informed regarding the Patent Prosecution of the Otsuka Patent Rights and will provide Ionis with all substantive correspondence received from any patent authority in connection therewith no later than [***] after receipt thereof. In addition, Otsuka will provide Ionis with drafts of all proposed substantive filings and correspondence to any patent authority in connection with the Patent Prosecution of the Otsuka Patent Rights for Ionis' review and comment at least [***] prior to the submission of such proposed filings and correspondence, which comments (if any) Ionis must provide no later than [***] after receipt of the applicable filing or correspondence. Otsuka will consider in good faith Ionis' reasonable comments on the Patent Prosecution of the Otsuka Patent Rights, but will have final decision-making authority regarding Patent Prosecution of such Patent Rights under this Section 10.2.2(b) (Review and Consult).

(c) **Abandonment.** If, at any time during the Term, Otsuka ceases the Patent Prosecution of a particular Otsuka Patent Right, then Otsuka will provide written notice to Ionis of such decision at least [***] prior to the date on which such Patent Right will become abandoned. Unless such written notice includes a reasonable strategic reason for ceasing such Patent Prosecution (e.g., continuing such Patent Prosecution would adversely affect Otsuka's Patent Prosecution or litigation strategy), Ionis may, upon written notice to Otsuka, assume the Patent Prosecution of any such Patent Right at Ionis' sole cost and expense.

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10.3 Enforcement Against Third Party Infringement or Misappropriation.

10.3.1 **Notice of Infringement or Misappropriation.** Each Party will promptly notify the other of any apparent, threatened, or actual Competitive Infringement of which it becomes aware.

10.3.2 **Otsuka's Enforcement Right.** Otsuka will have the first right, but not use, disclose, lecture upon the obligation, to enforce [***] against any Competitive Infringement in the Otsuka Territory and at its own cost and expense and using counsel of its own choice; provided that, (a) [***], Ionis will be entitled to attend any substantive meetings, hearings, or publish any Confidential Information or anything other proceedings related to such information infringement or misappropriation suit (together with its own counsel, at its own expense) and to review and comment on all substantive documents related to such infringement or misappropriation suit prior to filing or submission of such documents, and (b) with respect to [***], Otsuka shall keep Ionis reasonably informed of the status of any substantive meetings, hearings, or other proceedings related to such infringement or misappropriation suit. If Otsuka fails to initiate a suit or take other action to abate any such Competitive Infringement within the earlier of: (i) [***] and (ii) [***], then, in either case, Ionis will have the second right, but not the obligation, to attempt to resolve such Competitive Infringement, at its own expense, including the filing of an infringement or misappropriation suit, as applicable, to enforce the applicable Patent Rights or Know-How using counsel of its own choice; provided that, if Otsuka notifies Ionis during [***] that it is electing not to take steps to enforce the applicable Patent Rights against such Competitive Infringement [***].

10.3.3 **Ionis' Enforcement Right.** Ionis will have the sole right, but not the obligation, to enforce [***] against any Competitive Infringement in the Territory, in each case ((a) and (b)), at its own cost and expense and using counsel of its own choice; provided that Ionis shall keep Otsuka reasonably informed of the status of any substantive meetings, hearings, or other proceedings related to any infringement or misappropriation suit to enforce [***] against any Competitive Infringement in the Otsuka Territory. Ionis will have the first right, but not the obligation, to enforce any [***] in the Ionis Territory, in each case, at its own expense and using counsel of its own choice; provided that Otsuka will be entitled to attend any substantive meetings, hearings, or other proceedings related to such infringement or misappropriation suit (together with its own counsel, at its own expense) and to review and comment on all substantive documents related to such infringement or misappropriation suit prior to filing or submission of such documents. If Ionis fails to initiate a suit or take other action to abate any such Competitive Infringement with respect to [***] in the Ionis Territory within the earlier of: (i) [***] and (ii) [***], then, in either case, Otsuka will have the second right, but not the obligation, to attempt to resolve such Competitive Infringement, at its own expense, including the filing of an infringement or misappropriation suit, as applicable, to enforce the applicable Otsuka Technology or Joint Collaboration Technology using counsel of its own choice; provided that, if Ionis notifies Otsuka during [***] that it is electing not to take steps to enforce the applicable Patent Rights against such Competitive Infringement [***].

10.3.4 **Allocation of Recoveries.** Any recoveries resulting from an enforcement action relating to a claim of Competitive Infringement in the Territory will be first applied against payment of each Party's costs and expenses in connection therewith. Any such recoveries in excess of such costs and expenses will be [***]; provided that [***].

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10.3.5 Cooperation; Procedures. At the request and expense of the Party bringing an infringement or misappropriation action under this Section 10.3 (Enforcement Against Third Party Infringement or Misappropriation), the other Party will provide reasonable assistance and cooperation in any such action (including entering into a common interest agreement if reasonably deemed necessary by any Party) and agrees to be joined as a party to the suit if necessary for the initiating Party to bring or continue an infringement or misappropriation action hereunder. In addition, the Party bringing an infringement or misappropriation action under this Section 10.3 (Enforcement Against Third Party Infringement or Misappropriation) will provide the other Party with copies of all pleadings and other documents in advance of filing with the court and will consider reasonable input from the other Party during the course of the action. For clarity, the Party bringing an infringement or misappropriation action under this Section 10.3 (Enforcement Against Third Party Infringement or Misappropriation) will control such infringement or misappropriation action subject to the terms of this Section 10.3 (Enforcement Against Third Party Infringement or Misappropriation). Neither Party may settle any action or proceeding brought under this Section 10.3 (Enforcement Against Third Party Infringement or Misappropriation) or knowingly take any other action in the course thereof that disclaims, limits the scope of, admits the invalidity or unenforceability of, or grants a license, covenant not to sue or similar immunity under a Patent Right Controlled by the other Party without first obtaining the written consent of the Party that Controls the relevant Patent Right. Furthermore, Ionis may not [***]. The Parties will reasonably assist each other and cooperate with each other, at their own expense, in any such investigation, pre-litigation preparation, or litigation to ensure that there is an aligned global litigation and enforcement strategy.

10.4 Defense of Third-Party Patent Challenges. Each Party will promptly notify the other Party in writing after becoming aware of an actual or threatened Patent Challenge by a Third Party of any Ionis Patent Right, Otsuka Patent Right, and Joint Collaboration Patent Right (each, a "*Third Party Patent Challenge*").

10.4.1 Otsuka's Right to Defend. Subject to the terms of Section 10.4.3 (Cooperation; Procedures), and except as may be otherwise agreed by the Parties, Otsuka will have the first right, but not the obligation, to control the defense of any Third Party Patent Challenge relating to an Otsuka Patent Right or Joint Collaboration Patent Right in the Otsuka Territory, and to compromise, litigate, settle, or otherwise dispose of any such challenge, in each case at its own expense using counsel of its own choice; *provided* that (a) with respect to a Joint Collaboration Patent Right, Ionis will be entitled to attend any substantive meetings, hearings, or other proceedings related to such Third Party Patent Challenge (together with its own counsel, at its own expense) and to review and comment on all substantive documents related to such Third Party Patent Challenge, and (b) with respect to an Otsuka Patent Right, Otsuka shall keep Ionis reasonably informed of the status of any substantive meetings, hearings, or other proceedings related to such Third Party Patent Challenge, and if Otsuka fails to initiate the defense of such Third Party Patent Challenge of a Patent Right in the Otsuka Territory within [***] after the notice provided under Section 10.4 (Defense of Third Party Patent Challenges), or otherwise abandons or elects not to continue any such defense once initiated, then Ionis will have the second right, but not the obligation, to control the defense of such Third Party Patent Challenge at its own expense using counsel of its own choice.

10.4.2 Ionis' Right to Defend. Ionis will have the sole right, but not the obligation, to control the defense of any Third Party Patent Challenge relating to an (a) Ionis Product-Specific Patent in the Ionis Territory or (b) Ionis Core Technology Patent or Ionis Manufacturing and Analytical Patent in the Territory, and to compromise, litigate, settle, or otherwise dispose of any such challenge, in each case, at its own expense using counsel of its own choice. Subject to the terms of Section 10.4.3 (Cooperation; Procedures), Ionis will have the first right, but not the obligation, to control the defense of any Third Party Patent Challenge relating to an (i) Otsuka Patent Right or Joint Collaboration Patent Right in the Ionis Territory or (ii) Ionis Product-Specific Patent in the Otsuka Territory and to compromise, litigate, settle, or otherwise dispose of any such challenge, at its own expense using counsel of its own choice; *provided* that Otsuka will be entitled to attend any substantive meetings, hearings, or other proceedings related to such Third Party Patent Challenge (together with its own counsel, at its own expense) and to review and comment on all substantive documents related to such Third Party Patent Challenge. If Ionis fails to initiate the defense of such Third Party Patent Challenge of an Otsuka Patent Right or Joint Collaboration Patent Right in the Ionis Territory or an Ionis Product-Specific Patent in the Otsuka Territory, in each case, within [***] after the notice provided under Section 10.4 (Defense of Third Party Patent Challenges), or otherwise abandons or elects not to continue any such defense once initiated, then Otsuka will have the second right, but not the obligation, to control the defense of such Third Party Patent Challenge at its own expense using counsel of its own choice.

10.4.3 Cooperation; Procedures. At the request and expense of the Party controlling the defense of any Third Party Patent Challenge under this Section 10.4 (Defense of Third Party Patent Challenges), the other Party will provide reasonable assistance and cooperation in any such action. In addition, the Party controlling the defense of any Third Party Patent Challenge under this Section 10.4 (Defense of Third Party Patent Challenges) will provide the other Party with copies of all pleadings and other documents to be filed with the court and will consider reasonable input from the other Party during the course of the action. Otsuka may not settle any action or proceeding brought or defended under this Section 10.4 (Defense of Third-Party Patent Challenges) or knowingly take any other action in the course thereof without Ionis' prior written consent. Any permitted disclosures consent, unless such action or proceeding solely concerns the Otsuka Patent Rights. Ionis may not settle any action or proceeding brought or defended under this Section 10.4 (Defense of Third-Party Patent Challenges) or knowingly take any other action in the course thereof with respect to the Ionis Product-Specific Patents or Joint Collaboration Patent Rights in the Otsuka Territory, without Otsuka's prior written consent not to be unreasonably withheld, conditioned or delayed. The Parties will reasonably assist each other and cooperate with each other, at their own expense, in any such investigation, pre-litigation preparation, or litigation to ensure that there is an aligned global litigation strategy. Notwithstanding the above, in the case of any invalidity or unenforceability claims arising in an enforcement action under Section 10.3 (Enforcement Against Third Party Infringement or Misappropriation), the Party controlling the enforcement action pursuant to Section 10.3 (Enforcement Against Third Party Infringement or Misappropriation) shall control the response to such invalidity or unenforceability claims, *provided* such Party may not admit invalidity or unenforceability of any Patent Right Controlled by Advisor the other Party without the prior written consent of the other Party.

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10.5 Third Party Infringement Claims.

10.5.1 Infringement Claim; Patent Challenges of Third-Party IP. If a Third Party asserts that a Patent Right controlled by it is, or will be, *made* infringed by the Exploitation of a Licensed Product in *strict* compliance the Territory in accordance with this Agreement, then the Party first obtaining knowledge of such claim will promptly provide the other Party with prompt written notice thereof and the related facts in reasonable detail.

10.5.2 Responsibility to Defend. During the Term of this Agreement, if a Third Party asserts that a Patent Right controlled by such Third Party is infringed, or will be infringed, by the Exploitation of a Licensed Product, then the Parties will promptly discuss the matter and the appropriate course of action. If the Parties cannot agree on a course of action within [***] following the date on which the Parties receive notice of such Third Party claim, then, subject to [Article 13](#) (Indemnification): (a) Ionis will have the sole right, but not the obligation, to defend such claim in the Ionis Territory using counsel of its own choosing, and (b) Otsuka will have the first right, but not the obligation, to defend such claim in the Otsuka Territory using counsel of its own choosing. If Otsuka does not take affirmative steps to defend such claim in the Otsuka Territory within [***] (or such shorter period of time as is legally required to answer to such claim) and does not inform Ionis within such [***] period that it is electing not to defend such claim for strategic reasons intended to maintain the commercial value of the relevant Patent Rights or any product or subject matter Covered thereby or relating thereto, then Ionis may defend such claim in the Otsuka Territory. The Party defending such claim in the Otsuka Territory will (i) keep the other Party reasonably informed regarding any such assertion, including by providing the other Party with copies of all pleadings and other documents filed in any proceeding relating to such claim, (ii) consider reasonable input from the other Party during the course of the claim, and (iii) provide the other Party with the Ionis publication opportunity to attend any substantive meetings, hearings, or other proceedings related to such claim (together with its own counsel, at its own expense) and presentation clearance policy to review and comment on all substantive documents related to such claim prior to filing or submission of such documents. The Parties will reasonably assist each other and cooperate and share information with respect to any such claim. Each Party will bear its own costs and expenses with respect to any such claim.

10.5.3 The obligations of Section 5 Settlement. Subject to [Article 13](#) (Indemnification), neither Party will not apply to information that Advisor can establish by written records: (i) was known by Advisor prior pursue or enter into any settlement or license agreement with any Third Party with respect to the receipt Patent Rights that are the subject of Confidential Information; (ii) was disclosed to Advisor a claim brought by a third party having Third Party that a Patent Right controlled by such Third Party is infringed by the Exploitation of a Licensed Product in the Otsuka Territory without the other Party's prior written consent, not to be unreasonably withheld, conditioned, or delayed. Subject to [Article 13](#) (Indemnification), Otsuka will bear the costs of any amounts paid in settlement or to satisfy a judgment of a claim that the Exploitation of a Licensed Product infringes any Third Party Patent Right in the Otsuka Territory, except to the extent such costs [***].

10.6 Patent Challenges of Third-Party Patent Rights.

10.6.1 Notice of Third-Party Patent Right. If either Party becomes aware of a Third Party Patent Right that might form the basis for a claim that the Exploitation of a Licensed Product anywhere in the world infringes, or will infringe, such Patent Right, then the Party first obtaining knowledge of such Patent Right will promptly provide the other Party with written notice thereof and the related facts in reasonable detail, and the Parties will promptly meet to discuss the matter.

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10.6.2 Patent Challenges of Third-Party Patents. Ionis will have the sole right, but not the obligation, to initiate a Patent Challenge of any such Third Party Patent Right in the Ionis Territory using counsel of its own choosing. Otsuka will have the first right, but not the obligation, to initiate a Patent Challenge of such Third Party Patent Right in the Otsuka Territory, and if Otsuka notifies Ionis that it does not intend to initiate such a Patent Challenge, Ionis will have the second right, but not the obligation, to do so; (iii) was, provided that, [***]. The Party initiating such Patent Challenge will (a) keep the other Party reasonably informed regarding any such Patent Challenge, including by providing the other Party with copies of all pleadings and other documents filed in any proceeding relating to such Patent Challenge, (b) consider reasonable input from the other Party during the course of the Patent Challenge, and (c) provide the other Party with the opportunity to attend any substantive meetings, hearings, or subsequently became, other proceedings related to such Patent Challenge (together with its own counsel, at its own expense) and to review and comment on all substantive documents related to such Patent Challenge prior to filing or submission of such documents. The Parties will reasonably assist each other and cooperate and share information with respect to any such Patent Challenge. Each Party will bear its own costs and expenses with respect to any such Patent Challenge; provided, however, that the Parties will each bear [***] of the reasonable out-of-pocket costs incurred with respect to any such Patent Challenge in the public domain through no fault Otsuka Territory, and the non-controlling Party will reimburse the Party initiating such Patent Challenge in the Otsuka Territory for such costs within [***] after receiving an invoice with reasonable supporting documentation for such costs.

10.6.3 Restrictions on Settlement. Neither Party nor its Affiliates will pursue or enter into any settlement or license agreement with any Third Party with respect to the Patent Rights that are the subject of Advisor, its officers, directors, affiliates employees such Patent Challenge in the Otsuka Territory without the other Party's prior written consent.

10.7 Patent Term Extensions. With respect to any system for extending the term of Patent Rights in the Otsuka Territory established by any applicable Regulatory Authority or agents; (iv) was independently developed by Advisor without use patent office during the Term that is similar to the patent term extension system in the U.S., [***] for making all decisions regarding patent term extensions of Confidential Information; the Ionis Patent Rights or (v) was Joint Collaboration Patent Rights in the Otsuka Territory, including supplementary protection certificates and any other extensions that are now or become available in the future, that are applicable to the Ionis Patent Rights or Joint Collaboration Patent Rights licensed hereunder and that become available directly as a result of the Regulatory Approval of a Licensed Product in the Otsuka Territory; provided that Otsuka will consult with Ionis with respect to such decisions and consider in good faith the reasonable comments and concerns of Ionis.

10.8 Unified Patent Court; Patent Linkage Listing.

10.8.1 Otsuka will be solely responsible for making all decisions regarding the opting-out or opting-in of existing Patent Rights into the jurisdiction of the Unified Patent Court or the registration of Patent Rights with Unitary Effect; provided that Otsuka will consult with Ionis with respect to such decisions and will [***].

10.8.2 Otsuka will be solely responsible for making all decisions regarding the patent linkage listings (or other listings similar to the Orange Book listings in the U.S.) in the Otsuka Territory; provided that Otsuka will consult with Ionis with respect to such decisions and will [***].

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10.9 Common Interest. The Parties stipulate and agree that, with regard to such prosecution, maintenance, enforcement, and defense the interests of the Parties as collaborators and licensor and licensee are to obtain the strongest patent protection possible, and as such, are aligned and are legal in nature. The Parties stipulate and agree that they have not waived, and nothing in this Agreement constitutes a waiver of, any legal privilege concerning the Patent Rights under this Article 10 (Intellectual Property), including privilege under the common interest doctrine and similar or related doctrines. Notwithstanding any provision to the contrary set forth in this Agreement, to the extent a Party has a good faith belief that any information required to be disclosed by Advisor pursuant such Party to the other Party under this Article 10 (Intellectual Property) is protected by attorney-client privilege or any judicial, governmental other applicable legal privilege or stock exchange request, requirement immunity, such Party will not be required to disclose such information and the Parties will in good faith cooperate to agree upon a procedure (including entering into a specific common interest agreement, disclosing such information on a "for counsel eyes only" basis or order, so long as Advisor provided Ionis with sufficient prior notice in order to allow Ionis to contest similar procedure) under which such request, requirement information may be disclosed without waiving or order, breaching such privilege or immunity.

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6. **Inventions**

In the course of performing Advisory Services for Ionis, Advisor may develop new ideas or Inventions or make other contributions of value to Ionis.

10.10 **Product Trademarks.**

10.10.1 **Ownership.**

- (a) Advisor hereby assigns **Unitary Product Trademarks**. Ionis shall, at its sole cost and expense, develop, and shall use Commercially Reasonable Efforts to obtain and maintain, a unitary Trademark (and back-up Trademarks thereof) to be used for the Licensed Products worldwide (each, a "**Unitary Product Trademark**"); provided however, [***]. If Otsuka believes it is necessary or reasonably useful to develop Trademarks in local languages in the Otsuka Territory (such as a katakana Trademark, which is a Japanese notation of a Trademark to be used for Exploitation of Licensed Products in Japan), Otsuka will [***] (each, a "**Local Unitary Product Trademark**") will be deemed to be a Unitary Product Trademark for all purposes of this Agreement (including, for clarity, [***]). For clarity, it would be [***]. Ionis Advisor's entire will own all right, title, and interest in and to each Unitary Product Trademark (including each Local Unitary Product Trademark). Otsuka will use the Unitary Product Trademarks in the Otsuka Territory to the extent required by and in accordance with the Otsuka Territory Brand Strategy, subject to Section 6.4.1 (Global Brand Strategy and American Commercialization Operating Plan) and Section 6.4.2 (Otsuka Territory Brand Strategy and Commercialization Operating Plans).
- (b) **Ownership of Otsuka Product Trademarks.** As between the Parties, Otsuka will have the sole right to determine and will own all right, title, and interest in and to any Trademarks, other than the Unitary Product Trademarks, to be created or used by Otsuka or its Affiliates or its or their Sublicensees for the Exploitation of Licensed Product in the Otsuka Territory excluding any trademarks, service marks, names, or logos that include any corporate name or logo of the Parties or their Affiliates or its or their Sublicensees ("**Otsuka Product Trademarks**"); provided that such Otsuka Product Trademarks are consistent with the Global Brand Strategy, except to the extent such inconsistency is (i) [***], or (ii) [***]. Ionis will not [***]. Ionis will not [***].

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- (c) **Ownership of Ionis Product Trademarks.** As between the Parties, Ionis will have the sole right to determine and will own all right, title, and interest in and to the Trademarks (other than the Unitary Product Trademarks) to be used by Ionis or its Affiliates or its or their Sublicensees or licensees for the Exploitation of Licensed Product in the Ionis Territory excluding any trademarks, service marks, names, or logos that include any corporate name or logo of the Parties or their Affiliates or its or their Sublicensees or licensees ("**Ionis Product Trademarks**"); provided that such Ionis Product Trademarks are consistent with the Global Brand Strategy. Otsuka will not [***]. Otsuka will not [***].

10.10.2 Notice. Each Party will provide to the other Party prompt written notice of any actual or threatened infringement of the Otsuka Product Trademarks or Ionis Product Trademarks in the Territory and of any actual or threatened claim that the use of the Otsuka Product Trademarks or Ionis Product Trademarks in the Territory violates the rights of any Third Party, in each case, of which such Party becomes aware.

10.10.3 **Prosecution of Product Trademarks.**

- (a) **Unitary Product Trademarks.** Ionis shall be responsible, at its sole discretion and cost and expense using counsel of its own choice, for the filing, prosecution, registration, and maintenance (including the defense of opposition proceedings and any equivalent proceedings and including any legal actions to prevent or exclude Third Party Trademark registrations that are confusingly similar to any Unitary Product Trademark) of the Unitary Product Trademarks in the Territory (including the Local Unitary Product Trademarks in the Otsuka Territory) throughout the Term. Ionis shall keep Otsuka informed of material progress with regard to the prosecution, registration, and maintenance of the Unitary Product Trademarks in the Otsuka Territory, including the content and timing of the filing of the Unitary Product Trademarks in the Otsuka Territory, [***], and Ionis shall [***] the Unitary Product Trademarks in the Otsuka Territory.
- (b) **Otsuka Product Trademarks.** Otsuka will have the sole right to register, prosecute and maintain the Otsuka Product Trademarks in the Territory using counsel of its own choice. All costs and expenses of registering, prosecuting, and maintaining the Otsuka Product Trademarks in the Territory will be borne solely by Otsuka.
- (c) **Ionis Product Trademarks.** Ionis will have the sole right to register, prosecute and maintain the Ionis Product Trademarks in the Territory using counsel of its own choice. All costs and expenses of registering, prosecuting, and maintaining the Ionis Product Trademarks in the Territory will be borne solely by Ionis.

10.10.4 **Enforcement of Product Trademarks.**

(a) **Unitary Product Trademarks.** During the Term, each Party will promptly notify the other Party in writing of any alleged, threatened, or actual infringement, dilution, misappropriation or other violation of or unfair trade practices or any other like offense by a Third Party relating to any Unitary Product Trademark (including any Local Unitary Product Trademark) in the Otsuka Territory ("Otsuka Territory Trademark Infringement"). Otsuka will have the first right, but not the obligation, to take any reasonable measures it deems appropriate with respect to any Otsuka Territory Trademark Infringement, using counsel of its own choice, and at its own cost and expense, including initiating or prosecuting an infringement, misappropriation or other appropriate suit or action to enforce the Unitary Product Trademarks in the Otsuka Territory and, if requested by Otsuka, Ionis shall (i) join as a party to such suit or action and execute and cause its Affiliates to execute all documents necessary for Otsuka to initiate and maintain such suit or action and (ii) provide reasonable assistance to Otsuka in connection with such suit or action. Notwithstanding the foregoing, if Otsuka does not inform Ionis that it intends to initiate a suit or take other action against an Otsuka Territory Trademark Infringement within [***] after Otsuka becoming aware of such Otsuka Territory Trademark Infringement and does not [***] within such [***], then Ionis will have the second right, but not the obligation, to initiate a suit or take other action against such Otsuka Territory Trademark Infringement at its own cost and expense. Any recoveries resulting from such suit or other action will be first applied against payment of each Party's costs and expenses in connection therewith. Any such recoveries in excess of such costs and expenses will be [***].

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(b) **Otsuka Product Trademarks.** Otsuka will have the sole right to take such action as Otsuka deems necessary against a Third Party based on any alleged, threatened, or actual infringement, dilution, misappropriation or other violation of or unfair trade practices or any other like offense relating to, the Otsuka Product Trademarks by a Third Party in the Territory, at its sole cost and expense and using counsel of its own choice. Otsuka will retain any damages or other amounts collected in connection therewith.

(c) **Ionis Product Trademarks.** Ionis will have the sole right to take such action as Ionis deems necessary against a Third Party based on any alleged, threatened, or actual infringement, dilution, misappropriation or other violation of or unfair trade practices or any other like offense relating to, the Ionis Product Trademarks by a Third Party in the Territory, at its sole cost and expense and using counsel of its own choice. Ionis will retain any damages or other amounts collected in connection therewith.

10.10.5 Third Party Claims.

(a) **Unitary Product Trademarks.** If a Third Party brings suit alleging that Otsuka's or its Affiliate's or Sublicensee's Exploitation of a Licensed Product in the Otsuka Territory infringes or will infringe such Third Party's Trademarks or that the use or registration of any Unitary Product Trademark (including any Local Unitary Product Trademark) in the Otsuka Territory infringes, dilutes, misappropriates or otherwise violates any Trademark or other right of such Third Party ("Trademark Infringement Suit"), then the Party against whom such suit is brought will promptly notify the other Party of such Trademark Infringement Suit and Otsuka will have the first right, but not the obligation, to defend such Trademark Infringement Suit using counsel of its own choice. If Otsuka does not take affirmative steps to defend such Trademark Infringement Suit within [***] (or such shorter period of time as is legally required to answer to such suit) and does not [***], then Ionis may defend such Trademark Infringement Suit. The Party defending such Trademark Infringement Suit will (i) keep the other Party reasonably informed regarding such suit, including by providing the other Party with copies of all pleadings and other documents filed in any proceeding relating to such suit, (ii) consider reasonable input from the other Party during the course of the suit, and (iii) provide the other Party with the opportunity to attend any substantive meetings, hearings, or other proceedings related to such suit (together with its own counsel, at its own expense) and to review and comment on all substantive documents related to such suit prior to filing or submission of such documents. The Parties will reasonably assist each other and cooperate and share information with respect to any such suit. The Parties will [***] all of the costs incurred by either Party in defending a Trademark Infringement Suit and any and all Inventions (and damages paid in settlement or to satisfy a judgment in a Trademark Infringement Suit. Neither Party will enter into any settlement of a Trademark Infringement Suit that is instituted or threatened to be instituted against the other Party without the other Party's prior written consent, not to be unreasonably withheld, conditioned or delayed; *provided* that such consent will not be required if such settlement includes a release of all liability in favor of, and does not impose any obligation on, the other Party and contains no admission of liability by such settling Party. Further, neither Party shall settle or compromise any Trademark Infringement Suit, or knowingly take any other action in the course thereof, in a manner that materially adversely affects the other Party's rights or interests, without the other Party's prior written consent.

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(b) **Otsuka Product Trademarks.** Otsuka will have the sole right to defend against and settle any alleged, threatened or actual claim by a Third Party that the use or registration of the Otsuka Product Trademarks in the Territory infringes, dilutes, misappropriates or otherwise violates any Trademark or other right of that Third Party or constitutes unfair trade practices or any other like offense or any other claims as may be brought by a Third Party against a Party in connection with the use of the Otsuka Product Trademarks with respect to the Licensed Products in the Otsuka Territory, at its sole cost and expense and using counsel of its own choice. Otsuka will retain any damages or other amounts collected in connection therewith.

(c) **Ionis Product Trademarks.** Ionis will have the sole right to defend against and settle any alleged, threatened or actual claim by a Third Party that the use or registration of the Ionis Product Trademarks in the Territory infringes, dilutes, misappropriates or otherwise violates any Trademark or other right of that Third Party or constitutes unfair trade practices or any other like offense or any other claims as may be brought by a Third Party against a Party in connection with the use of the Ionis Product Trademarks with respect to the Licensed Products in the Ionis Territory, at its sole cost and expense and using counsel of its own choice. Ionis will retain any damages or other amounts collected in connection therewith.

10.10.6 Housemarks.

The Parties, through the Europe JSC or the Asia JSC, in consultation with regulatory experts, will [***].

10.10.7 Cooperation.

Each Party will, and will cause its Affiliates to, promptly assist and cooperate with the other Party, as may be reasonably requested by a Party from time to time, in connection with its activities set forth in this [Section 10.10](#) (Product Trademarks), including where necessary, furnishing a power of attorney solely for such purpose or joining in, or being named as a necessary party to, such action, and providing access to relevant documents and other evidence; *provided* that, except as provided otherwise in this [Section 10.10](#) (Product Trademarks) with respect to [***], the requesting Party will reimburse the other Party for its [***] incurred in connection therewith.

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ARTICLE 11
REPRESENTATIONS, WARRANTIES, AND COVENANTS

11.1 Mutual Representations and Warranties. Each of Otsuka and Ionis hereby represents and warrants to the other Party as of the Restatement Date that:

- 11.1.1 It is a corporation or limited company duly organized, validly existing, and in good standing under the laws of the jurisdiction of its organization, and it has the full right, power, and authority to enter into this Agreement and to perform its obligations hereunder.
- 11.1.2 All consents, approvals, and authorizations from all Governmental Authorities or other Third Parties required to be obtained by such Party in connection with this Agreement have been obtained.
- 11.1.3 The execution, delivery, and performance of this Agreement by it has been duly authorized by all requisite corporate action.
- 11.1.4 The execution and delivery of this Agreement and the performance of its obligations hereunder (a) do not conflict with or violate any requirement of Applicable Law or any provision of its articles of incorporation, bylaws, limited partnership agreement, or any similar instrument, as applicable, in any material way, and (b) do not conflict with, violate, or breach or constitute a default or require any consent under, any Applicable Law or any contractual obligation or court or administrative order by which it is bound.
- 11.1.5 It has not been debarred or suspended under 21 U.S.C. §335(a) or (b), is not the subject of a conviction described in Section 306 of the FD&C Act, has not been and is not excluded from a federal or governmental health care program, debarred from federal contracting, convicted of or pled *nolo contendere* to any felony, or to any federal or state legal violation (including misdemeanors) relating to prescription drug products or fraud, is not subject to OFAC sanctions or on the OFAC list of specially designated nationals, and is not subject to any similar sanction of any Governmental Authority in the Territory ("Debarred/Excluded"), and no proceeding that could result in it being Debarred/Excluded is pending, and neither it nor any of its Affiliates has used, in any capacity in the performance of obligations relating to the Licensed Products, any employee, subcontractor, consultant, agent, representative, or other Person who has been Debarred/Excluded.

11.2 Additional Ionis Representations and Warranties. Ionis hereby represents and warrants as of the Restatement Date to Otsuka that:

- 11.2.1 It has the right under the Ionis Technology to grant to Otsuka the licenses in the Asia Territory set forth in this Agreement, and it has not granted any license or other right under the Ionis Technology that is inconsistent with the licenses granted to Otsuka in the Asia Territory hereunder.
- 11.2.2 **SCHEDULE 1.111** (Ionis Core Technology Patents), **SCHEDULE 1.117** (Ionis Manufacturing and Analytical Patents), and **SCHEDULE 1.124** (Ionis Product-Specific Patents), collectively, list all Ionis Patent Rights existing as of the Restatement Date. With respect to any such Ionis Patent Right identified as being solely owned by Ionis, Ionis owns all rights, title, and interests in and to such Ionis Patent Rights.

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- 11.2.3 As of the Restatement Date, all issued Patent Rights in the Asia Territory within the Ionis Patent Rights are in full force and effect and, to Ionis' Knowledge, are valid and enforceable. To Ionis' Knowledge, all Ionis Patent Rights in the Asia Territory are being diligently prosecuted in the respective patent rights, copyrights, offices in the Asia Territory in accordance with Applicable Law and have been filed, prosecuted, and maintained properly and correctly, and all applicable fees have been paid on or before the due date for payment.
- 11.2.4 There is no pending or, to Ionis' Knowledge, threatened litigation, nor has Ionis received any written notice from any Third Party, asserting or alleging that the Exploitation of the Licensed Products in the Asia Territory prior to the Restatement Date infringed or misappropriated the Patent Rights, Know-How or other intellectual property rights of such Third Party or that the disclosing, copying, making, assigning, licensing or use of the Ionis Technology in the Asia Territory infringes or misappropriates any Patent Right, Know-How or other intellectual property rights of such Third Party.
- 11.2.5 To Ionis' Knowledge, the practice by Otsuka of the Ionis Technology in the Asia Territory and the Exploitation by Otsuka or its Affiliates or Sublicensee of the Licensed Products in the Asia Territory in the form existing as of the Restatement Date for the treatment of HAE, in each case, does not and will not infringe, misappropriate, or otherwise violate any Patent Rights, Know-How or other intellectual property rights of any Third Party.
- 11.2.6 To Ionis' Knowledge, there are no Third Party Know-How or Patent Rights that are necessary for the Exploitation of Licensed Products in the form existing as of the Restatement Date for the treatment of HAE in the Asia Territory, other than the Know-How and Patent Rights licensed to Ionis pursuant to the Existing Third-Party IP Agreements. To Ionis' Knowledge, other than the Patent Rights and Know-How licensed to Ionis pursuant to the Existing Third-Party IP Agreements, there are no Third Party Patent Rights in the Asia Territory that Cover the composition of matter of Licensed Compound or Licensed Products or any Third Party Patent Rights or Know-How in the Asia Territory that are used in the Manufacture of the Licensed Product in the form existing as of the Restatement Date.
- 11.2.7 There are no pending or, to Ionis' Knowledge, threatened, adverse actions, suits, or proceedings against Ionis in the Asia Territory involving the Ionis Technology.
- 11.2.8 To Ionis' Knowledge, no Person is infringing or threatening to infringe or misappropriating or threatening to misappropriate any Ionis Technology in the Asia Territory.
- 11.2.9 There are no legal claims, judgments, or settlements against or owed by Ionis or any of its Affiliates, or pending or, to Ionis' Knowledge, threatened, legal claims or litigation, in each case, relating to antitrust, anti-competition, or anti-corruption law violations in the Asia Territory.
- 11.2.10 **SCHEDULE 1.69** (Existing Third-Party IP Agreements) sets forth all Existing Third-Party IP Agreements in effect as of the Restatement Date, redacted copies of which have been provided to Otsuka prior to the date hereof. Other than the Existing Third-Party IP Agreements set forth in **SCHEDULE 1.69** (Existing Third-Party IP Agreements), as of the Restatement Date there are no agreements between Ionis and any Third Party pursuant to which Ionis Controls any Know-How or Patent Rights in the Asia Territory within the Ionis Technology.

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- 11.2.11 Except for Existing Third-Party IP Agreements, Ionis is not obligated under any contract or other agreement with a Third Party as of the Restatement Date to make any payments to any owner or licensor of, or other claimant to, any Patent Right, Know-How or other intellectual property or proprietary right with respect to the Exploitation of the Licensed Product in the Asia Territory in the form existing as of the Restatement Date for the treatment of HAE.

11.2.12 With respect to the Existing Third-Party IP Agreements, Ionis represents and warrants to Otsuka, as of the Restatement Date, that: (a) it is in full force and effect; (b) neither Ionis nor any of its Affiliates is in material breach thereof; (c) neither Ionis nor any of its Affiliates has received any notice from any counterparties thereto of any material breach or notice of threatened material breach thereof; (d) neither Ionis nor any of its Affiliates has received any notice from any counterparties thereto of any intent to reduce the scope of the field thereunder or render any of the licenses thereunder non-exclusive or otherwise terminate such Existing Third-Party IP Agreements, and, to Ionis' Knowledge no event, act or omission has occurred which would reasonably give rise to the right of any counterparties thereto to reduce the scope of the field thereof or render any of the licenses thereunder non-exclusive or otherwise terminate such agreement or any licenses thereunder (including with respect to any particular Patent Rights or other intellectual property); (e) neither Ionis nor any of its Affiliates have waived or relinquished any rights thereunder; (f) entering into this Agreement and granting the rights and licenses granted (or purported to be granted) to Otsuka hereunder complies with and will not result in a breach of the terms and conditions of any Existing Third-Party IP Agreement; and (g) Ionis has the right to grant sublicenses to Otsuka under the Existing Third-Party IP Agreements as contemplated herein, including to Develop, Manufacture, Commercialize and conduct Medical Affairs for the Licensed Products in the Field in the Asia Territory.

11.2.13 Neither Ionis nor any counterparty to any Existing Third-Party IP Agreement has in writing alleged or threatened that the other party has breached an Existing Third-Party IP Agreement (which has not been cured) or, to Ionis' Knowledge, threatened in writing to terminate an Existing Third-Party IP Agreement.

11.2.14 Each [***].

11.2.15 to Ionis' Knowledge: (a) [***]; and (b) [***].

11.2.16 All preclinical and clinical studies necessary for Regulatory Approval in the Asia Territory of the Licensed Products sponsored by Ionis or its Affiliates have been and as of the Restatement Date are being conducted in material compliance with Applicable Law, including [***]. Neither Ionis nor its Affiliates has received any written notice from the PMDA or any other Regulatory Authority in the Asia Territory performing functions similar to those performed by those with respect to any ongoing clinical or pre-clinical studies or tests of the Licensed Products requiring the termination, suspension, or material modification of such ongoing studies or tests, and no Governmental Authority in the Asia Territory has commenced any action to place a clinical hold order on, or otherwise terminate or suspend, any ongoing Clinical Trial of the Licensed Products conducted by or on behalf of Ionis or its Affiliates necessary for Regulatory Approval in the Asia Territory as of the Restatement Date.

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11.2.17 As of the Restatement Date, neither Ionis nor any of its Affiliates, and, to Ionis' Knowledge, none of its or their respective officers, employees, or agents, has made an untrue statement of material fact or fraudulent statement to the PMDA or any other Regulatory Authority in the Asia Territory with respect to the Development of the Licensed Compounds or the Licensed Products in the Asia Territory, failed to disclose a material fact required to be disclosed to the PMDA or any other Regulatory Authority in the Asia Territory with respect to the Development of the Licensed Compounds or the Licensed Products in the Asia Territory, or committed an act, made a statement, or failed to make a statement with respect to the Development of the Licensed Compounds or the Licensed Products in the Asia Territory that could reasonably be expected to provide a basis for the PMDA to invoke any laws or policies in the Asia Territory analogous to the FDA policy respecting "Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities", set forth in 56 Fed. Reg. 46191 (September 10, 1991).

11.2.18 As of the Restatement Date, Ionis has no Knowledge of [***] in the Asia Territory in the form existing as of the Restatement Date for the treatment of HAE.

11.3 Additional Representations and Warranties.

11.3.1 Otsuka represents and warrants to Ionis as of the Restatement Date that there are no Patent Rights Controlled by Otsuka or any of its Affiliates that are necessary to Exploit a Licensed Product in the Asia Territory.

11.3.2 Ionis' representations and warranties set forth in Section 11.2 of the Original Agreement are hereby incorporated by reference in this Agreement in their entirety (with all such defined terms contained therein having the applicable meanings set forth in the Original Agreement), with such representations and warranties being effective as of the Original Effective Date.

11.4 Additional Covenants. Each of Otsuka and Ionis hereby covenant to the other:

11.4.1 **Assignment of Inventions.** Each Party will require all of its and its Affiliates' employees and consultants to assign all Inventions that are developed or invented by such employees according to the ownership principles described in [Section 10.1](#) (Inventions).

11.4.2 **Compliance with Law.** It will, and will ensure that its Affiliates, comply with all Applicable Law and, to the extent applicable, Professional Requirements, with respect to the performance of its obligations under this Agreement, including, as applicable, the Approved Labeling, the European Data Protection Directive 95/46/EC, the European General Data Protection Regulation (Regulation (EU) 2016/679), and any other applicable national data protection legislation.

11.4.3 **No Bribery.** It will not in the future offer, promise, pay, authorize, or give, money or anything of value, directly or indirectly, to any Government Official or Other Covered Party for the purpose, pertaining to this Agreement, of: (a) influencing any act or decision of the Government Official or Other Covered Party; (b) inducing the Government Official or Other Covered Party to do or omit to do an act in violation of a lawful duty; (c) securing any improper advantage; or (d) inducing the Government Official or Other Covered Party to influence the act or decision of a government or government instrumentality, in order to obtain or retain business, or direct business to, any Person, in each case, in any way related to this Agreement.

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11.4.4 **Restricted Countries.** Neither it nor its Affiliates will export, transfer, or sell any Licensed Product (a) to any country or territory that is subject to comprehensive economic sanctions administered by OFAC, unless the sale of such Licensed Product would be permissible if Otsuka or its Affiliates or Sublicensees were subject to OFAC's jurisdiction, (b) to any other country or territory in which such activity would violate Applicable Law in the U.S., (c) to any Restricted Party unless the sale of such Licensed Product would be permissible if Otsuka or its Affiliates or Sublicensees was subject to OFAC's jurisdiction, or (d) in such a manner that would violate the Global Trade Control Laws.

11.4.5 **FCPA Compliance.** In performing under this Agreement, it and its Affiliates agree to comply with all applicable anti-corruption laws, including the Foreign Corrupt Practices Act of 1977 and the UK Bribery Act 2010, as amended from time-to-time; the anti-corruption laws of the Territory; and all laws enacted to implement the Organization for Economic Co-operation and Development Convention on Combating Bribery of Foreign Officials in International Business Transactions.

11.4.6 **Debarred/Excluded Persons.** It will not engage, in any capacity in connection therewith, hereinafter referred with this Agreement or any ancillary agreements, any officer, employee, contractor, consultant, agent, representative, or other Person who has been Debarred/Excluded. Each Party will inform the other Party in writing promptly if it or any Person engaged by it or any of its Affiliates who is performing any obligations under this Agreement or any ancillary agreements is Debarred/Excluded, or if any action, suit, claim, investigation, or legal or administrative proceeding is pending or, to each Party's Knowledge, is threatened, pursuant to which a Party, any of its Affiliates or any such Person performing obligations hereunder or thereunder may become Debarred/Excluded.

11.5 **Disclaimer.** EXCEPT AS EXPRESSLY SET FORTH HEREIN, THE INTELLECTUAL PROPERTY RIGHTS PROVIDED BY EACH PARTY ARE PROVIDED "AS IS" AND WITHOUT WARRANTY. EXCEPT AS EXPRESSLY SET FORTH HEREIN, EACH OF THE PARTIES EXPRESSLY DISCLAIMS ANY AND ALL WARRANTIES OF ANY KIND, EXPRESS OR IMPLIED, INCLUDING THE WARRANTIES OF DESIGN, MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE, VALIDITY, OR ENFORCEABILITY OF THEIR RESPECTIVE INTELLECTUAL PROPERTY RIGHTS, AND NONINFRINGEMENT OF THE INTELLECTUAL PROPERTY RIGHTS OF THIRD PARTIES, ARISING FROM A COURSE OF DEALING, USAGE, OR TRADE PRACTICES, IN ALL CASES WITH RESPECT THERETO.

11.6 **Limitation of Liability.** NEITHER OF THE PARTIES WILL BE ENTITLED TO RECOVER FROM THE OTHER PARTY ANY SPECIAL, INCIDENTAL, INDIRECT, CONSEQUENTIAL, OR PUNITIVE DAMAGES OR DAMAGES FOR LOSS OF PROFIT, LOSS OF REVENUE, OR LOST OPPORTUNITY IN CONNECTION WITH THIS AGREEMENT, ITS PERFORMANCE OR LACK OF PERFORMANCE HEREUNDER, OR ANY LICENSE GRANTED HEREUNDER, EXCEPT TO THE EXTENT THE DAMAGES RESULT FROM A BREACH OF THE OBLIGATIONS OF A PARTY UNDER [ARTICLE 12](#) (CONFIDENTIALITY) OR BREACH OF [SECTION 2.5.2](#) (NEGATIVE COVENANT) BY IONIS, MISAPPROPRIATION OR INFRINGEMENT OF INTELLECTUAL PROPERTY OWNED OR CONTROLLED BY THE OTHER PARTY, OR AMOUNTS REQUIRED TO BE PAID TO A THIRD PARTY AS PART OF A CLAIM FOR WHICH A PARTY PROVIDES INDEMNIFICATION UNDER [ARTICLE 13](#) (INDEMNIFICATION).

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ARTICLE 12 CONFIDENTIALITY

12.1 **Duty of Confidence.** Subject to the other provisions of this [Article 12](#) (Confidentiality):

12.1.1 except to the extent expressly authorized by this Agreement, the Receiving Party shall maintain in confidence and otherwise safeguard, and not publish or otherwise disclose, all Confidential Information of the Disclosing Party;

12.1.2 the Receiving Party will treat all Confidential Information provided by the Disclosing Party, at a minimum, with the same degree of care as the Receiving Party uses for its own similar information, but in no event less than a reasonable degree of care;

12.1.3 the Receiving Party may only use any Confidential Information of the Disclosing Party for the purposes of performing its obligations or exercising its rights under this Agreement;

12.1.4 a Receiving Party may only disclose Confidential Information of the Disclosing Party to: (a) such Receiving Party's Affiliates, licensees, and Sublicensees; and (b) employees, directors, officers, agents, contractors, attorneys, accountants and consultants, of the Receiving Party and its Affiliates, licensees, and Sublicensees, in each case ((a) and (b)), to the extent reasonably necessary for the purposes of, and for those matters undertaken pursuant to, this Agreement; *provided* that such Persons are bound by legally enforceable obligations of confidentiality and non-use with respect to the Disclosing Party's Confidential Information, no less stringent than the confidentiality and non-use obligations set forth in this Agreement, except that the term of such obligation will be customary for such recipient of Confidential Information. Each Party will remain responsible for any failure by its Affiliates, licensees, and Sublicensees, and its and its Affiliates', licensees', and Sublicensees' respective employees, directors, officers, agents, consultants, attorneys, accountants and contractors, in each case, to treat such Confidential Information as required under this [Section 12.1](#) (Duty of Confidence) (as if such Persons were Parties directly bound to the requirements of this [Section 12.1](#) (Duty of Confidence)); and

12.1.5 each Party will promptly notify the other Party of any misuse or unauthorized disclosure of the other Party's Confidential Information.

12.1.6 The confidentiality, non-use, and non-disclosure obligations set forth in this [Section 12.1](#) (Duty of Confidence) will be in full force and effect from the Restatement Date until [**] after expiration or termination of this Agreement, *provided* that, with respect to any Know-How that is a trade secret and is identified as such by the Disclosing Party at the time of disclosure, the obligations of this [Section 12.1](#) (Duty of Confidence) will continue for so long as such Know-How remains a trade secret.

12.2 **Confidential Information.** Notwithstanding anything to the contrary in the definition of "Confidential Information" set forth in [Appendix 1](#) (Definitions), the Ionis Product-Specific Know-How, any ROFN Exercise Notice, the Joint Collaboration Know-How and the terms of this Agreement will be the Confidential Information of both Parties, with each Party deemed to be the Receiving Party of such information; *provided* that Ionis Product-Specific Know-How will be deemed the Confidential Information of Ionis following any termination (but not expiration) of this Agreement. The Ionis Core Technology Know-How and the Ionis Manufacturing and Analytical Know-How will be the Confidential Information of Ionis. The Otsuka Know-How will be the Confidential Information of Otsuka. Except as provided in [Section 12.4](#) (Authorized Disclosures) and [Section 12.6](#) (Publicity; Use of Names), neither Party nor its Affiliates may disclose the existence or the terms of this Agreement.

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12.3 **Exemptions.** Information of a Disclosing Party will not be Confidential Information of such Disclosing Party to the extent that the Receiving Party can demonstrate through competent evidence that such information:

12.3.1 was already known by the Receiving Party or any of its Affiliates without an obligation of confidentiality at the time of its receipt from the Disclosing Party, and not through a prior disclosure by or on behalf of the Disclosing Party, as documented by the Receiving Party's business records;

12.3.2 was generally available to the public or otherwise part of the public domain before its receipt from the Disclosing Party;

12.3.3 became generally available to the public or otherwise part of the public domain after its disclosure by the Disclosing Party other than through any act or omission of the Receiving Party or any of its Affiliates or disclosees in breach of this Agreement;

12.3.4 is subsequently disclosed to the Receiving Party or any of its Affiliates without obligation of confidentiality by a Third Party who may rightfully do so and is not under a conflicting obligation of confidentiality to the Disclosing Party; or

12.3.5 is developed by the Receiving Party or any of its Affiliates independently and without use of or reference to any Confidential Information received from the Disclosing Party, as documented by the Receiving Party's business records.

No combination of features or disclosures will be deemed to fall within the foregoing exclusions merely because individual features are published or available to the general public or in the rightful possession of the Receiving Party unless the combination itself and principle of operation are published or available to the general public or in the rightful possession of the Receiving Party.

12.4 Authorized Disclosures.

12.4.1 **Permitted Circumstances.** Notwithstanding the obligations set forth in Section 12.1 (Duty of Confidence), a Party may disclose the other Party's Confidential Information (including this Agreement and the terms herein) to the extent such disclosure is reasonably necessary in the following situations:

- (a) the prosecution or enforcement of Ionis Patent Rights, Collaboration Patent Rights, or Otsuka Patent Rights, in each case, as contemplated by this Agreement;
- (b) Regulatory Submissions and other filings or communications with Governmental Authorities (including Regulatory Authorities), as necessary for the Exploitation of the Licensed Products in connection with the exercise of the rights and the performance of the obligations of the applicable Party under this Agreement;
- (c) disclosure of this Agreement, its terms, and the status and results of Exploitation of the Licensed Products to actual or *bona fide* potential investors, acquirors, (sub)licensees (including any counterparty to a Collaboration In-License), lenders, and other financial or commercial partners (including in connection with any royalty financing transaction), and their respective attorneys, accountants, banks, investors, and advisors, solely for the purpose of evaluating or carrying out an actual or *bona fide* potential investment, acquisition, (sub)license, debt transaction, or collaboration transaction; *provided* that, in each such case, (i) such Persons are bound by obligations of confidentiality and non-use, or subject to professional ethical obligations of confidentiality, at least as stringent as those set forth Article 12 (Confidentiality), except that the term of such obligation will be customary for such recipient of Confidential Information and such type of transaction and (ii) the scope of any such disclosure is limited to the maximum extent practicable for the particular context in which it is being disclosed;
- (d) such disclosure is required to comply with Applicable Law (whether generally or in pursuit of an application for listing of securities) including the United States Securities and Exchange Commission or equivalent foreign agency or regulatory body, or otherwise required by judicial or administrative process, *provided* that in each such event, as promptly as reasonably practicable and to the extent not prohibited by Applicable Law or judicial or administrative process, such Party will notify the other Party of such required disclosure and provide a draft of the disclosure to the other Party reasonably in advance of such filing or disclosure for the other Party's review and comment. The non-disclosing Party will provide any comments as soon as practicable, and the disclosing Party will consider in good faith any timely comments provided by the non-disclosing Party; *provided* that the disclosing Party may or may not accept such comments in its reasonable discretion. Confidential Information that is disclosed in order to comply with Applicable Law or by judicial or administrative process pursuant to this Section 12.4.1(d) (Permitted Circumstances), in each case, will remain otherwise subject to the confidentiality and non-use provisions of this Article 12 (Confidentiality) with respect to the Party disclosing such Confidential Information, and such Party will take all steps reasonably necessary, including seeking of confidential treatment or a protective order to the maximum extent permitted by Applicable Law or Governmental Authority, to ensure the continued confidential treatment of such Confidential Information, and each Party will be responsible for its own legal and other external costs in connection with any such filing or disclosure pursuant to this Section 12.4.1(d) (Permitted Circumstances); or
- (e) disclosure pursuant to Section 12.6 (Publicity; Use of Names).
- (f) If and whenever any Confidential Information is disclosed in accordance with this Section 12.4 (Authorized Disclosures), such disclosure will not cause any such information to cease to be Confidential Information except to the extent that such disclosure results in a public disclosure of such information (other than by breach of this Agreement).

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12.5 Publications.

12.5.1 **Otsuka's Right to Publish.** Otsuka will have the right to publicly present or publish any Clinical Trial data, non-clinical or preclinical data, or any associated results or conclusions generated by or on behalf of Ionis or Otsuka pursuant to this Agreement (each such proposed presentation or publication, an "**Proprietary Rights Otsuka Publication**"), [***]. If Otsuka desires to publicly present or publish an Otsuka Publication in accordance with the foregoing sentence, then Otsuka will provide Ionis (including Ionis' Alliance Manager and all Ionis members of the JSC) with a copy of such proposed Otsuka Publication as early as practicable but at least [***] prior to the earlier of its presentation or intended submission for publication (such applicable period, the "**Review Period**"). [***]. Notwithstanding any provision to contrary set forth in this Agreement, Otsuka will [***]. Otsuka will provide Ionis a copy of any Otsuka Publication at the time of the submission or presentation thereof. Otsuka agrees to determine the authorship of all Otsuka Publications in accordance with all applicable International Committee of Medical Journal Editors (ICMJE) guidelines. Otsuka will require its Affiliates and Sublicensees to comply with the obligations of this Section 12.5 (Publications) as if they were Otsuka, and Otsuka will be liable for any non-compliance of such Persons.

12.5.2 **Ionis' Right to Publish.** Ionis will have the right to publicly present or publish any Clinical Trial data, non-clinical or preclinical data, or any associated results or conclusions generated by or on behalf of Ionis pursuant to this Agreement (each such proposed presentation or publication, a "**Ionis Publication**") *whether* [***]. If Ionis desires to publicly present or publish an Ionis Publication in accordance with the foregoing sentence, then Ionis will provide Otsuka (including Otsuka's Alliance Manager and all Otsuka members of the JSC) with a copy of such proposed Ionis Publication for review during the applicable Review Period. [***]. Notwithstanding any provision to contrary set forth in this Agreement, Ionis will [***]. Ionis will provide Otsuka a copy of any Ionis Publication at the time of the submission or presentation thereof. Ionis agrees to determine the authorship of all Ionis Publications in accordance with all applicable International Committee of Medical Journal Editors (ICMJE) guidelines. Ionis will require its Affiliates to comply with the obligations of this Section 12.5 (Publications) as if they were Ionis, and Ionis will be liable for any non-compliance of such Persons.

12.5.3 **Subsequent Publications.** After any Otsuka Publication or Ionis Publication has been published or publicly presented in accordance with Section 12.5.1 (Otsuka's Right to Publish) or Section 12.5.2 (Ionis' Right to Publish), as applicable, either Party may make subsequent publications or presentations of the content of such previously published Otsuka Publication or Ionis Publication without further approval or review by the other Party; *provided*, that such subsequent publication or presentation does not *patentable* include any new data, information or *registerable* conclusions, or present the content in a form or manner that materially alters the conclusion or subject matter of the previous publication or public presentation.

12.6 Publicity; Use of Names.

12.6.1 Press Release. The Parties may issue a press release announcing this Agreement, on such date and time and in such form, in each case, as may be agreed by the Parties. Other than such press release and the public disclosures permitted by this Section 12.6.1 (Press Release) and Section 12.4 (Authorized Disclosures), the Parties agree that the portions of any other news release or other public announcement relating to this Agreement or the performance hereunder that would disclose information other than that already in the public domain will require prior review and approval by both Parties (with such approval not to be unreasonably withheld, conditioned, or delayed). However, the Parties agree that after (a) a disclosure pursuant to this Section 12.6 (Publicity; Use of Names) or Section 12.4 (Authorized Disclosures) or (b) the issuance of a press release (including the initial press release) or other public announcement pursuant to this Section 12.6.1 (Press Release) that has been reviewed and approved by the other Party, the disclosing Party may make subsequent public disclosures reiterating such information without having to obtain the other Party's prior consent and approval so long as the information in such press release or other public announcement remains true, correct, and such disclosure is consistent with prior disclosures approved by the other Party pursuant to this Section 12.6 (Publicity; Use of Names) and which do not reveal non-public information about the other Party. Similarly, after a Publication has been made available to the public, each Party may post such Publication or a link to it on its corporate website or social media platforms (or any website managed by such Party in connection with a Clinical Trial for the Licensed Products, as appropriate) without the prior written consent of the other Party, so long as the information in such Publication remains true, correct, and the most current information with respect to the subject matters set forth therein.

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12.6.2 Disclosures by Ionis. Notwithstanding any provision to the contrary set forth in this Agreement, Ionis has the right to publicly disclose (in written, oral, or other form): (a) the achievement of any Regulatory Milestone Event or Sales Milestone Event under patent, copyright this Agreement (including the timing of achievement of any such milestone event but without disclosing the amount of such milestone payment unless permitted pursuant to Section 12.4.1(d) (Permitted Circumstances)); (b) the commencement, completion, material data, or similar statutes, made key results of any Clinical Trials for the Licensed Products conducted by or conceived on behalf of Ionis; and (c) the achievement of Regulatory Approval for any Licensed Product throughout the world; provided that, subject to Section 12.4.1(d) (Permitted Circumstances), [***].

12.6.3 Use of Names. Each Party will have the right to use the other Party's name and logo in presentations, its website, collateral materials, and corporate overviews to describe the collaboration relationship, as well as in taglines of press releases issued pursuant to this Section 12.6 (Publicity; Use of Names); provided that neither Party will [***], and each Party will [***]. Except as permitted under this Section 12.6 (Publicity; Use of Names) or reduced with the prior express written permission of the other Party, neither Party will use the name, trademark, trade name, or logo of the other Party or its Affiliates or their respective employees in any publicity, promotion, news release, or disclosure relating to practice this Agreement or learned its subject matter except as may be required by Advisor, Applicable Law.

12.7 Acknowledgement.

12.7.1 To the extent permitted under Applicable Law in the Otsuka Territory, Otsuka will acknowledge in any press release, public presentation, or publication regarding a Licensed Product Ionis' role in discovering and developing the Licensed Products, that the Licensed Products are under license from Ionis, and [***].

12.7.2 Otsuka agrees that it will acknowledge Ionis' role in the discovery of a Licensed Product in any scientific, medical, and other Licensed Product-related communications [***], by including the words "Discovered by Ionis" or equivalent language (collectively, the "Ionis Attribution Language") in any such communications; provided, however, that [***].

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ARTICLE 13 INDEMNIFICATION

13.1 Indemnification by Ionis. Ionis will indemnify, hold harmless, and defend Otsuka and its Affiliates and their respective directors, officers, employees, and agents (each, an "Otsuka Indemnitee") from and against any and all Third Party suits, claims, actions, or demands ("Third Party Claims") and all liabilities, expenses, or losses (including reasonable attorneys' fees, court costs, witness fees, damages, judgments, fines, and amounts paid in settlement) ("Losses") arising therefrom to the extent that the applicable Third Party Claims and such Losses arise out of (a) a breach of this Agreement by Ionis, (b) the Exploitation of the Licensed Products by or on behalf of Ionis or any of its Affiliates, licensees (not including Otsuka or its Affiliates, Sublicensees, or its Subcontractors), Sublicensees, or Subcontractors, or (c) the negligence or willful misconduct of any Ionis Indemnitee. Notwithstanding the foregoing, Ionis will not have any obligation to indemnify Otsuka Indemnitees to the extent that any Losses arise out of any Third Party Claim for which Otsuka is responsible for indemnifying Ionis pursuant to Section 13.2 (Indemnification by Otsuka).

13.2 Indemnification by Otsuka. Otsuka will indemnify, hold harmless, and defend Ionis and its Affiliates, and their respective directors, officers, employees, and agents (each, an "Ionis Indemnitee") from and against any and all Third Party Claims and all Losses arising therefrom, to the extent that the applicable Third Party Claims and such Losses arise out of (a) a breach of this Agreement by Otsuka, (b) the Exploitation of the Licensed Products by or on behalf of Otsuka or any of its Affiliates, Sublicensees, or Subcontractors, or (c) the negligence or willful misconduct of any Otsuka Indemnitee. Notwithstanding any provision to the contrary set forth in this Agreement, Otsuka will not have any obligation to indemnify the Ionis Indemnitees to the extent that any Losses arise out of any Third Party Claim for which Ionis is responsible for indemnifying Otsuka pursuant to Section 13.1 (Indemnification by Ionis).

13.3 Indemnification Procedure. If either alone Party is seeking indemnification under Section 13.1 (Indemnification by Ionis) or jointly with others, Section 13.2 (Indemnification by Otsuka) (the “**Indemnified Party**”), then it will inform the other Party (the “**Indemnifying Party**”) of the Third Party Claim giving rise to such indemnification obligations within [***] after receiving written notice of the Third Party Claim (it being understood and agreed, however, that the failure or delay by an Indemnified Party to give such notice of a Third Party Claim will not affect the Indemnifying Party’s indemnification obligations hereunder except to the extent the Indemnifying Party will have been actually prejudiced as a result of performing Advisory Services such failure or delay to give notice). The Indemnifying Party will have the right to assume the defense of any such Third Party Claim for which it is obligated to indemnify the Indemnified Party. The Indemnified Party will cooperate with the Indemnifying Party and the Indemnifying Party’s insurer as the Indemnifying Party may reasonably request, and at the Indemnifying Party’s cost and expense. The Indemnified Party will have the right to participate, with counsel of its choice, in the defense of any Third Party that has been assumed by the Indemnifying Party, which participation will be at the Indemnified Party’s expense unless (a) the Indemnifying Party has agreed to pay such fees and expenses, or (b) the Indemnified Party has been advised by counsel that there are actual or potential conflicting interests between the Indemnifying Party and the Indemnified Party, including situations in which there are one or more legal defenses available to the Indemnified Party that are different from or additional to those available to the Indemnifying Party. Neither Party will have the obligation to indemnify the other Party in connection with any settlement made without the Indemnifying Party’s written consent, which consent will not be unreasonably withheld, conditioned, or delayed. The Indemnifying Party will not admit any fault or negligence on the part of the Indemnified Party, or impose any obligation on, or otherwise adversely affect, the Indemnified Party, without the Indemnified Party’s prior written consent, which consent will not be unreasonably withheld, conditioned, or delayed. If the Parties cannot agree as to the application of Section 13.1 (Indemnification by Ionis) or Section 13.2 (Indemnification by Otsuka) as to any Third Party Claim, then, pending resolution of the dispute pursuant to Article 15 (Dispute Resolution; Governing Law), then the Parties may conduct separate defenses of such Third Party Claims, with each Party retaining the right to claim indemnification from the other Party in accordance with Section 13.1 (Indemnification by Ionis) or Section 13.2 (Indemnification by Otsuka), as applicable, upon resolution of the underlying Third Party Claim.

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13.4 Insurance. Each Party will, at its own expense, procure and maintain insurance, including product liability insurance, adequate to cover its obligations hereunder and that is consistent with normal business practices of prudent companies similarly situated at all times during which any Licensed Product is being clinically tested in human subjects or commercially distributed or sold by such Party pursuant to this Agreement. It is understood that such insurance will not be construed to create a limit of either Party’s liability with respect to its indemnification obligations under this Article 13 (Indemnification). Each Party will provide the other Party with written evidence of such insurance upon request. Each Party will provide the other Party with [***].

ARTICLE 14 **TERM AND TERMINATION**

14.1 Term. The term of this Agreement will begin on the Restatement Date and, unless earlier terminated in accordance with this Article 14 (Term and Termination), will continue until Otsuka, its Affiliates, and its Sublicensees are no longer Commercializing any Licensed Product in any country in the Otsuka Territory (the “**Term**”).

14.2 Termination for Material Breach.

14.2.1 Material Breach. If either Party believes in good faith that the other Party is in material breach of its obligations under this Agreement with respect to a given Region, then the non-breaching Party may deliver notice of such breach to the other Party stating the cause and proposed remedy (“**Breach Notification**”). For any breach alleged in any Breach Notification arising from a failure to make a payment set forth in this Agreement, the allegedly breaching Party will have [***] from the receipt of the applicable Breach Notification to cure such breach. For all breaches other than a failure to make a payment as set forth in this Agreement, the allegedly breaching Party will have [***] from the date of the Breach Notification to cure such breach. If the allegedly breaching Party fails to cure the applicable breach within the applicable period set forth above, then the Party originally delivering the Breach Notification may terminate this Agreement with respect to the applicable Region effective on written notice of termination to such allegedly breaching Party. For clarity, if the material breach relates to this Agreement as a whole, then the non-breaching Party will have the right to terminate this Agreement in its entirety in accordance with this Section 14.2.1 (Material Breach).

14.2.2 Disagreement as to Material Breach. Notwithstanding Section 14.2.1 (Material Breach), if the Parties, reasonably and in good faith, disagree as to whether there has been a material breach of this Agreement, then: (a) the Party that disputes whether there has been a material breach may contest the allegation by referring such matter, within the cure period applicable to such alleged material breach, for resolution in accordance with Article 15 (Dispute Resolution; Governing Law); (b) the relevant cure period with respect to such alleged material breach will be tolled from the date on which the Party that disputes whether there has been a material breach notifies the other Party of such dispute and through the resolution of such dispute in accordance with Article 15 (Dispute Resolution; Governing Law); and (c) during the pendency of such dispute, all of the terms and conditions of this Agreement will remain in effect and the Parties will continue to perform all of their respective obligations hereunder.

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14.3 Termination by Otsuka for Convenience. At any time during the Term, Otsuka will have the right to terminate this Agreement (a) [***] or (b) [***].

14.4 Discontinuation of Development and Commercialization. If Otsuka and its Affiliates and Sublicensees have not conducted any material Development or Commercialization activities with respect to the Licensed Products in any country in the Otsuka Territory for a continuous period of [***], and such discontinuation of activity is not: (a) by written agreement of the Parties, (b) due to [***], or (c) due to a Force Majeure, then Ionis may, at its election, terminate this Agreement in its entirety upon [***] prior written notice to Otsuka. For purposes of this Section 14.4 (Discontinuation of Development and Commercialization), the use of reasonable efforts, to the extent possible, by Otsuka or its Affiliates or Sublicensees (as applicable) to resolve a Force Majeure, clinical hold or other action or inaction of a Regulatory Authority, or any scientific or technical issues, Manufacturing or supply interruption or other material adverse event outside of Otsuka’s control for the Licensed Product will, in each case, be considered material Development or Commercialization activities.

14.5 Termination for Patent Challenge. Except to the extent unenforceable under Applicable Law, Ionis may terminate this Agreement in its entirety upon [***] prior written notice of termination to Otsuka if Otsuka or its Affiliates or Sublicensees (individually or in association with any Person) commences or assists a Third Party in commencing or conducting a Patent Challenge with respect to any Ionis Patent Right, *provided that, Ionis shall not have the right to terminate this Agreement on account of such Patent Challenge* (a) if, within [***] after receipt by Otsuka of the written notice from Ionis as set forth above in this [Section 14.5 \(Termination for Patent Challenge\)](#), Otsuka or its Affiliate, as applicable, rescinds such Patent Challenge (or in the case of any ex-parte proceeding, multi-party proceeding, or other Patent Challenge that Otsuka or such Affiliate does not have the power to unilaterally withdraw or cause to be withdrawn, Otsuka and its Affiliate, as applicable, knowingly ceases providing any direction to any Person with respect to such Patent Challenge and, to the extent Otsuka or any of its Affiliates is a party to such Patent Challenge and to the extent permitted by the applicable tribunal, it withdraws from such Patent Challenge) and *provided that neither Otsuka nor any of its Affiliates thereafter continues such Patent Challenge or, knowingly provides any direction to any Person in respect of the same or (b) in the case of any Patent Challenge commenced by a Sublicensee of Otsuka or its Affiliate, if Otsuka or its Affiliate, as applicable, terminates such Sublicensee's sublicense under any Ionis Technology within [***] after receipt by Otsuka of the applicable written notice from Ionis as set forth above in this [Section 14.5 \(Termination for Patent Challenge\)](#). If Ionis has the right to terminate this Agreement in accordance with this [Section 14.5 \(Termination for Patent Challenge\)](#) but such termination is prohibited under Applicable Law, then in lieu of such termination, [***]. If Ionis [***], then [***]. Notwithstanding the foregoing, Ionis shall not have the right to terminate this Agreement pursuant to this [Section 14.5 \(Termination for Patent Challenge\)](#) if Otsuka or any of its Affiliates or its or their Sublicensees commences a Patent Challenge (i) in a proceeding involving an Ionis Patent Right in which Otsuka or any of its Affiliates or its or their Sublicensees has been compelled to participate in the proceeding by a court, patent office, or Third Party or (ii) that is necessary or reasonably required to assert a cross-claim or a counterclaim or to respond to a court request or order or administrative law request or order, including asserting any defense or counterclaim in, or otherwise responding to, an action for infringement of intellectual property asserted, filed or threatened to be filed against Otsuka or any of its Affiliates or its or their Sublicensees by Ionis or any of its Affiliates or its or their Sublicensees.*

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14.6 Termination for Insolvency. Each Party will have the right to terminate this Agreement upon delivery of written notice to the other Party if (a) such other Party files in any court or agency pursuant to any statute or regulation of any jurisdiction a petition in bankruptcy or insolvency or for reorganization or similar arrangement for the benefit of creditors or for the appointment of a receiver or trustee of such other Party or its assets, (b) such other Party is served with an involuntary petition against it in any insolvency proceeding and such involuntary petition has not been stayed or dismissed within [***] of its filing, or (c) such other Party makes an assignment of substantially all of its assets for the benefit of its creditors.

14.7 Rights in Bankruptcy. The Parties intend to take advantage of the protections of Section 365(n) (or any successor provision) of the U.S. Bankruptcy Code or any analogous provisions in any other country or jurisdiction to the maximum extent permitted by Applicable Law. All [Inventions](#) assigned rights and licenses granted under or pursuant to this Agreement shall be deemed to be "intellectual property" for the purposes of Section 365(n) or any analogous provisions in any other country or jurisdiction. The Parties shall retain and may fully exercise all of their rights and elections under the U.S. Bankruptcy Code or any analogous provisions in any other country or jurisdiction, including the right to obtain the intellectual property from another entity. In the event of the commencement of a bankruptcy proceeding by or against either Party under the U.S. Bankruptcy Code or any analogous provisions in any other country or jurisdiction, the Party that is not subject to such proceeding shall be entitled to a complete duplicate of (or complete access to, as appropriate) all such intellectual property (including all embodiments of such intellectual property), which, if not already in the non-subject Party's possession, shall be promptly delivered to it upon the non-subject Party's written request (a) upon commencement of a bankruptcy proceeding, unless the Party subject to such proceeding continues to perform all of its obligations under this Agreement, or (b) if not delivered pursuant to clause (a) above because the subject Party continues to perform, upon the rejection of this Agreement by or on behalf of the subject Party. Unless and until the subject Party rejects this Agreement, the subject Party shall perform this Agreement or provide the intellectual property (including all embodiments of such intellectual property) to the non-subject Party, and shall not interfere with the rights of the non-subject Party to such intellectual property, including the right to obtain the intellectual property from another entity.

14.8 Full Force and Effect During Notice Period. This Agreement will remain in full force and effect until the expiration of the applicable termination notice period. For clarity, if Otsuka or any of its Affiliates or Sublicensees achieve any Milestone Events during the termination notice period, then the corresponding Milestone Payment is accrued and Otsuka will remain responsible for the payment of such Milestone Payment even if the due date of such Milestone Payment occurs after the effective date of the termination.

14.9 Effects of Termination. If this Agreement is terminated by either Party pursuant to [Section 14.2 \(Termination for Material Breach\)](#) or [Section 14.6 \(Termination for Insolvency\)](#), by Otsuka pursuant to [Section 14.3 \(Termination by Otsuka for Convenience\)](#), or by Ionis pursuant to [Section 14.4 \(Discontinuation of Development and Commercialization\)](#), or [Section 14.5 \(Termination for Patent Challenge\)](#), then all rights in the Licensed Products in the Terminated Regions will revert to Ionis, and the following will apply with respect to the Licensed Products in the Terminated Regions:

14.9.1 Termination of Licenses. As of the effective date of termination of this [section](#) Agreement, all rights licensed to Otsuka under [Section 2.1 \(License Grants to Otsuka\)](#) or otherwise under this Agreement (except for the licenses granted under [Section 2.4 \(Collaboration Technology Enabling License\)](#)), in each case, will be known as "each terminate with respect to the Terminated Region, but each Party will retain its joint ownership interests in the Joint Collaboration Technology.

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14.9.2 [Company Inventions Reversion License](#).

(a) License Grant. Advisor agrees that all Proprietary Ionis will have, and Otsuka hereby grants to Ionis, effective upon such termination, a worldwide, [***] license under any Patent Rights and [Company Inventions](#) are Ionis' sole property. Advisor agrees, upon request, to execute, verify and deliver assignments Know-How Controlled by Otsuka as of the effective date of such Proprietary termination, other than any Otsuka Technology, that, in each case, are used by Otsuka or its Affiliates in the Exploitation of any Licensed Product in the Terminated Region(s) prior to or as of the effective date of such termination solely to Exploit the Licensed Products in the Terminated Region(s) (the "**Reversion License**"). Except as otherwise provided in [Section 14.9.8 \(Sell-Off\)](#), Otsuka will not have the right to Commercialize any Licensed Product in the Terminated Region(s) upon and following the effective date of termination of this Agreement with respect to such Terminated Region(s).

(b) **Reversion Royalty.** Ionis will pay, on a Calendar Quarter basis during the applicable Royalty Term (defined *mutatis mutandis* with respect to the Reversion License except that, for clarity, references to the Ionis Patent Rights in such definition will instead refer to any Patent Rights licensed by Otsuka to Ionis under the Reversion License) a [**] royalty on Ionis' Net Sales (defined *mutatis mutandis* with respect to the Reversion License) of each Licensed Product in the Terminated Region(s). The provisions of Section 9.3.4 (Royalty Payments and Reports) through Section 9.11 (Late Payments; Disputed Payments) will apply to such payment obligation *mutatis mutandis*. Notwithstanding the foregoing, in no event will the total amount of the reversion royalty payments under this Section 14.9.2(b) (Reversion Royalty) exceed [**].

14.9.3 Transition Services.

(a) **Scope.** Ionis may request that Otsuka perform transition activities with respect to any Licensed Products in the Terminated Region(s) that are necessary to transition the responsibilities under all Regulatory Approvals for the Licensed Products in the Terminated Region(s) and ongoing Clinical Trials in the Terminated Region(s) for Licensed Products to Ionis or its designee. **Advisor understands** if Ionis requests that Otsuka perform any such transition activities, then the Parties will enter into a transition agreement containing a plan for Otsuka to perform the transition services listed in SCHEDULE 14.9.3 (Transition Services), to the extent **this Agreement** applicable at the time of termination, and such other transition services that the Parties mutually agree to (such plan, the "**Transition Plan**" and such activities, the "**Transition Services**").

(b) **Transition Plan.** Ionis may elect to have Otsuka perform the Transition Services by providing written notice to Otsuka no later than [**] following the effective date of the termination in the Terminated Region(s). If Ionis requests that Otsuka perform the Transition Services, then Ionis will propose a draft of the Transition Plan setting forth the Transition Services to be performed by Otsuka and the Parties will negotiate and enter into the Transition Plan, which will be **constructed consistent with this Section 14.9.3** (Transition Services) and will include, to the extent applicable, the services listed on SCHEDULE 14.9.3 (Transition Services), within [**] after such request. In addition, the Parties will, within [**] after such request, establish a transition committee consisting of at least each Party's Alliance Managers, a representative from each Party's CMC group who was responsible for the Licensed Product prior to the termination in the Terminated Region(s), and up to two additional representatives from each Party who are from other relevant functional groups to facilitate a smooth transition. While Otsuka is providing Transition Services, Otsuka and Ionis will mutually agree on talking points and a communication plan to customers, specialty pharmacies, physicians, Regulatory Authorities, patient advocacy groups, and clinical study investigators, in each case, in the Terminated Region(s), and Otsuka will make all such communication to such entities in accordance with the **laws of any state which precludes a requirement in an agreement to assign certain classes of inventions made by an individual acting as a Advisor, this section will be interpreted not to apply to any inventions that a court rules and/or Ionis agrees falls within such classes.** mutually agreed talking points.

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(b) (c) **Advisor further agreesCosts.** Ionis will pay Otsuka for [**]. In addition, Ionis will reimburse Otsuka for [**]. Otsuka will submit an invoice, together with supporting documentation of [**], to assist Ionis quarterly for the foregoing costs incurred by or on behalf of Otsuka in **every proper way** such Calendar Quarter, and Ionis will pay the undisputed invoiced amounts within [**] after the date of such invoice (and will pay any disputed amounts within [**] following resolution of the dispute and determination that such amounts are owed).

14.9.4 Return of Confidential Information. Each Party will return or destroy (at the other Party's election) all Confidential Information of the other Party to obtain, from time to time, and to enforce United States and foreign Proprietary Rights the extent relating to Company Inventions the Terminated Region(s) in any and all countries. To that end Advisor will execute, verify and deliver such documents and perform such other acts (including appearances as a witness) as Ionis may reasonably request for use in applying for, obtaining, sustaining and enforcing such Proprietary Rights relating to Company Inventions. Advisor's obligation to assist Ionis in obtaining and enforcing Proprietary Rights relating to Company Inventions in any and all countries will continue beyond its possession upon termination of this Agreement but in such Terminated Region(s) and, if applicable, the Receiving Party will provide a written confirmation of such destruction within [**] of such request. Notwithstanding the foregoing or any provision to the contrary set forth in this Agreement: (a) the foregoing terms of this Section 14.9.4 (Return of Confidential Information) will not apply to any Confidential Information that is necessary to allow the Receiving Party to perform its obligations or exercise any of its rights that expressly survive the applicable termination of this Agreement in such Terminated Region(s), and the Receiving Party may retain one copy of such Confidential Information for its legal archives; and (b) the Receiving Party will not be required to destroy electronic files containing such Confidential Information that are made in the ordinary course of its business information back-up procedures pursuant to its electronic record retention and destruction practices that apply to its own general electronic files and information.

14.9.5 Sublicenses. If this Agreement is terminated prior to expiration, then Ionis will compensate Advisor shall grant to each Sublicensee of Otsuka with respect to one or more Terminated Regions, at each such Sublicensee's written request to Ionis within [**] of the effective date of termination in such Terminated Region(s), a reasonable rate after direct license, **provided** that such termination for the time actually spent by Advisor at Ionis' request Sublicensee (a) is not then in connection with such assistance. If Ionis is unable, after reasonable effort, default of its sublicense agreement or this Agreement, (b) agrees in writing to secure Advisor's signature on any document needed to apply for or prosecute any Proprietary Rights relating to a Company Invention, Advisor hereby irrevocably designates and appoints Ionis and its duly authorized officers and agents as her agent and attorney in fact, to act for and on Advisor's behalf to execute, verify and file any such applications and to do all other lawfully permitted acts to further the prosecution and issuance of any such Proprietary Rights comply with the terms of this Agreement to the extent applicable to the rights originally sublicensed to such Sublicensee by Otsuka, and (c) agrees to pay directly to Ionis such Sublicensee's payments under such sublicense agreement. The scope of such direct license shall be no less than the scope of the license granted herein and sublicensed to such Sublicensee, and Ionis shall have no obligation to perform any task for such Sublicensee beyond the obligations owed to Otsuka hereunder. Each Sublicensee will be an intended Third Party beneficiary of this Section 14.9.5 (Sublicenses) with the right to enforce the same **legal force and effect as if executed by Advisor** against Ionis.

14.9.6 Assignment. To the extent requested by Ionis in writing following the date that a Party provides notice of termination of this Agreement in the Terminated Region(s), Otsuka will promptly (and in any event no later than [**] after the effective date of termination in the Terminated Region(s) unless agreed otherwise in the Transition Plan or expressly specified otherwise below).

(a) During provide to Ionis for its review unredacted copies of all clinical trial agreements and distribution agreements with respect to one or more Terminated Regions (to the term extent assignable, not cancelled, and solely related to the Licensed Products), in each case, that are necessary or reasonably useful for the Exploitation of this Agreement, Advisor will promptly disclose the Licensed Products in the Terminated Region(s), and, following such review, upon Ionis' written request within [**] after entering into a Transition Plan or [**] after the effective date of termination in the Terminated Region(s) if Ionis does not elect to enter into a Transition Plan, assign and transfer to Ionis or its designee all of Otsuka's rights, title, and interests in and to any persons designated by it, fully and in writing and will hold in trust for the sole right and benefit of such agreements;

(b) assign to Ionis any and all Company Inventions, whether Potential In-Licenses with respect to one or not patentable more Terminated Regions entered into by Otsuka pursuant to Section 2.7.2 (Potential In-Licenses);

(c) assign any agreements or protectable by copyright. At the time of each such disclosure, Advisor will advise Ionis in writing of any Inventions that Advisor believes are not subject arrangements with Third Party vendors (including distributors) with respect to one or more Terminated Regions solely related to the assignment provisions of Section 6(a) above, and Advisor will at that time provide Licensed Products or, to the extent any such Third Party agreement or arrangement is not assignable to Ionis, in writing all evidence necessary reasonably cooperate with Ionis to substantiate that belief. Advisor will not be obligated to disclose information received by Advisor from others under continue to provide such services for a contract of confidentiality. In addition, reasonable time after termination of this Agreement Advisor will in the Terminated Region(s) to facilitate the orderly transition of all Commercialization and other activities then being performed by or on behalf of Otsuka or its Affiliates or Sublicensees for the Licensed Products in the Terminated Region(s) to Ionis or its designee;

(d) assign and transfer to Ionis or its designee, as of the effective date of termination in the Terminated Region(s), all of Otsuka's rights, title, and interests in and to the Otsuka Product Trademarks in the Terminated Region(s) and any domain names associated with the Otsuka Product Trademarks (to the extent that Otsuka or its Affiliates has any) in the Terminated Region(s) and promptly provide to Ionis all information necessary to maintain such domain names;

(e) assign and transfer to Ionis or its designee, as of the effective date of termination in the Terminated Region(s), all of Otsuka's rights, title, and interests in and to any Product Materials in the Terminated Region(s) specifically related to the Licensed Products, and copyrights and any registrations for the foregoing (to the extent that Otsuka or its Affiliates has any); and

(f) within [**] after entering into a Transition Plan or [**] after the effective date of termination in the Terminated Region(s) if Ionis does not elect to enter into a Transition Plan, disclose to Ionis or its designee all patent applications filed documents, records, and materials that embody any of the foregoing and that are Controlled by Advisor relating to any Company Inventions or relating to any work performed by Advisor on behalf of Ionis, Otsuka.

7. To the extent that any agreement or other asset described in this Section 14.9.6 (Assignment) is not assignable by Otsuka, then such agreement or other asset will not be assigned, and upon the request of Ionis, Otsuka will take such steps as may be necessary to allow Ionis to obtain and to enjoy the benefits of such agreement or other asset, in the form of a license or other right to the extent Otsuka has the right and ability to do so; Previous Advisory Relationships provided

Advisor represents that Advisor's performance of Advisory Services, as well as Advisor's performance such steps will not require Otsuka to [**] in order to obtain and enjoy such benefits. For clarity, Ionis will have the right to request that Otsuka take any or all of the rest of Advisor's obligations under the terms of this Agreement, will not breach any agreement to keep foregoing actions in confidence any proprietary information acquired by Advisor in confidence whole or in trust from another entity prior part, or with respect to all or any portion of the date of this Agreement. Advisor agrees not to bring to Ionis or to use assets set forth in the performance of Advisory Services for Ionis any materials or documents of a present or former employer or client of Advisor, or any materials or documents obtained by Advisor under a confidentiality agreement imposed by reason of another of Advisor's Advisory relationships, unless such materials or documents are generally available to the public or Advisor has authorization from such present or former employer or client for the possession and unrestricted use of such materials.

8. Termination; Survival

(a) This Agreement will become effective on the Effective Date and will end on the Scheduled End Date unless earlier terminated in accordance with this Agreement. Advisor may terminate this Agreement by providing Ionis with at least 60 days advance written notice. Ionis may only terminate this Agreement for Cause. "Cause" means a determination by Ionis after consultation with the nominating governance and review committee of the Board that this Agreement shall be terminated by Ionis for any of the following reasons: (i) Advisor's failure or refusal to comply in any material respect with lawful policies, standards or regulations of Ionis; (ii) Advisor's violation of a federal or state law or regulation applicable to the business of Ionis; (iii) Advisor's conviction or plea of no contest to a felony under the laws of the United States or any State; (iv) Advisor's fraud or misappropriation of any material property belonging to Ionis or its affiliates; (v) Advisor's breach, in any material respect, of the terms of any confidentiality, invention assignment or proprietary information agreement with Ionis or with any former employer, or (vi) Advisor's failure to perform a material obligation under this agreement; provided solely in the case of (i), (v) or (vi) after Ionis provides Advisor with written notice of such failure and provided Advisor at least 60 days to cure such failure. foregoing provisions.

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(b) Upon expiration or termination of this Agreement, each party will be released from all obligations and liabilities to the other occurring or arising after the date of such expiration or termination, except that any termination or expiration of this Agreement will not relieve Advisor of Advisor's obligations under Sections 4, 5, 6, 7, 9 and 10 hereof, nor will any such expiration or termination relieve Advisor or Ionis from any liability arising from any breach of this Agreement. Upon expiration or termination of this Agreement for any reason whatsoever, Advisor will promptly surrender and deliver to Ionis any and all notes, business records, memoranda, specifications, devices, formulas, molecules, cells, storage media, including calculations, sequences, data and other materials of any nature

pertaining to Advisory Services for Ionis, as well as any documents or data of any description (or any reproduction of any documents or data) containing or pertaining to any Trade Secret Information or Ionis' Confidential Information.

9. Arbitration⁷³

(a) Ionis and Advisor agree to resolve by arbitration all disputes, claims or controversies ("Claims"), past, present or future, whether or not arising out of this Agreement or its termination, that Ionis may have against Advisor or that Advisor may have against any of the following (i) Ionis; (ii) Ionis officers, directors, employees or agents; (iii) Ionis' subsidiary or affiliated entities, joint ventures, or joint employers; (iv) Ionis' benefit plans or the plans' sponsors, fiduciaries, administrators, affiliates and agents; and/or (v) all successors and assigns of any of the foregoing. The Claims covered by this Agreement include all disputes that Ionis or Advisor could otherwise pursue in state or federal court including, but not limited to, Claims based on any state, federal, or local statute, regulation or ordinance (including Claims for discrimination, retaliation, harassment, unpaid wages or violation of state or federal wage and hour laws), as well as common law Claims (including Claims for breach of contract, breach of the implied covenant of good faith and fair dealing, wrongful discharge, defamation, misrepresentation, fraud, or infliction of emotional distress). Ionis and Advisor anticipates that this Section 9 provides the benefits of a speedy, less formal, impartial, final and binding dispute resolution procedure. Advisor represents and warrants to Ionis that Advisor is not aware of any set of facts or circumstances that may reasonably give rise to any Claim, litigation or other legal proceeding between Advisor and Ionis.

(b) To the maximum extent permitted by law, Advisor hereby waives any right to bring on behalf of persons other than Advisor, or to otherwise participate with other persons in, any class, collective or representative action (i.e. a type of lawsuit in which one or several persons sue on behalf of a larger group of persons).

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14.9.7 **Regulatory Submissions and Regulatory Approvals.** Otsuka will and hereby does, and will cause its Affiliates and Sublicensees to, (a) no later than [**] after the effective date of termination of this Agreement in the Terminated Region(s), at Ionis' request either (i) assign and transfer to Ionis or its designee all of Otsuka's rights, title, and interests in and to all Regulatory Submissions, Regulatory Approvals, and Reimbursement Approvals in the Terminated Region(s) or (ii) solely with respect to any Terminated Region(s) in the Asia Territory, withdraw all Regulatory Submissions, Regulatory Approvals, and Reimbursement Approvals in such Terminated Region(s), in each case ((i) or (ii)), solely for the Licensed Products in the Terminated Region(s) then Controlled by Otsuka or any of its Affiliates or Sublicensees (for any Sublicensees that do not become a direct licensee of Ionis pursuant to Section 14.9.5 (Sublicenses)), and (b) to the extent any assignment requested pursuant to clause (a) is delayed or is not permitted by the applicable Regulatory Authority, permit Ionis to cross-reference and rely upon any such Regulatory Submissions, Regulatory Approvals, and Reimbursement Approvals filed by Otsuka or any of its Affiliates or Sublicensees (for any Sublicensees that do not become a direct licensee of Ionis pursuant to Section 14.9.5 (Sublicenses)). Otsuka will execute and deliver, or will cause to be executed and delivered, to Ionis or its designee such endorsements, assignments, commitments, acknowledgements, and other documents as may be necessary to effect the foregoing assignment, including submitting to each applicable Regulatory Authority or other Governmental Authority a letter or other necessary documentation (with copy to Ionis) notifying such Regulatory Authority or other Governmental Authority of, or otherwise giving effect to, the transfer of ownership to Ionis of all such assigned Regulatory Submissions, Regulatory Approvals, and Reimbursement Approvals in the Terminated Region(s). In addition, upon Ionis' written request, Otsuka will, [**] (other than in the event of termination of this Agreement by Otsuka pursuant to Section 14.2 (Termination for Material Breach) or Section 14.6 (Termination for Insolvency), in which case Ionis shall [**]), provide to Ionis copies of all material related documentation, including material non-clinical, preclinical, and clinical data related to the Licensed Products in the Terminated Region(s) that are held by or reasonably available to Otsuka or its Affiliates or Sublicensees (for any Sublicensees that do not become a direct licensee of Ionis pursuant to Section 14.9.5 (Sublicenses)).

(c) **Sell-Off.** If Otsuka is Commercializing any Licensed Product in any country in the Terminated Region(s) as of the applicable effective date of termination in such Terminated Region(s), then, [**], either (a) Otsuka will appoint Ionis or its designee as its exclusive distributor of such Licensed Product in such country and grant Ionis or its designee the right to appoint sub-distributors, to the extent not prohibited by any written agreement between Otsuka or any of its Affiliates and a Third Party or (b) Otsuka will have the continued right to sell the Licensed Products in the Terminated Region(s) from its inventory; *provided, however,* that Otsuka's obligations under this Agreement with respect to the Licensed Products that Otsuka sells in the Terminated Region(s), including the obligation to pay Royalties to Ionis hereunder, will continue in full force and effect during such period. If Ionis elects to be appointed as the exclusive distributor pursuant to the foregoing clause (a), then the Parties will enter into a distribution agreement with respect to such appointment and Ionis will use good faith efforts to distribute such Licensed Product in such country, or otherwise distribute such Licensed Product in such country, in accordance with the terms of the distribution agreement.

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14.9.9 **Inventory.** [**].

14.9.10 **Wind Down and Transition.** Otsuka will be responsible, [**] (other than in the event of termination of this Agreement by Otsuka pursuant to Section 14.2 (Termination for Material Breach) or Section 14.6 (Termination for Insolvency), in which case Ionis shall [**]), for the wind-down of Otsuka's and its Affiliates' and Sublicensees (for any Sublicensees that do not become a direct licensee of Ionis pursuant to Section 14.9.5 (Sublicenses)) activities with respect to the Licensed Products in the Terminated Region(s). Otsuka will, and will cause its Affiliates and such Sublicensees to, reasonably cooperate with Ionis to facilitate orderly transition to Ionis or its designee of all Commercialization and other activities then being performed by or on behalf of Otsuka or its Affiliates for the Licensed Products in the Terminated Region(s).

14.9.11 **Cost of Transition Activities.** Notwithstanding any provision to the contrary in this Section 14.9 (Effects of Termination), but without limiting Section 14.9.3(c) (Costs), if Otsuka terminates this Agreement pursuant to Section 14.2 (Termination for Material Breach) or Section 14.6 (Termination for Insolvency), Ionis will be responsible for, and will pay Otsuka, [**]. Otsuka will submit an invoice, together with supporting documentation of [**], to Ionis quarterly for the foregoing costs incurred by or on behalf of Otsuka in such Calendar Quarter, and Ionis will pay the undisputed invoiced amounts within [**] after the date of any such invoice (and will pay any disputed amounts within [**] following resolution of the dispute and determination that such amounts are owed).

14.9.12 **Other Assistance; Further Assurances.** Otsuka will provide any other assistance reasonably requested by Ionis for the purpose of allowing Ionis or its designee to proceed expeditiously with the Exploitation of the Licensed Products in the Terminated Region(s) for a period of [**] after the effective date of termination of this Agreement in such Terminated Region(s). Otsuka will execute all documents, and take all such further actions as may be reasonably requested by Ionis in order to give effect to the requirements in this Section 14.9 (Effects of Termination).

14.10 Survival; Accrued Rights. Expiration or termination of this Agreement with respect to Terminated Region(s) will not relieve the Parties of any liability that accrued hereunder prior to the effective date of such expiration or termination in such Terminated Region(s) nor preclude either Party from pursuing all rights and remedies it may have hereunder or at law or in equity with respect to any breach of this Agreement, nor prejudice either Party's right to obtain performance of any obligation. Without limiting the foregoing, the following provisions of this Agreement will survive the expiration or termination of this Agreement with respect to Terminated Region(s): Section 2.2 (License Grant to Ionis); Section 2.4 (Collaboration Technology Enabling License); Section 4.6 (Development Records; Cooperation) (solely with respect to the obligation to maintain records for at least [***] after the end of the Term or for such longer period as may be required by Applicable Law); Article 9 (Payments) (solely with respect to amounts that accrued prior to the effective date of termination and, with respect to Section 9.5 (Financial Records and Audits), solely for [***] after the effective date of termination); Section 10.1 (Inventions); Section 11.5 (Disclaimer); Section 11.6 (Limitation of Liability); Article 12 (Confidentiality, excluding Section 12.5 (Publications)); Article 13 (Indemnification); Section 14.9 (Effects of Termination); this Section 14.10 (Survival; Accrued Rights); Article 15 (Dispute Resolution; Governing Law); Article 16 (Miscellaneous); and Appendix 1 (Definitions).

ARTICLE 15

DISPUTE RESOLUTION; GOVERNING LAW

15.1 Executive Officers; Disputes. Each Party will ensure that an Executive Officer is designated for such Party at all times during the Term for dispute resolution purposes, and will promptly notify the other Party of any change in its designated Executive Officer. In the event of a dispute, controversy or claim arising under, relating to, or in connection with this Agreement (except for disputes arising at the Executive Committee, any JSC, or any other Subcommittee, which will be resolved in accordance with Section 8.5 (Decision-Making) and Section 8.6 (Resolution of Committee Disputes)) (a "**Disputed Matter**"), then the Parties will refer such dispute to their respective Executive Officer, and such Executive Officers or designees will attempt in good faith to resolve such dispute. If the Parties are unable to resolve any such dispute within [***] after both Parties have referred such dispute to their designated Executive Officers pursuant to this Section 15.1 (Executive Officers; Disputes), then either Party will have the right to pursue any and all remedies available at law or equity, as set forth in Section 15.2 (Arbitration) or Section 15.3 (Intellectual Property Disputes), as applicable.

15.2 Arbitration.

15.2.1 If the Parties are unable to resolve a Disputed Matter using the process described in Section 15.1 (Executive Officers; Disputes) and Section 15.3 (Intellectual Property Disputes) does not apply, then a Party seeking further resolution of the Disputed Matter will submit the Disputed Matter to resolution by final and binding arbitration in accordance with this Section 15.2 (Arbitration).

15.2.2 The seat, or legal place, of arbitration will be New York, New York. The arbitration will be administered by the International Chamber of Commerce pursuant to its Rules of Arbitration in effect at the time of the arbitration, (the "**Rules**"), except they may be modified as set forth herein, and applying the substantive law specified in Section 15.5 (Governing Law; English Language). The language of the arbitration will be English.

15.2.3 Unless a Party elects for application of the ICC's Expedited Procedure Rules pursuant to Section 15.2.4 (Arbitration) or the Expedited Procedure Rules otherwise apply because of the amount in dispute, the arbitration will be conducted by a single neutral tribunal of three arbitrators. The claimant will nominate an arbitrator in accordance with its request for arbitration; the then-current Commercial Arbitration and Mediation Procedures respondent will nominate an arbitrator within [***] of receipt of the American Arbitration Association ("request for arbitration; and the two-party nominated arbitrators will nominate the third, who will serve as chair of the tribunal, within [***AAA]" of the second arbitrator's appointment. If any of the three arbitrators are not nominated within the time prescribed above, then the ICC will appoint the arbitrator(s). The Within [***] of the commencement of arbitration, the Parties will attempt in good faith to reach agreement upon and thereafter follow procedures directed at assuring that the arbitration will take place be concluded and the award rendered within no more than [***] from the date the ICC Secretariat transmits the file to the arbitral tribunal. Failing such agreement, the arbitral tribunal will design and the Parties will follow procedures directed at meeting such a time schedule. Each arbitrator must have at least [***] of business or legal experience in San Diego, California. Ionis will pay the arbitrator's fee and will bear all administrative charges by AAA. All parties pharmaceutical industry. An arbitrator will be entitled deemed to engage in reasonable pre-hearing discovery meet these qualifications unless a Party objects within [***] after the arbitrator is nominated.

15.2.4 Notwithstanding Section 15.2.3 (Arbitration), if the Disputed Matter involves the dispute of a Breach Notification for any default other than a determination of an alleged failure to obtain information use Commercially Reasonable Efforts to prosecute Develop or defend Commercialize the asserted claims. Any disputes between Licensed Product, the parties regarding non-breaching Party may elect on notice to the nature or scope breaching Party to apply the ICC Expedited Procedure Rules to the arbitration and, if such election is made, the number of discovery arbitrators will be decided one and the period for the rendering of the final award will be [***] from the date of the case management conference.

15.2.5 The Parties agree that any dispute concerning the propriety of the commencement of the arbitration or the scope and applicability of the agreement to arbitrate will be determined by the arbitrator. The arbitrator will hear and issue a written ruling upon any dispositive motions brought by either party, including but not limited to, motions for summary judgment or summary adjudication arbitrator(s).

15.2.6 No tribunal of issues. After the hearing, the arbitrator will issue a written decision setting forth the award, if any, and explaining the basis therefore. The arbitrator will have the power to award damages excluded pursuant to Section 11.6 (Limitation of Liability).

15.2.7 Article 38 of the Rules will apply with respect to the costs of the arbitration.

15.2.8 Except as may be required by Applicable Law, neither a Party nor any type arbitrator may disclose the existence, content, or results of relief that would be available in court, any arbitration hereunder without the prior written consent of both Parties, unless to protect or pursue a legal right. The arbitrator's arbitral award will be final and binding upon on the parties Parties and the Parties will carry out the award without delay. Judgment on the award so rendered may be entered as a judgment in any court of competent jurisdiction. If there is conflict No award or procedural order made in the arbitration procedures shall be published.

15.3 Intellectual Property Disputes. Notwithstanding any provision to the contrary set forth in this Agreement, if a dispute arises under this Agreement with respect to the validity, scope, enforceability, or ownership of any Patent Right or other intellectual property rights, and the AAA rules specified above, the AAA rules will control. Notwithstanding the foregoing, and regardless of what is provided by the AAA rules, the arbitrator will not have authority or jurisdiction to consolidate claims of different individuals or entities into one proceeding, nor will the arbitrator have authority or jurisdiction to hear the arbitration as a class action. As noted above, Advisor has agreed to waive any right to bring any class, collective or representative action. To the extent that the class, collective or representative action waiver described above such dispute is not enforceable, the issue of whether resolved in accordance with [Section 15.1](#) (Executive Officers; Disputes), then such dispute will be submitted to certify any alleged or putative class for a class action proceeding must be decided by a court of competent jurisdiction. The arbitrator jurisdiction in the jurisdiction in which such Patent Right or other intellectual property right was granted or arose.

15.4 Equitable Remedies. Notwithstanding any provision to the contrary set forth in this Agreement, the Parties each stipulate and agree that (a) the other Party's Confidential Information includes highly sensitive trade secret information such that a breach of [Article 12](#) (Confidentiality) by a Party will cause irrevocable harm for which monetary damages would not have authority or jurisdiction to decide class certification, collective or representative action issues. Until any class certification, collective, or representative action issues are decided by provide a sufficient remedy; and (b) in such case of such breach of [Article 12](#) (Confidentiality), the court, all arbitration proceedings non-breaching Party will be stayed, and the arbitrator will take no action with respect entitled to the matter. However, once any issues regarding class certification, collective, seek equitable relief, including specific performance, temporary or representative action have been decided by the court, the arbitrator will have authority to decide the substantive claims.

10. Miscellaneous

(a) The rights and liabilities of the parties hereto will bind and inure to the benefit of their respective successors, heirs, executors and administrators, as the case may be; provided that, as Ionis has specifically contracted for Advisor's services, Advisor may not assign or delegate Advisor's obligations under this Agreement either in whole or in part without Ionis' prior written consent.

(b) Because Advisor's services are personal and unique and because Advisor has access to and become acquainted with Ionis' Confidential Information, the parties agree that in the event of a threatened or actual material breach of this Agreement by Advisor injunctive relief would be appropriate. As such, Ionis has the right to enforce this Agreement and any of its provisions by permanent restraining orders, preliminary injunction, specific performance permanent injunction, or other equitable relief without prejudice the posting of any bond or other security. In addition, and notwithstanding any provision to the contrary set forth in this Agreement, in the event of any other rights actual or threatened breach hereunder, the aggrieved Party may seek interim equitable relief (including temporary restraining orders, or other provisional equitable relief) from any court of competent jurisdiction without first submitting to the dispute resolution procedures set forth in [Article 15](#) (Dispute Resolution; Governing Law) and remedies shall retain that Ionis may have for a breach right after the appointment of this Agreement: the arbitrator(s).

(c) **15.5 Governing Law; English Language.** This Agreement and all amendments, modifications, alterations, or supplements hereto, and the rights of the Parties, will be construed under and governed by and construed according to the laws of the State of California New York, United States, exclusive of its conflicts of laws principles. This Agreement has been prepared in the English language and the English language will control its interpretation. All consents, notices, reports, and other written documents to be delivered or provided by a Party under this Agreement will be in the English language, and in the event of any conflict between the provisions of any document and the English language translation thereof, the terms of the English language translation will control.

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ARTICLE 16 MISCELLANEOUS

16.1 Assignment. This Agreement may not be assigned or otherwise transferred, nor may any right or obligation hereunder be assigned or transferred, by either Party without the prior written consent of the other Party. Notwithstanding the foregoing, (a) Ionis may assign its rights to receive payments under this Agreement to one or more Persons (including as part of a royalty monetization transaction) (a "Payment Assignment") without consent of Otsuka; provided that Ionis shall give prompt written notice to Otsuka upon making a Payment Assignment, and any assignee of a Payment Assignment shall not have any rights, including any audit rights, hereunder (other than the right to receive payments under this Agreement) unless Otsuka provides express prior written consent, which Otsuka may grant or withhold in its discretion, and (b) either Party may, without consent of the other Party, assign this Agreement and its rights and obligations hereunder (i) in whole or in part to an Affiliate of such Party (for so long as such laws Affiliate remains an Affiliate), or (ii) in whole to its successor-in-interest in connection with the sale of all or substantially all of its assets, whether in a merger, acquisition, or similar transaction or series of related transactions. If there is an assignment pursuant to the foregoing clauses (b)(i) or (b)(ii), then such assignment will only be effective if the Person to whom this Agreement is assigned agrees in writing to assume all of the assigning Party's obligations under this Agreement and the assigning Party provides written notice of such assignment to the non-assigning Party within [***] after the effective date of such assignment. Any attempted assignment of this Agreement in violation of this [Section 16.1](#) (Assignment) will be null, void, and of no legal effect. Any permitted assignee will assume all assigned obligations of its assignor under this Agreement. This Agreement will be binding on and will inure to the benefit of the permitted successors and assigns of the Parties.

16.2 Entire Agreement; Amendment.

16.2.1 This Agreement and the Ancillary Agreements, together with all exhibits and schedules attached hereto, is in effect from and after the Restatement Date. This Agreement constitutes the entire agreement between the Parties with respect to the subject matter hereof, and supersedes and merges all prior and contemporaneous negotiations, representations, and understandings regarding the same except, with respect to the Original Agreement, as set forth in [Section 16.2.2](#) (Entire Agreement; Amendment) (including that certain mutual confidential disclosure agreement between the Parties dated [***] ("Confidential Disclosure Agreement")). All information shared by the Parties pursuant to the Confidential Disclosure Agreement and the Original Agreement will be Confidential Information under this Agreement from and after the Restatement Date, and the use and disclosure thereof will be governed by [Article 12](#) (Confidentiality). This Agreement may not be modified or amended, except by another agreement in writing executed by duly authorized signatories of each Party.

16.2.2 The Original Agreement is amended and restated in its entirety and superseded as of the Restatement Date by this Agreement; *provided* that such amendment and restatement of the Original Agreement does not relieve the Parties of any liability that accrued under the Original Agreement prior to the Restatement Date nor preclude either Party from pursuing all rights and remedies it may have hereunder or at law or in equity with respect to any breach of the Original Agreement, nor prejudice either Party's right to obtain performance of any obligation that was due during the Original Agreement Term. Notwithstanding any provision to the contrary in the Original Agreement, including Section 14.10 (Survival; Accrued Rights), the following provisions of the Original Agreement will survive the amendment and restatement of the Original Agreement: Section 4.6 (Development Records; Cooperation) (solely with respect to the obligation to maintain records for at least three years after the end of the Original Agreement Term or for such longer period as may be required by Applicable Law); Article 9 (Payments) (solely with respect to amounts that accrued prior to the Restatement Date and, with respect to Section 9.5 (Financial Records and Audits), solely for 36 months after the Restatement Date); Section 11.5 (Disclaimer); Section 11.6 (Limitation of Liability); Article 13 (Indemnification); Article 15 (Dispute Resolution; Governing Law); Article 16 (Miscellaneous) (solely to extent applicable to other surviving provisions); and Appendix 1 (Definitions) (solely to the extent applicable to other surviving provisions).

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16.3 **No Strict Construction; Interpretation.** This Agreement has been prepared jointly and will not be strictly construed against either Party. Ambiguities, if any, in this Agreement will not be construed against any Party, irrespective of which Party may be deemed to have authored the ambiguous provision. Except where the context expressly requires otherwise, (a) whenever any provision of this Agreement uses the term "including" (or "includes"), such term will be deemed to mean "including without limitation" and "including but not limited to" (or "includes without limitations" and "includes but is not limited to") regardless of whether the words "without limitation" or "but not limited to" actually follow the term "including" (or "includes"); (b) "herein," "hereby," "hereunder," "hereof," and other equivalent words will refer to this Agreement in its entirety and not solely to the particular portion of this Agreement in which any such word is used; (c) all definitions set forth herein will be deemed applicable whether the words defined are applied used herein in the singular or the plural; (d) wherever used herein, any pronoun or pronouns will be deemed to contracts entered into include both the singular and performed entirely within plural and to cover all genders; (e) the schedules and exhibits to this Agreement, and the terms and conditions incorporated in such State schedules and exhibits will be deemed integral parts of this Agreement and all references in this Agreement to this Agreement will encompass such schedules and exhibits and the terms and conditions incorporated in such schedules and exhibits; *provided* that if there is a conflict between the terms and conditions of this Agreement and any terms and conditions set forth in the schedules, or exhibits, then the terms of this Agreement will control; (f) in the event of any conflict between the terms and conditions of this Agreement and any terms and conditions that may be set forth on any order, invoice, or verbal agreement by the Parties pursuant to this Agreement, the terms and conditions of this Agreement will govern; (g) unless otherwise provided, all references to Sections, Articles, and Schedules in this Agreement are to Sections, Articles, and Schedules of and to this Agreement; (h) any reference to any federal, national, state, local, or foreign statute or law will be deemed to also refer to all rules and regulations promulgated thereunder, and any reference to any law, rule, or regulation will be deemed to include the then-current amendments thereto or any replacement or successor law, rule, or regulation thereof; (i) wherever used, the word "shall" and the word "will" are each understood to be imperative or mandatory in nature and are interchangeable with one another; (j) the term "or" will be interpreted in the inclusive sense commonly associated with the term "and/or"; (k) references to a particular Person include such Person's successors and assigns to the extent not prohibited by this Agreement; (l) the section headings and captions used herein are inserted for convenience of reference only and will not be construed to create obligations, benefits, or limitations; (m) any definition of or reference to any agreement, instrument, or other document herein will be construed as referring to such agreement, instrument, or other document as from time to time amended, supplemented, or otherwise modified (subject to any restrictions on such amendments, supplements, or modifications set forth herein); (n) the word "notice" means notice in writing (whether or not specifically stated) and will include notices, consents, approvals, and other written communications contemplated under this Agreement; and (o) provisions that require that a Party, the Parties, or any committee hereunder "agree," "consent," or "approve" or the like will require that such agreement, consent, or approval be specific and in writing, whether by written agreement, letter, approved minutes, or otherwise (but excluding email and instant messaging).

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16.4 **Severability.** If any provision of this Agreement is held to be declared invalid by a court of last resort or becomes invalid, illegal by any court or unenforceable, other governmental body the decision of which an appeal is not taken within the time provided by law, then and in such provision event, this Agreement will be validly reformed deemed to approximate have been terminated only as to the portion thereof that relates to the provision invalidated by that decision and only in the relevant jurisdiction, but this Agreement will remain in force, in all other respects and all other jurisdictions; *provided, however*, that if the provision so invalidated is essential to this Agreement as a whole, then the Parties will negotiate in good faith to amend the terms hereof as nearly as possible practical to carry out the original intent of the parties Parties, and, failing such amendment, either Party may submit the remainder of this Agreement matter for resolution pursuant to Article 15 (Dispute Resolution; Governing Law).

16.5 **Force Majeure.** Neither Party will not be affected thereby and will remain valid and enforceable held liable or responsible to the greatest extent permitted by law.

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(d) This Agreement, and all other documents mentioned herein, constitute the final, exclusive and complete understanding and agreement of the parties hereto and supersedes all prior understandings and agreements; provided the employee proprietary information and invention agreement between Advisor and Ionis will remain Party nor be deemed to be in full force and effect. Any waiver, modification default under, or amendment in breach of any provision of, this Agreement for failure or delay in fulfilling or performing any obligation of this Agreement when such failure or delay is due to Force Majeure. For purposes of this Agreement, "**Force Majeure**" is defined as any cause beyond the control of the affected Party and without the fault or negligence of such Party, which may include acts of God; material changes in Applicable Law; war; civil commotion; destruction of production facilities or materials by fire, flood, earthquake, explosion, or storm; labor disturbances; epidemic; pandemic; quarantine; and failure of public utilities or common carriers. Notwithstanding the foregoing, a Party will not be effective only if excused from making payments owed hereunder due to any such Force Majeure circumstances affecting such Party. The Party affected by Force Majeure will immediately notify the other Party of such inability and of the period for which such inability is expected to continue. The Party giving such notice will thereupon be excused from such of its obligations under this Agreement as it is thereby disabled from performing for so long as it is so disabled for up to [***], after which time the Parties will promptly meet to discuss in writing good faith how to best proceed in a manner that maintains and signed abides by this Agreement. To the parties hereto extent possible, each Party will use reasonable efforts to minimize the duration of any Force Majeure.

(e) 16.6 Any Notices. All notices that are required or permitted hereunder will be in writing and sufficient if delivered by internationally recognized overnight courier or sent by registered or certified mail, postage prepaid, return receipt requested, and in each case, addressed as follows (with a courtesy copy sent by email, which will not constitute notice):

If to Ionis:

Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: Chief Business Officer

With a copy (which will not constitute notice for purposes of this Agreement) to:

[***]
Attention: General Counsel

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If to Otsuka:

Otsuka Pharmaceutical Co., Ltd.
Shinagawa Grand Central Tower
2-16-4 Konan, Minato-ku
Tokyo, 108-8242 Japan
Attn: Director, Global Business Development
Email: [***]

With a copy (which will not constitute notice for purposes of this Agreement) to:

Otsuka Pharmaceutical Co., Ltd.
Shinagawa Grand Central Tower
2-16-4 Konan, Minato-ku
Tokyo, 108-8242 Japan
Attn: Director, Legal Affairs Department
Email: [***]

Otsuka Pharmaceutical Europe Ltd.
2 Windsor Dials, Arthur Road,
Windsor, SL4 1RS, United Kingdom
Attn: General Counsel
Email: [***]

or to such other address as the Party to whom notice is to be given may have furnished to the other Party in writing in accordance herewith. Any such notice will be deemed to have been given: (a) on the Business Day after dispatch if sent by internationally recognized overnight courier; or (b) on the fifth Business Day after dispatch if sent by registered or certified mail, postage prepaid, return receipt requested.

16.7 Further Assurances. The Parties agree to the appropriate party at the address specified on the Summary Page or reasonably cooperate with each other in connection with any actions required to be taken as part of their respective obligations under this Agreement, and will (a) furnish to each other such further information; (b) execute and deliver to each other such other address as the party will specify in writing. Such notice will be deemed given upon personal delivery to the appropriate address, or by facsimile transmission (receipt verified documents); and with confirmation copy followed by another permitted method, sent by express courier service, or, if sent by certified or registered mail, three (3) days after the date of mailing.

(f) Each party will execute, acknowledge and deliver such further instruments, and (c) do all such other acts and things (including working collaboratively to correct any clerical, typographical, or other similar errors in this Agreement), all as the other Party may be necessary or appropriate in order to carry reasonably request for the purpose of carrying out the expressly stated purposes and the clear intent of this Agreement.

[END OF EXHIBIT A] **16.8 Performance by Affiliates.** Notwithstanding any provision to the contrary set forth in this Agreement, either Party will have the right to perform any or all of its obligations and exercise any or all of its rights under this Agreement through any Affiliate. Each Party hereby guarantees the performance by its Affiliates of such Party's obligations under this Agreement and will cause its Affiliates to comply with the provisions of this Agreement in connection with such performance.

A] 16.8

16.9 Agency. Neither Party is, nor will be deemed to be an employee, agent, or representative of the other Party for any purpose. Each Party is an independent contractor, not an employee or partner of the other Party. Neither Party will have the authority to speak for, represent, or obligate the other Party in any way without prior written authority from the other Party.

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16.10 Binding Effect; No Third-Party Beneficiaries or Obligors. As of the Restatement Date, this Agreement will be binding upon and inure to the benefit of the Parties and their respective permitted successors and assigns. Except as set forth in Article 13 (Indemnification), no Person other than Ionis, Otsuka, and their respective permitted successors and assigns hereunder will be deemed an intended beneficiary hereunder, nor have any right to enforce any obligation of any Party to this Agreement, nor will any Person other than Ionis and Otsuka and their respective permitted successors and assigns have any obligations to any Party under this Agreement.

16.11 No Waiver. Any omission or delay by either Party at any time to enforce any right or remedy reserved to it, or to require performance of any of the terms, covenants, or provisions hereof, by the other Party, will not constitute a waiver of such Party's rights to the future enforcement of its rights under this Agreement. Any waiver by a Party of a particular breach or default by the other Party will not operate or be construed as a waiver of any subsequent breach or default by the other Party.

16.12 Cumulative Remedies. No remedy referred to in this Agreement, including termination of this Agreement, is intended to be exclusive, but each will be cumulative and in addition to any other remedy referred to in this Agreement or otherwise available under law.

16.13 Counterparts. This Agreement may be executed in one or more counterparts, all of which taken together will be regarded as one and the same instrument. Each Party may execute this Agreement in Adobe™ Portable Document Format (PDF) sent by electronic mail. PDF signatures of authorized signatories of the Parties will be deemed to be original signatures, will be valid and binding upon the Parties, and, upon delivery, will constitute due execution of this Agreement.

[Remainder of page intentionally left blank; Signature page follows.]

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CONFIDENTIAL

IN WITNESS WHEREOF, the Parties have executed this Agreement through their duly authorized representatives to be effective as of the Restatement Date.

IONIS PHARMACEUTICALS, INC.

By: /s/ Brett Monia, PhD

Name: Brett Monia, PhD

Title: Chief Executive Officer

OTSUKA PHARMACEUTICAL CO., LTD.

By: /s/ Makoto Inoue

Name: Makoto Inoue

Title: President and Representative Director

Otsuka Pharmaceutical Co., Ltd.

By: /s/ Takeshi Watanabe

Name: Takeshi Watanabe, PhD, MBA

Title: VP, Global Head of Business Development

8 [Signature Page to Amended and Restated License Agreement]

CONFIDENTIAL

Appendix 1

Definitions

For purposes of **8** this Agreement, whether used in the singular or plural, the following terms will have the meanings set forth below:

1.1 "Accounting Standards" means, with respect to a Party or its Affiliate or Sublicensee, GAAP or IFRS, as such Person uses for its financial reporting standards from time to time, in each case, as consistently applied.

1.2 "Affiliate" means, with respect to a Person, any corporation or other business entity controlled by, controlling, or under common control with such Person, with "control" meaning (a) direct or indirect beneficial ownership of more than 50% of the voting stock or other ownership interest of, or more than 50% interest in the income of, the applicable entity, or (b) the possession, directly or indirectly, of the power to direct the management or policies of the applicable entity, whether through the ownership of voting securities or other equity rights, by contract relating to voting rights or corporate governance, or otherwise. Notwithstanding the foregoing, for purposes of this Agreement, "Affiliates" will not include, (a) with respect to an entity, *bona fide* venture capital investors in such entity or *bona fide* institutional investors in such entity, in each case, that routinely make venture capital investments for the potential financial return on such investments and not with any view to acquisition or for other strategic purpose, or Affiliates of such venture capital or institutional investors, or (b) with respect to Otsuka, any entities that are controlled by Otsuka Holdings Co., Ltd. but are not subsidiaries of Otsuka.

1.3 "Alliance Manager" has the meaning set forth in **Section 8.8 (Alliance Managers)**.

1.4 "[]"** means any [**].

1.5 "American Commercialization Operating Plan" has the meaning set forth in **Section 6.4.1 (Global Brand Strategy and American Commercialization Operating Plan)**.

1.6 "American Medical Affairs Operating Plan" has the meaning set forth in **Section 6.6.1 (Global Medical Affairs Strategy and American Medical Affairs Operating Plan)**.

1.7 "Ancillary Agreements" means the Pharmacovigilance Agreement, each Supply Agreement, and each Quality Agreement.

1.8 "Applicable Law" means applicable (with respect to the particular activity, task, or obligation under this Agreement to which such term applies) laws, statutes, rules, regulations, and other pronouncements having the effect of law of any Governmental Authority that may be in effect from time to time, including for clarity any applicable rules, regulations, guidelines, or other requirements of any Regulatory Authority that may be in effect from time to time.

1.9 "Approved Labeling" means, with respect to a Licensed Product and a jurisdiction: (a) the applicable Regulatory Authority-approved full prescribing information for such Licensed Product in such jurisdiction; and (b) the applicable Regulatory Authority-approved labels and any other written, printed, or graphic materials on any container, wrapper, or any package insert that is used with or for such Licensed Product in such jurisdiction.

1.10 "Asia JSC" has the meaning set forth in **Section 8.2.1 (Formation and Purposes of the Joint Steering Committees)**.

1.11 "Asia ROFN Period" has the meaning set forth in **Section 2.8.1 (ROFN Exercise)**.

1.12 "Asia-Specific Non-Clinical HAE Development Activities" has the meaning set forth in **Section 4.2.2(b) (Asia Territory)**.

1.13 "**Asia Territory**" means, individually, each of the Major Asian Countries, Australia, Egypt, Hong Kong, Indonesia, Malaysia, Myanmar, New Zealand, Pakistan, the Philippines, Singapore, Taiwan, Thailand, Turkey, and Vietnam, excluding all countries in any Terminated Region.

1.14 "**Asia Territory Brand Strategy**" has the meaning set forth in [Section 6.4.2](#) (Otsuka Territory Brand Strategy and Commercialization Operating Plans).

1.15 "**Asia Territory Commercialization Operating Plan**" has the meaning set forth in [Section 6.4.2](#) (Otsuka Territory Brand Strategy and Commercialization Operating Plans).

1.16 "**Asia Territory Medical Affairs Plan**" has the meaning set forth in [Section 6.6.2](#) (Otsuka Territory Medical Affairs Plans).

1.17 "**Asia Territory-Specific Development Plan**" has the meaning set forth in [Section 4.3.2](#) (Asia Territory-Specific Development Plan).

1.18 "**ASMF**" has the meaning set forth in [Section 5.3](#) (Correspondences with Regulatory Authorities).

1.19 "**Blocking Identified Rights**" has the meaning set forth in [Section 2.7.2\(a\)\(ii\)](#) (Acquisition of Potential In-Licenses).

1.20 "**Breach Notification**" has the meaning set forth in [Section 14.2.1](#) (Material Breach).

1.21 "**Business Day**" means a day other than (a) a Saturday, Sunday, (b) a day on which banking institutions in California, Tokyo, Japan, or London, England are required by Applicable Law to remain closed or (c) the nine consecutive days beginning on December 24 and continuing through January 1, to the extent not already covered in clause (a) or clause (b).

1.22 "**Calendar Quarter**" means, with respect to the first Calendar Quarter during the Term, the period beginning on the Restatement Date and ending on the last day of the Calendar Quarter within which the Restatement Date falls, and thereafter each successive period of three calendar months ending on (and including) each of March 31, June 30, September 30, and December 31; except that the last Calendar Quarter during the Term will end upon the expiration of the Term.

1.23 "**Calendar Year**" means the period of 12 consecutive calendar months beginning on January 1 and ending on December 31; except that (a) the first Calendar Year during the Term will begin on the Restatement Date and end on December 31 of the Calendar Year within which the Restatement Date falls, and (b) the last Calendar Year during the Term will end upon expiration of the Term.

1.24 "**Change of Control**" means, with respect to a Party, that: (a) any Third Party acquires directly or indirectly the beneficial ownership of any voting security of such Party, or if the percentage ownership of such Third Party in the voting securities of such Party is increased through stock redemption, cancellation, or other recapitalization, and immediately after such acquisition or increase such Third Party is, directly or indirectly, the beneficial owner of voting securities representing more than 50% of the total voting power of all of the then outstanding voting securities of such Party; (b) a merger, consolidation, recapitalization, or reorganization of such Party is consummated that would result in shareholders or equity holders of such Party immediately prior to such transaction owning 50% or less of the outstanding voting securities of the surviving entity (or its parent entity) immediately following such transaction; or (c) the sale or transfer to a Third Party, in one or more related transactions, of all or substantially all of such Party's consolidated assets taken as a whole.

1.25 "**Clinical Supply Agreement**" has the meaning set forth in [Section 7.2.1](#) (Clinical Supply Agreement).

1.26 "**Clinical Trial**" means any clinical trial in humans.

1.27 "**CMC**" means chemistry, manufacturing, and controls.

1.28 "**CMO**" has the meaning set forth in [Section 7.3.1](#) (By Otsuka).

1.29 "**Collaboration In-License**" means (a) any Potential In-License that [***] in accordance with [Section 2.7.2\(b\)](#) (Collaboration In-Licenses) and (b) any Existing Third-Party IP Agreement.

1.30 "**Collaboration Know-How**" means all Know-How developed or invented by a Party's or its Affiliates', licensees', Sublicensees', or Subcontractors' employees, agents, or independent contractors, or any Persons contractually required to assign or license such Know-How to such Party or any Affiliate of such Party, either alone or jointly with the other Party's or its Affiliates', licensees', Sublicensees', or Subcontractors' employees, agents, or independent contractors, or any Persons contractually required to assign or license such Know-How to such other Party or any Affiliate of such other Party, in each case, in the performance of activities under the Original Agreement during the Original Agreement Term or under this Agreement during the Term.

1.31 "**Collaboration Patent Rights**" means any Patent Right that (a) has a priority date after the Original Effective Date and (b) Covers any Invention included in the Collaboration Know-How.

1.32 "**Combination Product**" has the meaning set forth in [Section 1.158](#) of this [Appendix 1](#) (Definitions).

1.33 "**Combination Product Net Sales**" has the meaning set forth in [Section 1.158](#) of this [Appendix 1](#) (Definitions).

1.34 "**Commercial Supply Agreement**" has the meaning set forth in [Section 7.2.2](#) (Commercial Supply Agreement).

1.35 "**Commercialization**" means any and all activities directed to the marketing, promotion, distribution, pricing, reimbursement, offering for sale, and sale of a pharmaceutical or biologic product and interacting with Regulatory Authorities following receipt of Regulatory Approval in the applicable country or region for such pharmaceutical or biologic product regarding the foregoing, including seeking and maintaining any required Reimbursement Approval, but excluding activities directed to Manufacturing or Development. "**Commercialize**," "**Commercializing**," and "**Commercialized**" will be construed accordingly.

1.36 "**Commercially Reasonable Efforts**" means, with respect to the Exploitation of a Licensed Product by a Party, [***].

1.37 "**Competitive Infringement**" means any infringement, unauthorized use, misappropriation or threatened infringement or misappropriation by a Third Party with respect to any Ionis Technology, Otsuka Technology, or Joint Collaboration Technology by reason of the making, using, offering to sell, selling, or importing of a compound, product, method, or process that would be competitive with a Licensed Product then being Developed or Commercialized in the Field.

1.38 "**Confidential Disclosure Agreement**" has the meaning set forth in [Section 16.2](#) (Entire Agreement; Amendment).

1.39 "**Confidential Information**" means, subject to [Section 12.3](#) (Exemptions), (a) Know-How and any technical, scientific, trade, research, Manufacturing, business, financial, marketing, product, supplier, intellectual property, and other non-public or proprietary data or information (including unpublished patent applications) that may be disclosed by one Party (the "**Disclosing Party**") or its Affiliates to the other Party (the "**Receiving Party**") or its Affiliates pursuant to this Agreement (including information disclosed prior to the Restatement Date pursuant to the Confidential Disclosure Agreement or the Original Agreement), regardless of whether such information is specifically marked or designated as confidential and regardless of whether such information is in written, oral, electronic, or other form, and (b) the terms of this Agreement.

1.40 **"Continuing Know-How Transfer"** has the meaning set forth in [Section 3.1](#) (Initial Know-How Transfer).

1.41 **"Control"** or **"Controlled"** means the possession by a Party (whether by ownership, license, or otherwise other than pursuant to this Agreement) of, (a) with respect to any materials or other tangible Know-How, the legal authority or right to physical possession of such materials or tangible Know-How, with the right to provide such materials or tangible Know-How to the other Party on the terms set forth herein, (b) with respect to Patent Rights, Regulatory Approvals, Regulatory Submissions, intangible Know-How, or other intellectual property, the legal authority or right to grant a license, sublicense, access, or right to use (as applicable) to the other Party under such Patent Rights, Regulatory Approvals, Regulatory Submissions, intangible Know-How, or other intellectual property on the terms set forth herein, in each case ((a) and (b)), without breaching or otherwise violating the terms of any arrangement or agreement with a Third Party in existence as of the time such Party or its Affiliates would first be required hereunder to grant the other Party such access, right to use, licenses, or sublicense or incurring any additional payment obligations to a Third Party that would not be incurred but for such access, right to use, licenses, or sublicense, other than payment obligations incurred under a Collaboration In-License, and (c) with respect to any product, the possession by a Party of the ability (whether by sole or joint ownership, license, or otherwise, other than pursuant to the licenses granted under this Agreement) to grant an exclusive license or sublicense of Patent Rights that Cover such product or proprietary Know-How that is used in connection with the Exploitation of such product. Notwithstanding the foregoing, [***].

1.42 **"Core or Manufacturing Identified Rights"** has the meaning set forth in [Section 2.7.2\(a\)\(i\)](#) (Acquisition of Potential In-Licenses).

1.43 **"Core or Manufacturing Potential In-License"** has the meaning set forth in [Section 2.7.2\(a\)\(i\)](#) (Acquisition of Potential In-Licenses).

1.44 **"Cost Overrun"** has the meaning set forth in [Section 4.4.2\(b\)](#) (Cost Overruns).

1.45 **"Cover"** means, with respect to a particular subject matter at issue and a relevant Patent Right or individual claim in such Patent Right, as applicable, that the manufacture, use, sale, offer for sale, or importation of such subject matter would fall within the scope of one or more claims in such Patent Right.

1.46 **"Cross-Territory Clinical Development Plan"** has the meaning set forth in [Section 4.2.1](#) (Cross-Territory Clinical Development Plan).

1.47 **"Cross-Territory Clinical Studies"** has the meaning set forth in [Section 4.2.1](#) (Cross-Territory Clinical Development Plan).

1.48 **"Debarred/Excluded"** has the meaning set forth in [Section 11.1.5](#) (Mutual Representations and Warranties).

1.49 **"Development"** means all internal and external research, development and regulatory activities regarding pharmaceutical or biologic products, including (a) research, process development, non-clinical testing, toxicology, non-clinical activities, IND-enabling studies, and Clinical Trials, and (b) preparation, submission, review, and development of data or information for the purpose of submission to a Regulatory Authority to obtain authorization to conduct Clinical Trials and to obtain, support, or maintain Regulatory Approval of a pharmaceutical or biologic product, but excluding activities directed to Manufacturing or Commercialization. Development will include development and regulatory activities for additional presentations or indications for a product after receipt of Regulatory Approval of such product, including Post-Approval Mandatory Studies. **"Develop," "Developing," and "Developed"** will be construed accordingly.

1.50 **"Disclosing Party"** has the meaning set forth in [Section 1.39](#) (Confidential Information) of this [Appendix 1](#) (Definitions).

1.51 **"Disputed Matter"** has the meaning set forth in [Section 15.1](#) (Executive Officers; Disputes).

1.52 **"Eligible Cross-Territory Development Costs"** has the meaning set forth in [Section 4.4.3](#) (Shared Cross-Territory Development Costs).

1.53 **"EMA"** means the European Medicines Agency or any successor agency thereto.

1.54 **"Establishing Committee"** has the meaning set forth in [Section 8.3.1](#) (Formation; Authority).

1.55 **"Europe JSC"** has the meaning set forth in [Section 8.2.1](#) (Formation and Purposes of the Joint Steering Committees).

1.56 **"Europe Regulatory Subcommittee"** has the meaning set forth in [Section 5.2](#) (Europe Regulatory Subcommittee).

1.57 **"Europe ROFN Period"** has the meaning set forth in [Section 2.8.1](#) (ROFN Exercise).

1.58 **"Europe Territory"** means (a) all members of the European Union or the European Economic Area (EEA) as of the Original Effective Date, and (b) the following countries: Iceland, Liechtenstein, Norway, Switzerland, and the United Kingdom, excluding all countries in any Terminated Region.

1.59 **"Europe Territory Brand Strategy"** has the meaning set forth in [Section 6.4.2](#) (Otsuka Territory Brand Strategy and Commercialization Operating Plans).

1.60 **"Europe Territory Commercialization Operating Plan"** has the meaning set forth in [Section 6.4.2](#) (Otsuka Territory Brand Strategy and Commercialization Operating Plans).

1.61 **"Europe Territory Medical Affairs Plan"** has the meaning set forth in [Section 6.6.2](#) (Otsuka Territory Medical Affairs Plans).

1.62 **"Europe Territory-Specific Development Plan"** has the meaning set forth in [Section 4.3.1](#) (Europe Territory-Specific Development Plan).

1.63 **"European Union"** or **"E.U."** means the economic, scientific, and political organization of member states of the European Union as it may be constituted from time to time.

1.64 **"Ex-Japan Asia Territory"** means the Asia Territory, except for Japan.

1.65 **"[***]"** has the meaning set forth in [Section 7.2.6](#) ([***]).

1.66 **"Executive Committee"** has the meaning set forth in [Section 8.1.1](#) (Formation and Purpose of the Executive Committee).

1.67 **"Executive Committee Co-Chairperson"** has the meaning set forth in [Section 8.1.2](#) (Membership).

1.68 **"Executive Officer"** means (a) with respect to Otsuka, its President and Representative Director or their designee and (b) with respect to Ionis, the Chief Executive Officer or their designee.

1.69 **"Existing Third-Party IP Agreement"** means any agreement between Ionis (or any of its Affiliates) and any Third Party entered into prior to the Original Effective Date or any time during the Original Agreement Term under which Ionis (or any of its Affiliates) obtained a license or other right to any of such Third Party's Know-How or Patent Rights that fall within the definition of any of the Ionis Technology.

1.70 **"Exploit"** means to make, have made, use, offer to sell, sell, Develop, Manufacture, Commercialize, or otherwise exploit. **"Exploitation"** will be construed accordingly.

1.71 **"External Costs"** mean, with respect to a Party, the documented actual expenses paid to Third Parties (or payable to Third Parties and accrued in accordance with such Party's Accounting Standards) by such Party (or its Affiliate) in consideration of the performance of activities under this Agreement, without mark-up, and excluding any costs or expenses included under the FTE Rate.

1.72 "**FD&C Act**" means the United States Federal Food, Drug and Cosmetic Act, as amended from time-to-time, together with any rules, regulations, and requirements promulgated thereunder (including all additions, supplements, extensions, and modifications thereto).

1.73 "**FDA**" means the U.S. Food and Drug Administration or any successor agency thereto.

1.74 "**Field**" means for the treatment or prevention of any diseases and conditions in humans.

1.75 "**Filing Party**" has the meaning set forth in [Section 5.5](#) (Regulatory Submissions).

1.76 "**First Commercial Sale**" means, with respect to a Licensed Product in a country, the first sale for end use or consumption to a Third Party of such Licensed Product in such country by a Party, or its Affiliates or Sublicensees after the receipt of Regulatory Approval and Reimbursement Approval in the Field for such Licensed Product by the relevant Regulatory Authority in such country. First Commercial Sale excludes any sale or other distribution for use in a Clinical Trial or other Development activity or for compassionate use, named-patient use, or expanded access, indigent or other patient access programs when sold or distributed at or below the applicable Selling Party's costs.

1.77 "[***]" has the meaning set forth in [Section 9.3.4\(a\)](#) ([***]).

1.78 "**Follow-On Product**" has the meaning set forth in [Section 2.8.1](#) (ROFN Exercise).

1.79 "**Follow-On Product Activities**" has the meaning set forth in [Section 2.8.3](#) (Follow-On Product Activities).

1.80 "**Force Majeure**" has the meaning set forth in [Section 16.5](#) (Force Majeure).

1.81 "**FTE**" means the equivalent of the work of one duly qualified employee of a Party full time for one year (consisting of a total of [***] hours per year) directly carrying out [***] activities under this Agreement. Overtime, and work on weekends, holidays and the like will not be counted with any multiplier (e.g., time-and-a-half or double time) toward the number of hours that are used to calculate the FTE contribution, and no individual may be charged at greater than one FTE, regardless of that individual's hours worked during that year. The portion of an FTE billable by a Party for one employee during a given accounting period will be determined by dividing the number of hours worked directly by such employee on the work to be conducted under this Agreement during such accounting period by the number of FTE hours applicable for such accounting period based on [***] working hours per Calendar Year. For clarity, travel time spent by an employee, unless also spent working directly on activities under this Agreement, will not be included in the number of hours used to calculate the FTE contribution.

1.82 "**FTE Rate**" means [***] per FTE per hour. For the avoidance of doubt, such FTE Rate will be [***].

1.83 "**Future Cross-Territory Studies**" has the meaning set forth in [Section 4.2.1](#) (Cross-Territory Clinical Development Plan).

1.84 "**GAAP**" means the generally accepted accounting principles in the United States.

1.85 "**Generic Product**" means, with respect to a Licensed Product in a country, a pharmaceutical product (other than such Licensed Product) that (a) is expected to be sold by a Third Party other than a Sublicensee under license from Otsuka in such country, (b) is authorized for use in such country in one or more of the indications for which such Licensed Product has Regulatory Approval in such country; and (c) contains the same active pharmaceutical ingredient(s) as such Licensed Product. A product will not be considered to be a Generic Product if (i) Otsuka or any of its Affiliates or Sublicensees was involved in or authorized the Development or Commercialization of such product, (ii) Otsuka or any of its Affiliates or Sublicensees has granted a license to such Third Party in respect of such product, or (iii) such product is Commercialized by any Person who obtained such product in a chain of distribution that included Otsuka or any of its Affiliates or Sublicensees.

1.86 "**Global Brand Strategy**" has the meaning set forth in [Section 6.4.1](#) (Global Brand Strategy and American Commercialization Operating Plan).

1.87 "**Global Medical Affairs Strategy**" has the meaning set forth in [Section 6.6.1](#) (Global Medical Affairs Strategy and American Medical Affairs Operating Plan).

1.88 "**Global Trade Control Laws**" means the U.S. Export Administration Regulations, the U.S. International Traffic in Arms Regulations, the economic sanctions regulations administered by the U.S. Treasury Department's Office of Foreign Assets Control, E.U. Council Regulations on export controls, including Nos. 428/2009, 267/2012, other E.U. Council sanctions regulations, as implemented in the E.U. member states, United Nations sanctions policies, and all relevant regulations made under any of the foregoing.

1.89 "**Good Clinical Practices**" or "**GCP**" means the then-current good clinical practice standards, practices, and procedures promulgated or endorsed by the applicable Regulatory Authority as set forth in the guidelines imposed by such Regulatory Authority, as may be updated from time-to-time.

1.90 "**Good Laboratory Practices**" or "**GLP**" means the then-current good laboratory practice standards, practices, and procedures promulgated or endorsed by the applicable Regulatory Authority as set forth in the guidelines imposed by such Regulatory Authority, as may be updated from time-to-time.

1.91 "**Good Manufacturing Practices**" or "**GMP**" means the then-current good manufacturing practice standards, practices, and procedures promulgated or endorsed by the applicable Regulatory Authority as set forth in the guidelines imposed by such Regulatory Authority, as may be updated from time-to-time.

1.92 "**Government Official**" means any official, officer, employee, or representative of: (a) any federal, state, provincial, administrative division, county, or municipal government or any department or agency thereof; (b) any public international organization or any department or agency thereof; or (c) any company or other entity owned or controlled by any government or Governmental Authority.

1.93 "**Governmental Authority**" means any court, agency, department, authority, tribunal, or other instrumentality of any supra-national, national, state, provincial, county, city, or other political subdivision. For clarity, Governmental Authorities include all Regulatory Authorities.

1.94 "**HAE**" means hereditary angioedema.

1.95 "**Identified Rights**" has the meaning set forth in [Section 2.7.1](#) (Identification of New In-License Agreements).

1.96 "**IFRS**" means International Financial Reporting Standards, consistently applied.

1.97 "**IND**" means an Investigational New Drug application required pursuant to 21 C.F.R. Part 312 or any comparable filings outside of the U.S. required to commence human clinical trials in such country or region (such as an application for a Clinical Trial Authorization in the E.U.), and all supplements or amendments that may be filed with respect to the foregoing.

1.98 "**Indemnified Party**" has the meaning set forth in [Section 13.3](#) (Indemnification Procedure).

1.99 "**Indemnifying Party**" has the meaning set forth in [Section 13.3](#) (Indemnification Procedure).

1.100 "Initial Know-How Transfer" has the meaning set forth in [Section 3.1](#) (Initial Know-How Transfer).

1.101 "Initial Royalties" has the meaning set forth in [Section 9.3.1](#) (Royalty Payments During the Initial Royalty Term).

1.102 "Initial Royalty Term" has the meaning set forth in [Section 9.3.1](#) (Royalty Payments During the Initial Royalty Term).

1.103 "Initiation" means dosing of the first patient in a Clinical Trial.

1.104 "Internal Costs" means, for any period of time, the product obtained by multiplying (a) the total FTEs (or portion thereof) devoted to the performance of activity under this Agreement during such period, by (b) the applicable FTE Rate for such period; *provided* that [***].

1.105 "Invention" means any process, method, composition of matter, article of manufacture, discovery, or finding that is conceived or reduced to practice (whether or not patentable).

1.106 "Ionis Attribution Language" has the meaning set forth in [Section 12.7.2](#) (Acknowledgement).

1.107 "Ionis Collaboration Know-How" has the meaning set forth in [Section 10.1.2\(a\)](#) (Ownership of Arising Intellectual Property).

1.108 "Ionis Collaboration Patent Rights" has the meaning set forth in [Section 10.1.2\(a\)](#) (Ownership of Arising Intellectual Property).

1.109 "Ionis Core Technology" means Ionis Core Technology Know-How and the Ionis Core Technology Patents.

1.110 "Ionis Core Technology Know-How" means, subject to [Section 4.4.4\(b\)](#) ([***] by Ionis), all Know-How, including Ionis Collaboration Know-How but excluding Ionis Product-Specific Know-How, Ionis Manufacturing and Analytical Know-How and Ionis' interest in any Joint Collaboration Know-How, that (a) is Controlled by Ionis or its Affiliates as of the Original Effective Date or at any time during the Original Agreement Term or the Term, (b) is necessary or reasonably useful to Exploit a Licensed Product, and (c) relates generally to oligonucleotide.

1.111 "Ionis Core Technology Patents" means, subject to [Section 4.4.4\(b\)](#) ([***] by Ionis), any Patent Rights, including Ionis Collaboration Patent Rights but excluding Ionis Product-Specific Patents, Ionis Manufacturing and Analytical Patents and Ionis' interest in any Joint Collaboration Patent Rights, that (a) are Controlled by Ionis or its Affiliates as of the Original Effective Date or at any time during the Original Agreement Term or the Term, (b) are necessary or reasonably useful (or, with respect to patent applications, would be necessary or reasonably useful if such patent applications were to issue as patents) to Exploit a Licensed Product and (c) Cover subject matter generally applicable to oligonucleotides. A list of the Ionis Core Technology Patents as of the Restatement Date is set forth on [SCHEDULE 1.111](#) (Ionis Core Technology Patents); *provided* that, any Patent Right existing as of the Restatement Date that otherwise would be included in the definition of Ionis Core Technology Patents but is not included on [SCHEDULE 1.111](#) (Ionis Core Technology Patents) will still be considered an Ionis Core Technology Patent.

1.112 "Ionis Incurred Development Costs" has the meaning set forth in [Section 4.4.1\(c\)\(ii\)](#) (Shared Development Costs).

1.113 "Ionis Indemnitee" has the meaning set forth in [Section 13.2](#) (Indemnification by Otsuka).

1.114 "Ionis Internal Oligonucleotide Safety Database" has the meaning set forth in [Section 5.12.1](#) (Ionis Internal Oligonucleotide Safety Database).

1.115 "Ionis Know-How" means the Ionis Core Technology Know-How, Ionis Manufacturing and Analytical Know-How, and Ionis Product-Specific Know-How.

1.116 "Ionis Manufacturing and Analytical Know-How" means, subject to [Section 4.4.4\(b\)](#) ([***] by Ionis), Know-How, including Ionis Collaboration Know-How but excluding Ionis' interest in any Joint Collaboration Know-How, that (a) is Controlled by Ionis or its Affiliates as of the Original Effective Date or at any time during the Original Agreement Term or the Term, (b) is necessary or reasonably useful to Exploit a Licensed Product, and (c) relates to any Manufacturing Technology.

1.117 "Ionis Manufacturing and Analytical Patents" means, subject to [Section 4.4.4\(b\)](#) ([***] by Ionis), Patent Rights, including Ionis Collaboration Patent Rights but excluding Ionis' interest in any Joint Collaboration Patent Rights, that (a) are Controlled by Ionis or its Affiliates as of the Original Effective Date or at any time during the Original Agreement Term or the Term, (b) are necessary or reasonably useful (or, with respect to patent applications, would be necessary or reasonably useful if such patent applications were to issue as patents) to Exploit a Licensed Product, and (c) Cover Manufacturing Technology. A list of Ionis Manufacturing and Analytical Patents as of the Restatement Date is set forth on [SCHEDULE 1.117](#) (Ionis Manufacturing and Analytical Patents); *provided* that, any Patent Right existing as of the Restatement Date that otherwise would be included in the definition of Ionis Manufacturing and Analytical Patent but is not included on [SCHEDULE 1.117](#) (Ionis Manufacturing and Analytical Patents) will still be considered an Ionis Manufacturing and Analytical Patent.

1.118 "Ionis Manufacturing and Analytical Technology" means Ionis Manufacturing and Analytical Know-How and Ionis Manufacturing and Analytical Patents.

1.119 "Ionis [**] Costs" has the meaning set forth in [Section 4.4.4\(c\)](#) (Otsuka Opt-In).

1.120 "Ionis [**] Development" has the meaning set forth in [Section 4.4.4\(b\)](#) ([***] by Ionis).

1.121 "Ionis [**]" means [**] generated by or on behalf of Ionis in the [**] in accordance with [Section 4.4.4\(b\)](#) ([***] by Ionis).

1.122 "Ionis Patent Rights" means the Ionis Core Technology Patents, Ionis Manufacturing and Analytical Patents, and Ionis Product-Specific Patents.

1.123 "Ionis Product-Specific Know-How" means, subject to [Section 4.4.4\(b\)](#) ([***] by Ionis), all Know-How, including Ionis Collaboration Know-How but excluding Ionis' interest in any Joint Collaboration Know-How, that is (a) Controlled by Ionis or its Affiliates as of the Original Effective Date or at any time during the Original Agreement Term or the Term, (b) necessary or reasonably useful to Exploit a Licensed Product in the Field, and (c) specifically relating to (i) the composition of matter of a Licensed Product or (ii) methods of using a Licensed Product for the Field; *provided however*, Know-How that (i) consists of subject matter applicable to oligonucleotide compounds or products in general or (ii) relates to an oligonucleotide compound that does not specifically modulate expression of PKK via the binding, partially or wholly, of such compound to RNA that encodes PKK, will not be considered Ionis Product-Specific Know-How, and in each case of (i) and (ii), such Know-How will be considered Ionis Core Technology Know-How.

1.124 "*Ionis Product-Specific Patents*" means, subject to Section 4.4.4(b) ([**]) by Ionis, all Product-Specific Patents, excluding Ionis' interest in any Joint Collaboration Patent Rights, that are (a) Controlled by Ionis or its Affiliates as of the Original Effective Date or at any time during the Original Agreement Term or the Term and (b) necessary or reasonably useful (or, with respect to patent applications, would be necessary or reasonably useful if such patent applications were to issue as patents) to Exploit a Licensed Product; *provided, however*, that Patent Rights that include only claims that are directed to (i) subject matter applicable to oligonucleotide compounds or products in general or (ii) an oligonucleotide compound that does not specifically modulate expression of PKK via the binding, partially or wholly, of such compound to RNA that encodes PKK, will not be considered Ionis Product-Specific Patents, and in each case of (i) and (ii), such Patent Rights will be considered Ionis Core Technology Patents. A list of Ionis Product-Specific Patents as of the Restatement Date is set forth on SCHEDULE 1.124 (Ionis Product-Specific Patents); *provided* that, any Patent Right existing as of the Restatement Date that otherwise would be included in the definition of Ionis Product-Specific Patent but is not included on SCHEDULE 1.124 (Ionis Product-Specific Patents) will still be considered an Ionis Product-Specific Patent.

1.125 "*Ionis Product-Specific Technology*" means Ionis Product-Specific Know-How and Ionis Product-Specific Patents.

1.126 "*Ionis Product Trademarks*" has the meaning set forth in Section 10.10.1(c) (Ownership of Ionis Product Trademarks).

1.127 "*Ionis Prosecuted Patent Rights*" has the meaning set forth in Section 10.2.1(a) (Right to Prosecute).

1.128 "*Ionis Publication*" has the meaning set forth in Section 12.5.2 (Ionis' Right to Publish).

1.129 "*Ionis Regulatory Activities*" has the meaning set forth in Section 5.1 (Regulatory Responsible Party).

1.130 "*Ionis Technology*" means the Ionis Know-How, the Ionis Patent Rights, and Ionis' interest in the Joint Collaboration Technology.

1.131 "*Ionis Territory*" means worldwide, except for the Otsuka Territory.

1.132 "*IRS*" has the meaning set forth in Section 9.10.3 (Tax Cooperation).

1.133 "*Joint Collaboration Know-How*" means all Collaboration Know-How that is developed or invented jointly by a Party's or its Affiliates', licensees', Sublicensees', or Subcontractors' employees, agents, or independent contractors, or any Persons contractually required to assign or license such Collaboration Know-How to such Party or any Affiliate of such Party, on the one hand, and the other Party's or its Affiliates', licensees', Sublicensees', or Subcontractors' employees, agents, or independent contractors, or any Persons contractually required to assign or license such Collaboration Know-How to such Party or any Affiliate of such Party, on the other hand.

1.134 "*Joint Collaboration Patent Rights*" means all Collaboration Patent Rights that Cover Joint Collaboration Know-How.

1.135 "*Joint Collaboration Technology*" means the Joint Collaboration Know-How and the Joint Collaboration Patent Rights.

1.136 "*JSCs*" has the meaning set forth in Section 8.2.1 (Formation and Purposes of the Joint Steering Committees) and "*JSC*" means the Europe JSC or the Asia JSC, as the case may be.

1.137 "*Know-How*" means proprietary Inventions, discoveries, trade secrets, materials, information, experience, data, formulas, procedures, technology, and results (whether or not patentable), including practices, knowledge, know-how, experience and test data (including physical, chemical, biological, toxicological, pharmacological, clinical and veterinary data), dosage regimens, assays, diagnostics, product specifications, manufacturing techniques and costs, analytical and quality control data and marketing, pricing and distribution costs, and sales practices, methods, data, and descriptions.

1.138 "*Knowledge*" means the actual knowledge, without any inquiry or investigation, of (a) with respect to Ionis, its [**]; and (b) with respect to Otsuka, its [**].

1.139 "*Licensed Compound*" means the GalNAc-conjugated antisense oligonucleotide compound known as donidalorsen.

1.140 "*Licensed Product*" means any pharmaceutical product that contains, comprises, or incorporates the Licensed Compound, in all current and future formulations and in any dosage strengths, presentations, or package configuration, and for any mode of administration. For clarity, any combination product comprised of an autoinjector pre-filled with the Licensed Compound is considered a Licensed Product. All products containing or comprising the same Licensed Compound, regardless of the formulation, indication, line extension or otherwise, will be considered the same Licensed Product for all purposes of this Agreement.

1.141 "*Local Unitary Product Trademark*" has the meaning set forth in Section 10.10.1(a) (Unitary Product Trademarks).

1.142 "*Losses*" has the meaning set forth in Section 13.1 (Indemnification by Ionis).

1.143 "*MAA*" or "*Marketing Authorization Application*" means any (a) New Drug Application as defined in the FD&C Act, (b) a marketing authorization application filed with (i) the EMA under the centralized EMA filing procedure to gain approval to market a biopharmaceutical in the E.U., or (ii) a Regulatory Authority in any country in the E.U. if the centralized EMA filing procedure is not used to gain approval to market a biopharmaceutical in the E.U., or (c) a marketing authorization application filed with the PMDA in Japan, or (d) substantially similar application or submission to those set forth in the foregoing clauses filed with a Regulatory Authority in a country or group of countries to obtain Regulatory Approval to Commercialize a biopharmaceutical or diagnostic product in that country or in that group of countries, in each case ((a) through (d)), including any amendments thereto, and supplemental applications, but excluding Reimbursement Approval applications.

1.144 "*MAA Acceptance*" means, with respect to a Marketing Authorization Application filed for a Licensed Product, the receipt of written notice of acceptance by the EMA of such Marketing Authorization Application for filing under the centralized filing procedure.

1.145 "[**]" means, [**].

1.146 "[**]" means, [**].

1.147 "*Manufacture*" means activities directed to manufacturing, processing, packaging, labeling, filling, finishing, assembly, quality assurance, quality control, testing, and release, shipping, or storage of any pharmaceutical or biologic product (or any components or process steps involving any product or any companion diagnostic), placebo, or comparator agent, as the case may be, including qualification, validation, and scale-up, pre-clinical, clinical, and commercial manufacture and analytic development, product characterization, and stability testing, but excluding activities directed to Development, or Commercialization. "*Manufacturing*" and "*Manufactured*" will be construed accordingly.

1.148 "*Manufacturing Costs*" means, with respect to a Licensed Product [**].

1.149 "*Manufacturing Handover Date*" has the meaning set forth in Section 7.1.2 (Otsuka Manufacturing).

1.150 "*Manufacturing Handover Notice*" has the meaning set forth in Section 7.1.2 (Otsuka Manufacturing).

1.151 "**Manufacturing Technology**" means any or all of (a) methods or materials used in the synthesis or analysis of an oligonucleotide or a Licensed Product regardless of sequence or chemical modification, (b) methods of manufacturing components of an oligonucleotide, and (c) methods or materials used in Manufacturing a Licensed Product.

1.152 "**Manufacturing Technology Transfer**" has the meaning set forth in [Section 7.4](#) (Manufacturing Technology Transfer).

1.153 "**Manufacturing Technology Transfer Agreement**" has the meaning set forth in [Section 7.4](#) (Manufacturing Technology Transfer).

1.154 "**Medical Affairs**" means activities conducted by a Party's medical affairs department (or, if a Party does not have a medical affairs department, the equivalent function thereof), including real world evidence, communications with key opinion leaders, continuing medical education, symposia, advisory boards (to the extent related to medical affairs or clinical guidance), activities performed in connection with patient registries, review and approval of materials consistent with a Party's or its Affiliate's internal SOPs and Applicable Law, interactions and engagements with patient advocacy groups and other key stakeholders, and other similar medical programs and communications.

1.155 "**Milestone Events**" means the Regulatory Milestone Events and the Sales Milestone Events.

1.156 "**Milestone Payments**" means the Regulatory Milestone Payments and the Sales Milestone Payments.

1.157 "[***]" has the meaning set forth in [Section 2.7.2\(a\)](#) (Acquisition of Potential In-Licenses).

1.158 "**Net Sales**" means, with respect to any Licensed Product, the amount invoiced by Otsuka or its Affiliates or Sublicensees (each a "**Selling Party**") for sales of such Licensed Product in arm's length transactions to Third Parties in all countries in the Otsuka Territory, less deduction (if not already deducted in the amount invoiced) of the following items with respect to sales of such Licensed Product:

- (a) Normal and customary trade, quantity, or cash discounts to non-affiliated brokers, agents or customers to the extent actually allowed and taken, *provided that* such discounts are not applied disproportionately to the Licensed Products when compared to the other products of the Selling Party, as applicable;
- (b) Actual amounts repaid or credited by reason of rejections, returns, defects, price adjustments, billing errors, or trial prescriptions, including amounts repaid, discounted or credited by reason of risk sharing schemes with respect to the Licensed Product with any Governmental Authority;
- (c) To the extent separately stated on purchase orders, invoices, or other documents of sale, any taxes, tariffs, duties, excises or other governmental charges (including any value added tax, sales tax, consumption tax or similar tax, other than any taxes based on income) imposed or levied on the production, sale, transportation, delivery, or use, exportation or importation of the Licensed Products;
- (d) Rebates, reimbursements, fees, clawbacks, discounts or chargeback payments paid, granted or credited to managed health care organizations, pharmacy benefit managers (or equivalent thereof), national, state/provincial, local, and other governments or Governmental Authorities, their agencies/purchasers/reimbursement providers (including those requested by any Governmental Authority any time after the actual sale of a Licensed Product), or to any Third Party payor, administrator, contractee or purchaser, including trade customers, including any fees levied by any Governmental Authority as a result of healthcare reform policies, and including those offered as a result of the clinical or real-world performance of the Licensed Product after it is marketed and sold;
- (e) Outbound transportation costs prepaid or allowed and costs of insurance in transit, with the exclusion of storage and warehousing costs;
- (f) Any invoiced amounts that are not collected, including bad debts; and
- (g) Any other deductions that are consistent with the Selling Party's Accounting Standards and are not duplicative of the above deductions;

provided that the following deductions are not allowed in the calculation of Net Sales: (i) co-payment assistance; (ii) discounts offered to insurers to facilitate patient access to the product; (iii) program and data management fees paid to wholesalers/distributors; (iv) commissions paid to third-party logistics (3PL) providers; and (v) product samples shipped to indirect customers.

If a Selling Party makes any adjustments to such deductions after the associated Net Sales have been reported pursuant to this Agreement, then the adjustments will be reported and reconciled with the next report and payment of any royalties due.

Net Sales will not include (i) any payments among Selling Parties, unless such paying party is the end user of the relevant Licensed Product, (ii) any payments in consideration of supplies of the applicable Licensed Product for use in Clinical Trials, or (iii) payments for promotional samples, compassionate use, named-patient use, or expanded access, indigent or other patient access programs, in each case when sold or distributed at or below the applicable Selling Party's costs (including supply price paid).

SCHEDULE If a Selling Party sells a Licensed Product in the Otsuka Territory as part of a therapy or product in combination with other pharmaceutical or biologic products, diagnostic products, ingredients, delivery devices or other components other than the Licensed Compound (each, an "**Other Product**") whether combined in a single formulation or package, formulated or packaged separately but sold under a single label approved by a Regulatory Authority, packaged together for sale or shipment as a single unit, or marketed or sold collectively as a single product, but, in all cases, sold together for a single price (a "**Combination Product**"), Net Sales of such Combination Product for the purposes of determining payments based on Net Sales hereunder will be calculated by multiplying actual Net Sales of such Combination Product as determined in the first paragraph of this Net Sales definition ("**Combination Product Net Sales**") by the fraction A/(A+B) where A is the average selling price of the Licensed Compound sold separately in such country during the applicable reporting period, and B is the sum of the average selling price(s) of the Other Product(s) in the Combination Product in such country during the same reporting period. If the Licensed Compound is sold separately in an applicable reporting period in a country in the Otsuka Territory, but the Other Product(s) are not sold separately in the same country in the same reporting period, then Net Sales of such Combination Product will be calculated by multiplying the Combination Product Net Sales by the fraction A/C where A is the average selling price of the Licensed Compound sold separately in such country during such reporting period, and C is the average selling price of the Combination Product in such country during such reporting period. If neither the Licensed Compound nor the Other Product(s) are sold separately in the same country in the same reporting period, then Net Sales of such Combination Product will be calculated by multiplying the Combination Product Net Sales by a fraction that reflects the value of the Licensed Compound relative to the value of the Other Product(s) in such Combination Product, which fraction shall be determined by Otsuka in its reasonable judgment, and reasonably acceptable to Ionis, and in such event, Otsuka shall provide Ionis with supporting documentation for such determination. Notwithstanding the foregoing, the Parties agree that the Licensed Product Manufactured and supplied by Ionis

pursuant to the Supply Agreements in the form of an autoinjector pre-filled with Licensed Compound will not be subject to the terms of this paragraph, and such autoinjector will not be deemed an Other Product for purposes of calculating Net Sales.

1.159 "*******" has the meaning set forth in [Section 4.4.4\(a\)](#) (Shared Costs).

1.160 "*******" has the meaning set forth in [Section 4.4.4\(a\)](#) (Shared Costs).

1.161 "**Non-Clinical Asia HAE Development Plan**" has the meaning set forth in [Section 4.2.2\(b\)](#) (Asia Territory).

1.162 "**Non-Clinical Europe HAE Development Plan**" has the meaning set forth in [Section 4.2.2\(a\)](#) (Europe Territory).

1.163 "**Non-Clinical HAE Development Plans**" means the Non-Clinical Asia HAE Development Plan and the Non-Clinical Europe HAE Development Plan.

1.164 "**OFAC**" means the Office of Foreign Assets Control of the United States Department of the Treasury or any successor agency thereto.

1.165 "**Ongoing Cross-Territory Studies**" has the meaning set forth in [Section 4.2.1](#) (Cross-Territory Clinical Development Plan).

1.166 "**Opt-In Fee**" has the meaning set forth in [Section 4.4.4\(c\)](#) (Otsuka Opt-In).

1.167 "**Opt-In Notice**" has the meaning set forth in [Section 4.4.4\(c\)](#) (Otsuka Opt-In).

1.168 "**Original Agreement**" has the meaning set forth in the Recitals.

1.169 "**Original Agreement Term**" means the period of time commencing on the Original Effective Date and continuing until the Restatement Date.

1.170 "**Original Effective Date**" has the meaning set forth in the Recitals.

1.171 "**Other Covered Party**" means any political party or party official, or any candidate for political office.

1.172 "*******" has the meaning set forth in [Section 2.7.2\(c\)](#) ([***] Potential In-Licenses).

1.173 "**Other Product**" has the meaning set forth in [Section 1.158](#) of this [Appendix 1](#) (Definitions).

1.174 "**Otsuka Collaboration Know-How**" has the meaning set forth in [Section 10.1.2\(b\)](#) (Ownership of Arising Intellectual Property).

1.175 "**Otsuka Collaboration Patent Rights**" has the meaning set forth in [Section 10.1.2\(b\)](#) (Ownership of Arising Intellectual Property).

1.176 "**Otsuka Indemnitee**" has the meaning set forth in [Section 13.1](#) (Indemnification by Ionis).

1.177 "**Otsuka Know-How**" means all Collaboration Know-How (excluding Otsuka's interest in Joint Collaboration Know-How) that is (a) Controlled by Otsuka or any of its Affiliates during the Term and (b) necessary or reasonably useful to Exploit a Licensed Product.

1.178 "**Otsuka Patent Rights**" means all Collaboration Patent Rights (excluding Otsuka's interest in Joint Collaboration Patent Rights) that are (a) Controlled by Otsuka or any of its Affiliates during the Term and (b) necessary or reasonably useful (or, with respect to patent applications, would be necessary or reasonably useful if such patent applications were to issue as patents) to Exploit a Licensed Product.

1.179 "**Otsuka Product Trademarks**" has the meaning set forth in [Section 10.10.1\(b\)](#) (Ownership of Otsuka Product Trademarks).

1.180 "**Otsuka Publication**" has the meaning set forth in [Section 12.5.1](#) (Otsuka's Right to Publish).

1.181 "**Otsuka Technology**" means Otsuka Know-How, Otsuka Patent Rights, and Otsuka's interest in the Joint Collaboration Technology.

1.182 "**Otsuka Territory**" means the Asia Territory and the Europe Territory.

1.183 "**Otsuka Territory Brand Strategy**" has the meaning set forth in [Section 6.4.2](#) (Otsuka Territory Brand Strategy and Commercialization Operating Plans).

1.184 "**Otsuka Territory Commercialization Operating Plans**" has the meaning set forth in [Section 6.4.2](#) (Otsuka Territory Brand Strategy and Commercialization Operating Plans).

1.185 "**Otsuka Territory Medical Affairs Plans**" has the meaning set forth in [Section 6.6.2](#) (Otsuka Territory Medical Affairs Plans).

1.186 "**Otsuka Territory-Specific Development Plans**" has the meaning set forth in [Section 4.3.2](#) (Asia Territory-Specific Development Plan).

1.187 "**Otsuka Territory Trademark Infringement**" has the meaning set forth in [Section 10.10.4\(a\)](#) (Unitary Product Trademark).

1.188 "**Packaging and Labeling**" means primary, secondary, or tertiary packaging and labeling of a Licensed Product (in its commercial packaging presentation) for sale or use in a country, including the Approved Labeling and insertion of materials such as patient inserts, patient medication guides, and professional inserts and any other written, printed, or graphic materials accompanying such Licensed Product and any brand security or anti-counterfeiting measures included in the packaging elements for such Licensed Product considered to be part of the finished packaged Licensed Product, and all testing and release thereof.

1.189 "**Party Vote**" has the meaning set forth in [Section 8.5.1](#) (General Decision-Making Process).

1.190 "**Patent Challenge**" means, with respect to a Person, that such Person contests or assists a Third Party in contesting the scope, validity, or enforceability of a Patent Right or any foreign counterpart thereof anywhere in the world in any court, tribunal, arbitration proceeding, or other proceeding, including the U.S. Patent and Trademark Office and the U.S. International Trade Commission. A Patent Challenge includes: (a) filing an action under 28 U.S.C. §§ 2201-2202 seeking a declaration of invalidity or unenforceability of any such Patent Right; (b) filing, or joining in, a petition under 35 U.S.C. § 311 to institute *inter partes* review of any such Patent Right; (c) filing, or joining in, a petition under 35 U.S.C. § 321 to institute post-grant review of any such Patent Right or any portion thereof; (d) filing or commencing any opposition, nullity, or similar proceedings challenging the validity of any such Patent Right in the Territory; or (e) any foreign equivalent of clauses (a), (b), (c), or (d), including any proceeding in any country or patent office in any country or region in the Otsuka Territory.

1.191 "**Patent Prosecution**" means activities directed to (a) preparing, filing, and prosecuting applications (of all types) for any Patent Right, (b) maintaining any Patent Right, and (c) deciding whether to abandon or maintain any Patent Right.

1.192 "**Patent Rights**" means (a) all patents, patent applications, and utility models in any country or jurisdiction, including provisional applications, priority applications, and international applications, (b) all patent applications filed either from such patents or patent applications or from an application claiming priority from any of these, including divisionals, continuations, and continuations-in-part, (c) any and all patents that have issued or in the future issue from the foregoing patent applications, (d) any and all substitutions, renewals, registrations, confirmations, revalidations, reissues, and re-examinations of the foregoing patents or patent applications, and (e) extensions, restorations, supplemental protection certificates, and the like based on any of the foregoing patents or patent applications.

1.193 "**Payment Assignment**" has the meaning set forth in [Section 16.1](#) (Assignment).

1.194 "**Payment Forms**" means one copy of each of the following documents which, at the time Ionis provides such documents to Otsuka, must be currently effective (un-expired), completed and signed: the United States Internal Revenue Service Form 6166 (United States Residency Certification) as received from the United States Internal Revenue Service; Form 3 (Application Form for Income Tax Convention); and Form 17 (Attachment Form for Limitation on Benefits Article).

1.195 "**Person**" means any corporation, limited or general partnership, limited liability company, joint venture, trust, unincorporated association, governmental body, authority, bureau, or agency, or any other entity or body, or an individual.

1.196 "**Pharmacovigilance Agreement**" means an agreement regarding receipt, investigation, and reporting of product complaints, adverse events, product recalls, and any other information related to the safety of the Licensed Products in the Territory.

1.197 "**Phase 3 Clinical Trial**" means a Clinical Trial of a Licensed Product that satisfies the requirements for a Phase 3 study as defined in 21 CFR § 312.21(c) (or any amended or successor regulations) or that satisfies the requirements of similar laws or regulations outside the United States.

1.198 "[***]" means the [***].

1.199 "**PMDA**" means the Pharmaceuticals and Medical Devices Agency or any successor agency thereto.

1.200 "**Post-Approval Cross-Territory Mandatory Studies**" has the meaning set forth in [Section 4.2.1](#) (Cross-Territory Clinical Development Plan).

1.201 "**Post-Approval Mandatory Study**" means any Clinical Trial or other study of a pharmaceutical or biologic product initiated following receipt of Regulatory Approval or to be conducted after receipt of Regulatory Approval, in each case, that was mandated by the applicable Regulatory Authority in any country in the Territory as a condition of receiving or maintaining a Regulatory Approval for a product with respect to a particular indication in such country (such as post-marketing approval studies and observational studies, if required by any Regulatory Authority in any country in the Territory to support or maintain Regulatory Approval for a product in such country) or that is required for a label extension for a product in such country. For clarity, a [***] is a Post-Approval Mandatory Study.

1.202 "**Potential In-License**" has the meaning set forth in [Section 2.7.2\(a\)](#) (Acquisition of Potential In-Licenses).

1.203 "**Product Materials**" has the meaning set forth in [Section 6.8](#) (Product Materials).

1.204 "**Product-Specific Patents**" means Patent Rights Controlled by a Party or any of its Affiliates as of or after the Original Effective Date claiming: (a) the composition of matter of a Licensed Product, or (b) methods of using a Licensed Product.

1.205 "**Professional Requirements**" means (a) the codes and standards of the European Accreditation Council for Continuing Medical Education (EACCME) and the European Federation of Pharmaceutical Industries and Associations (EFPIA), (b) the codes of the Prescription Medicines Code of Practice Authority (PMCPA) and the Association of the British Pharmaceutical Industry (ABPI), (c) FDA's regulations, guidance, and enforcement letters concerning the advertising of prescription drug products, (d) the American Medical Association's Guidelines on Gifts to Physicians from Industry, (e) the Accreditation Council for Continuing Medical Education (ACCME) Standards for Commercial Support of Continuing Medical Education, (f) the Pharmaceutical Supply Chain Initiative (PSCI) and Pharmaceutical Industry Principles for Responsible Supply Chain Management, (g) the Code on Interactions with Healthcare Professionals promulgated by the Pharmaceutical Research and Manufacturers of America (PhRMA Code), (h) the Department of Health and Human Services Office of Inspector General Compliance Program Guidance for Pharmaceutical Manufacturers (OIG Compliance Guidance), and (i) all other accepted national and international pharmaceutical industry codes of practice in and for the relevant countries in the Territory, as any of the foregoing may be amended from time-to-time.

1.206 "**Publication**" has the meaning set forth in [Section 12.5](#) (Publications).

1.207 "**PV Subcommittee**" has the meaning set forth in [Section 5.11](#) (Pharmacovigilance Subcommittee).

1.208 "[***]" means [***].

1.209 "**Quality Agreement**" has the meaning set forth in [Section 7.2.3](#) (Quality Agreements).

1.210 "**Receiving Party**" has the meaning set forth in [Section 1.39](#) (Confidential Information) of this [Appendix 1](#) (Definitions).

1.211 "**Reduced Royalties**" has the meaning set forth in [Section 9.3.3](#) (Reduced Royalty Term).

1.212 "**Reduced Royalty Term**" has the meaning set forth in [Section 9.3.3](#) (Reduced Royalty Term).

1.213 "[***]" has the meaning set forth in [Section 9.3.2\(c\)](#) ([***]).

1.214 "**Region**" means each of the (a) Asia Territory and (b) the Europe Territory.

1.215 "**Regulatory Approval**" means, with respect to a particular country or other regulatory jurisdiction, any approval of an MAA or other approval, product, or establishment license, registration, or authorization of any Regulatory Authority necessary for the commercial sale of a pharmaceutical, diagnostic, or biologic product in such country or other regulatory jurisdiction, excluding, in each case, Reimbursement Approval.

1.216 "**Regulatory Authority**" means, in a particular country or jurisdiction, any applicable Governmental Authority involved in granting Regulatory Approval in such country or jurisdiction, including (a) in the U.S., the FDA and any other applicable Governmental Authority in the U.S. having jurisdiction over any pharmaceutical, diagnostic, or biologic product, (b) in the E.U., the EMA and any other applicable Governmental Authority in the E.U. having jurisdiction over any pharmaceutical, diagnostic, or biologic product, (c) in Japan, the PMDA and any other applicable Governmental Authority in Japan having jurisdiction over any pharmaceutical, diagnostic, or biologic product, and (d) in other countries, other analogous Governmental Authorities having jurisdiction over any pharmaceutical, diagnostic, or biologic product.

1.217 "**Regulatory Exclusivity**" means, with respect to a Licensed Product in a country in the Otsuka Territory, the period of time during which: (a) Otsuka or its Affiliate or Sublicensee has been granted the exclusive legal right by a Regulatory Authority (or is otherwise entitled to the exclusive legal right by operation of Applicable Law) in such country to market and sell such Licensed Product, and such right precludes a Third Party from making such Licensed Product available for purchase for any indication; or (b) the data and information submitted by Otsuka or its Affiliate or Sublicensee to the relevant Regulatory Authority in such country for purposes of obtaining Regulatory Approval of such Licensed Product may not be referenced, or relied upon in any way by a Third Party or such Regulatory Authority to support the Regulatory Approval or marketing of any product by a Third Party in such country, or if such data and information is referenced, or relied upon to support a Regulatory Approval granted to a Third Party in such country, the product may not be placed on the market for any indication.

1.218 **"Regulatory Milestone Events"** has the meaning set forth in [Section 9.2.1](#) (Regulatory Milestones).

1.219 **"Regulatory Milestone Payments"** has the meaning set forth in [Section 9.2.1](#) (Regulatory Milestones).

1.220 **"Regulatory Responsible Party"** means the Party designated under [Section 5.1](#) (Regulatory Responsible Party).

1.221 **"Regulatory Submission"** means any filing, application, or submission with any Regulatory Authority in support of the Development, Manufacture, Commercialization, or other Exploitation of a pharmaceutical, diagnostic, or biologic product (including to obtain, support, or maintain Regulatory Approval from that Regulatory Authority), and all written or electronic correspondence or communication with or from the relevant Regulatory Authority, as well as minutes of any material meetings, telephone conferences, or discussions with the relevant Regulatory Authority. Regulatory Submissions include all INDs, MAAs, and other applications for Regulatory Approval and their equivalents.

1.222 **"Regulatory Support"** has the meaning set forth in [Section 5.6](#) (Cooperation).

1.223 **"Reimbursed Manufacturing Tech Transfer Costs"** has the meaning set forth in [Section 7.4](#) (Manufacturing Technology Transfer).

1.224 **"Reimbursement Approval"** means, as applicable, (a) the Governmental Authority approval, agreement, determination, or other decision establishing prices that can be charged for a product in regulatory jurisdictions where the applicable Governmental Authority approves or determines the prices charged to end-users for pharmaceutical, diagnostic, or biologic products, or (b) the Governmental Authority approval, agreement, determination or decision establishing the prices at which a product will be reimbursed in regulatory jurisdictions where the applicable Governmental Authority approves, determines or recommends the reimbursement or use of pharmaceutical, diagnostic, or biologic products.

1.225 **"Remedial Action"** has the meaning set forth in [Section 5.13.1](#) (Notification and Determination).

1.226 **"Representatives"** means, with respect to a Person, such Person's employees, officers, directors, consultants, contractors, Subcontractors, and agents, in each case, who are authorized to act on behalf of such Person.

1.227 **"Requested Assistance"** has the meaning set forth in [Section 3.2](#) (Technology Transfer Costs).

1.228 **"Restatement Date"** has the meaning set forth in the Preamble.

1.229 **"Restatement Upfront Payment"** has the meaning set forth in [Section 9.1](#) (Upfront Payment).

1.230 **"Restricted Party"** means any individual or entity on one or more of the Restricted Party Lists.

1.231 **"Restricted Party List"** means the list of sanctioned entities maintained by the United Nations; the Specially Designated Nationals and Blocked Persons List, the Foreign Sanctions Evaders List and the Sectoral Sanctions Identifications List, all administered by OFAC; the U.S. Denied Persons List, the U.S. Entity List, and the U.S. Unverified List, all administered by the U.S. Department of Commerce; and the entities subject to restrictive measures and the consolidated list of Persons, Groups, and Entities Subject to E.U. Financial Sanctions, as implemented by the E.U. Common Foreign & Security Policy; and similar lists of restricted parties maintained by the Governmental Authorities of the countries that have jurisdiction over the activities conducted under this Agreement.

1.232 **"Reversion License"** has the meaning set forth in [Section 14.9.2\(a\)](#) (License Grant).

1.233 **"Review Period"** has the meaning set forth in [Section 12.5.1](#) (Otsuka's Right to Publish).

1.234 **"ROFN Exercise Notice"** has the meaning set forth in [Section 2.8.1](#) (ROFN Exercise).

1.235 **"ROFN Negotiation Period"** has the meaning set forth in [Section 2.8.2](#) (Negotiation).

1.236 **"ROFN Notice and Package"** has the meaning set forth in [Section 2.8.1](#) (ROFN Exercise).

1.237 **"ROFN Territory"** has the meaning set forth in [Section 2.8.1](#) (ROFN Exercise).

1.238 **"Royalties"** has the meaning set forth in [Section 9.3.3](#) (Reduced Royalty Term).

1.239 **"Royalty Report"** has the meaning set forth in [Section 9.3.4\(b\)](#) (Royalty Report).

1.240 **"Royalty Term"** has the meaning set forth in [Section 9.3.3](#) (Reduced Royalty Term).

1.241 **"[***]"** has the meaning set forth in [Section 9.3.1](#) (Royalty Payments During the Initial Royalty Term).

1.242 **"Rules"** has the meaning set forth in [Section 15.2.2](#) (Arbitration).

1.243 **"Sales Milestone Events"** has the meaning set forth in [Section 9.2.2](#) (Sales Milestones).

1.244 **"Sales Milestone Payments"** has the meaning set forth in [Section 9.2.2](#) (Sales Milestones).

1.245 **"Selling Party"** has the meaning set forth in [Section 1.158](#) of this Appendix 1 (Definitions).

1.246 **"[***]"** has the meaning [set forth in [Section 4.4.1\(c\)](#) (Shared Development Costs)].

1.247 **"Shared Cross-Territory Development Costs"** has the meaning set forth in [Section 4.4.1\(c\)](#) (Shared Development Costs).

1.248 **"Shared Development Budget"** has the meaning set forth in [Section 4.4.2\(a\)](#) (Shared Development Budget).

1.249 **"Subcommittee"** has the meaning set forth in [Section 8.3.1](#) (Formation; Authority).

1.250 **"Subcommittee Co-Chairperson"** has the meaning set forth in [Section 8.3.2](#) (Subcommittee Leadership and Meetings).

1.251 **"Subcontractors"** has the meaning set forth in [Section 2.3.2](#) (Right to Subcontract).

1.252 **"Sublicensee"** means, with respect to a Party, any Third Party to which such Party or its Affiliate grants a sublicense under any of the rights licensed to the applicable Party under this Agreement other than a Subcontractor.

1.253 **"Supply Agreements"** has the meaning set forth in [Section 7.2.2](#) (Commercial Supply Agreement).

1.254 **"Tax" or "Taxes"** means any present or future taxes, levies, imposts, duties, charges, assessments or fees of any nature (including any interest thereon), including value add, sales, excise or similar taxes.

1.255 "**Technology Transfer**" has the meaning set forth in [Section 3.1](#) (Initial Know-How Transfer).

1.256 "**Term**" has the meaning set forth in [Section 14.1](#) (Term).

1.257 "**Terminated Region**" means (a) any Region pursuant to which the non-breaching Party terminates this Agreement pursuant to [Section 14.2](#) (Termination for Material Breach), (b) the Europe Territory, the Asia Territory, or any country other than Japan in the Asia Territory, in each case, for which Otsuka terminates this Agreement pursuant to [Section 14.3](#) (Termination by Otsuka for Convenience), or (c) all countries in the Territory if either Party terminates this Agreement in its entirety pursuant to [Section 14.2](#) (Termination for Material Breach), [Section 14.4](#) (Discontinuation of Development and Commercialization), [Section 14.5](#) (Termination for Patent Challenge), or [Section 14.6](#) (Termination for Insolvency).

1.258 "**Territory**" means (a) the Otsuka Territory, with respect to Otsuka, (b) the Ionis Territory, with respect to Ionis, and (c) collectively, worldwide.

1.259 "**Third Party**" means any Person other than a Party or its Affiliates.

1.260 "**Third Party Claims**" has the meaning set forth in [Section 13.1](#) (Indemnification by Ionis).

1.261 "[**]" has the meaning set forth in [Section 2.8.2](#) (Negotiation).

1.262 "**Third Party Patent Challenge**" has the meaning set forth in [Section 10.4](#) (Defense of Third Party Patent Challenges).

1.263 "**Third Party Payments**" means, with respect to a Licensed Product, any (a) payments (including upfront payments, milestone payments, license fees, royalties and monetary damages) made by Otsuka or its Affiliate to a Third Party (i) pursuant to an agreement between Otsuka or its Affiliate and such Third Party entered into following the Original Effective Date in accordance with [Section 2.7.2](#) (Potential In-Licenses) to obtain rights to Patent Rights or Know-How from such Third Party that would be infringed or misappropriated by the Exploitation of a Licensed Product in the Otsuka Territory or (ii) pursuant to an agreement between Otsuka or its Affiliate and such Third Party, or otherwise, as part of a settlement or to satisfy a judgment in accordance with [Section 10.5.3](#) (Settlement), or (b) amounts for which Otsuka reimburses Ionis under a Collaboration In-License, in each case ((a) or (b)), that are directly in consideration for or reasonably allocable to a license or sublicense (as applicable) to Otsuka or its Affiliate under, or are paid in settlement or to satisfy a judgment of a claim relating to, Patent Rights or Know-How Controlled by such Third Party that would, but for a license thereunder, be infringed or misappropriated by the Exploitation of such Licensed Product.

1.264 "**Trademark**" means any word, name, symbol, color, shape, designation or any combination thereof, including any trademark, service mark, trade name, brand name, sub-brand name, domain name, trade dress, product configuration, program name, delivery form name, certification mark, collective mark, logo, tagline, slogan, design or business symbol, that functions as an identifier of source or origin, whether or not registered and all statutory and common law rights therein and all registrations and applications therefor, together with all goodwill associated with, or symbolized by, any of the foregoing.

1.265 "**Trademark Infringement Suit**" has the meaning set forth in [Section 10.10.5\(a\)](#) (Unitary Product Trademarks).

1.266 "**Transition Plan**" has the meaning set forth in [Section 14.9.3\(a\)](#) (Scope).

1.267 "**Transition Services**" has the meaning set forth in [Section 14.9.3\(a\)](#) (Scope).

1.268 "**Unitary Product Trademark**" has the meaning set forth in [Section 10.10.1\(a\)](#) (Unitary Product Trademarks).

1.269 "**U.S.**" means the United States of America (including all possessions and territories thereof, including Puerto Rico).

1.270 "**U.S. Dollars**" or "**\$**" means the legal tender of the U.S.

1.271 "**Valid Claim**" means a claim of an issued and unexpired patent (as may be adjusted through a patent term adjustment or extended through supplementary protection certificate or patent term extension or the like) that has not been revoked, held invalid, or held unenforceable by a patent office or other Governmental Authority of competent jurisdiction in a final and non-appealable judgment (or judgment from which no appeal was taken within the allowable time period), and [**].

1.272 "**Withheld Amount**" has the meaning set forth in [Section 9.10.2](#) (Withholding Tax).

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SCHEDULE 1.69
Existing Third-Party IP Agreements

[**]

Compensation for Advisory Services

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SCHEDULE 1.111
Ionis Core Technology Patents

Ionis File No.	Country/Treaty	Application No./ Patent No.	Filing Date	Grant Date	Title
[**]	[**]	[**]	[**]	[**]	[**]
[**]	[**]	[**]	[**]	[**]	[**]
[**]	[**]	[**]	[**]	[**]	[**]
[**]	[**]	[**]	[**]		[**]
[**]	[**]	[**]	[**]		[**]
[**]	[**]	[**]	[**]		[**]
[**]	[**]	[**]	[**]		[**]

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SCHEDULE 1.117

Ionis Manufacturing and Analytical Patents

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SCHEDULE 1.124
Ionis Product-Specific Patents

Ionis File No.	Country/ Treaty	Status	Application No./ Patent No.	Filing Date	Grant Date	Title
[***]	[***]	[***]	[***]	[***]		[***]
[***]	[***]	[***]	[***]	[***]		[***]
[***]	[***]	[***]	[***]	[***]		[***]
[***]	[***]	[***]	[***]	[***]		[***]
[***]	[***]	[***]	[***]	[***]		[***]
[***]	[***]	[***]	[***]	[***]		[***]
[***]	[***]	[***]	[***]	[***]		[***]

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SCHEDULE 4.2.1
Cross-Territory Clinical Development Plan
[***]

For your Advisory services, after the Start Date Ionis will pay you flat monthly fee of \$12,500 through September 30, 2024 and thereafter a flat monthly fee of \$6,250.

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SCHEDULE 4.2.2

Since you are transitioning seamlessly from an Ionis employee to a consultant, the stock options and RSUs you received for your previous service as an Ionis employee (collectively, Non-Clinical Europe HAE Development Plan

[***]

CONFIDENTIAL

"EMPLOYEE EQUITY AWARDS"

) will continue to vest so long as your Continuous Service (as defined in the applicable equity plan) continues. If your Continuous Service (as defined in the applicable equity plan) continues through the Scheduled End date, you will be eligible to exercise your stock options for up to 18 months after the termination of your Continuous Service.

SCHEDULE 4.4.2

Shared Development Budget

[***]

SCHEDULE 14.9.3
Transition Services

[***]

Schedule A

Page 1

EXHIBIT 31.1

CERTIFICATION

I, Brett P. Monia, 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: **May 7, 2024** **August 1, 2024**

/s/ BRETT P. MONIA
 Brett P. Monia, 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: **May 7, 2024** **August 1, 2024**

/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, Brett P. Monia, 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 **March 31, 2024** **June 30, 2024**, to which this Certification is attached as Exhibit 32.1 (the "Periodic Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and
2. The information contained in the Periodic Report fairly presents, in all material respects, the financial condition of the Company at the end of the period covered by the Periodic Report and the results of operations of the Company for the period covered by the Periodic Report.

Dated: **May 7, 2024** **August 1, 2024**

/s/ BRETT P. MONIA
Brett P. Monia, Ph.D.
Chief Executive Officer

/s/ ELIZABETH L. HOUGEN
Elizabeth L. Hougen
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.

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