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 June 30, 2025

OR

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

For the transition period from _____ to _____

Commission file number 000-19125

Ionis Pharmaceuticals, Inc.

(Exact name of Registrant as specified in its charter)

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

760-931-9200

(Registrant's telephone number, including area code)

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

Title of each class	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 ☒

The number of shares of voting common stock outstanding as of July 24, 2025 was 159,391,229.

IONIS PHARMACEUTICALS, INC.
FORM 10-Q
INDEX

TRADEMARKS

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

PART I — FINANCIAL INFORMATION

ITEM 1. FINANCIAL STATEMENTS

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

	June 30, 2025 (unaudited)	December 31, 2024
ASSETS		
Current assets:		
Cash and cash equivalents	$ 297,304	$ 242,077
Short-term investments	1,992,676	2,055,579
Contracts receivable	52,580	92,188
Inventories	8,481	12,512
Other current assets	226,109	217,934
Total current assets	2,577,150	2,620,290
Property, plant and equipment, net	111,951	94,251
Right-of-use assets	163,933	161,856
Deposits and other assets	132,099	127,278
Total assets	$ 2,985,133	$ 3,003,675
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 22,800	$ 42,964
Accrued compensation	46,564	69,614
Accrued liabilities	98,957	108,438
Income taxes payable	81	34
0 percent convertible senior notes, net	630,118	-
Current portion of deferred contract revenue	75,910	78,989
Other current liabilities	22,806	9,279
Total current liabilities	897,236	309,318
Long-term deferred contract revenue	125,095	156,504
1.75 percent convertible senior notes, net	566,420	565,026
0 percent convertible senior notes, net	-	628,535
Liability related to sale of future royalties, net	541,205	542,212
Long-term lease liabilities	164,379	161,805
Long-term obligations	59,074	51,924
Total liabilities	2,353,409	2,415,324
Stockholders' equity:		
Common stock, $0.001 par value; 300,000,000 shares authorized, 159,196,782 and 157,908,815 shares issued and outstanding at June 30, 2025 and December 31, 2024, respectively	159	158
Additional paid-in capital	2,932,747	2,868,812
Accumulated other comprehensive income	(27,987)	(30,811)
Accumulated deficit	(2,273,195)	(2,249,808)
Total stockholders' equity	631,724	588,351
Total liabilities and stockholders' equity	$ 2,985,133	$ 3,003,675

See accompanying notes.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2025	**2024**	**2025**	**2024**
Revenue:				
Commercial revenue:				
Product sales, net	$ 19,273	$ -	$ 25,561	$ -
Royalty revenue	69,952	63,844	134,117	113,229
Other commercial revenue	13,531	8,192	19,246	18,400
Total commercial revenue	102,756	72,036	178,924	131,629
Research and development revenue:				
Collaborative agreement revenue	336,921	141,524	381,951	190,870
WAINUA joint development revenue	12,372	11,690	22,785	22,249
Total research and development revenue	349,293	153,214	404,736	213,119
Total revenue	452,049	225,250	583,660	344,748
Expenses:				
Cost of sales	4,151	4,164	5,614	6,314
Research, development and patent	217,460	222,064	418,219	436,280
Selling, general and administrative	90,622	65,113	166,872	117,758
Total operating expenses	312,233	291,341	590,705	560,352
Income (loss) from operations	139,816	(66,091)	(7,045)	(215,604)
Other income (expense):				
Investment income	24,687	25,599	49,354	51,884
Interest expense	(4,114)	(4,490)	(8,223)	(8,641)
Interest expense related to sale of future royalties	(18,648)	(18,296)	(37,470)	(36,254)
Loss on investments, net	(18,312)	(3,533)	(20,476)	(1,200)
Other income, net	102	610	569	887
Income (loss) before income tax benefit (expense)	123,531	(66,201)	(23,291)	(208,928)
Income tax benefit (expense)	20	(64)	(96)	(140)
Net income (loss)	$ 123,551	$ (66,265)	$ (23,387)	$ (209,068)
Basic net income (loss) per share	$ 0.78	$ (0.45)	$ (0.15)	$ (1.43)
Diluted net income (loss) per share	$ 0.70	$ (0.45)	$ (0.15)	$ (1.43)
Shares used in computing basic net income (loss) per share	159,137	145,958	158,937	145,748
Shares used in computing diluted net income (loss) per share	182,331	145,958	158,937	145,748

See accompanying notes.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2025	**2024**	**2025**	**2024**
Net income (loss)	$ 123,551	$ (66,265)	$ (23,387)	$ (209,068)
Unrealized gains (losses) on debt securities, net of tax	367	150	1,997	(2,056)
Currency translation adjustment	595	(24)	827	(137)
Comprehensive income (loss)	$ 124,513	$ (66,139)	$ (20,563)	$ (211,261)

See accompanying notes.

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

Description	Common Stock Shares	Common Stock Amount	Additional Paid in Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Stockholders' Equity
Balance at March 31, 2024	145,845	$ 146	$ 2,270,047	$ (34,964)	$ (1,938,714)	$ 296,515
Net loss	-	-	-	-	(66,265)	(66,265)
Change in unrealized gains, net of tax	-	-	-	150	-	150
Foreign currency translation	-	-	-	(24)	-	(24)
Issuance of common stock in connection with employee stock plans, net	180	-	2,594	-	-	2,594
Stock-based compensation expense	-	-	30,728	-	-	30,728
Balance at June 30, 2024	146,025	$ 146	$ 2,303,369	$ (34,838)	$ (2,004,979)	$ 263,698
Balance at March 31, 2025	159,041	$ 159	$ 2,901,262	$ (28,949)	$ (2,396,746)	$ 475,726
Net income	-	-	-	-	123,551	123,551
Change in unrealized gains, net of tax	-	-	-	367	-	367
Foreign currency translation	-	-	-	595	-	595
Issuance of common stock in connection with employee stock plans, net	156	-	1,286	-	-	1,286
Stock-based compensation expense	-	-	30,199	-	-	30,199
Balance at June 30, 2025	159,197	$ 159	$ 2,932,747	$ (27,987)	$ (2,273,195)	$ 631,724

See accompanying notes.

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

Description	Common Stock Shares	Common Stock Amount	Additional Paid in Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Stockholders' Equity
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, net	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
Balance at December 31, 2024	157,909	$ 158	$ 2,868,812	$ (30,811)	$ (2,249,808)	$ 588,351
Net loss	-	-	-	-	(23,387)	(23,387)
Change in unrealized gains, net of tax	-	-	-	1,997	-	1,997
Foreign currency translation	-	-	-	827	-	827
Issuance of common stock in connection with employee stock plans, net	1,288	1	3,527	-	-	3,528
Stock-based compensation expense	-	-	60,408	-	-	60,408
Balance at June 30, 2025	159,197	$ 159	$ 2,932,747	$ (27,987)	$ (2,273,195)	$ 631,724

See accompanying notes.

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

	Six Months Ended June 30,	
	2025	**2024**
Operating activities:		
Net loss	$ (23,387)	$ (209,068)
Adjustments to reconcile net loss to net cash provided by (used in) operating activities:		
Depreciation	4,494	5,013
Amortization of right-of-use operating lease assets	5,177	4,957
Amortization of other assets	1,180	1,260
Amortization of discount on investments, net	(12,978)	(19,143)
Amortization of debt issuance costs	3,288	3,338
Non-cash royalty revenue related to sale of royalties	(24,894)	(16,236)
Non-cash interest related to sale of future royalties	37,165	35,949
Stock-based compensation expense	59,408	62,068
Loss on investments, net	20,471	1,201
Non-cash losses related to other assets	297	389
Changes in operating assets and liabilities:		
Contracts receivable	39,608	70,519
Inventories	(12,465)	(298)
Other current and long-term assets	(22,536)	(9,381)
Accounts payable	(20,309)	(17,064)
Income taxes	47	(1,867)
Accrued compensation	(23,050)	(32,709)
Accrued liabilities and other current liabilities	3,535	(39,201)
Deferred contract revenue	(34,488)	(109,545)
Net cash provided by (used in) operating activities	563	(269,818)
Investing activities:		
Purchases of short-term investments	(802,657)	(803,867)
Proceeds from sale of short-term investments	880,545	968,413
Purchases of property, plant and equipment	(24,882)	(10,727)
Acquisition of licenses and other assets, net	(2,615)	(15,264)
Net cash provided by investing activities	50,391	138,555
Financing activities:		
Proceeds from issuance of common stock through equity plans, net	3,528	26,205
Principal payments on mortgage debt	(82)	(78)
Net cash provided by financing activities	3,446	26,127
Effects of exchange rates on cash	827	(137)
Net increase (decrease) in cash and cash equivalents	55,227	(105,273)
Cash and cash equivalents at beginning of period	242,077	399,266
Cash and cash equivalents at end of period	$ 297,304	$ 293,993
Supplemental disclosures of cash flow information:		
Interest paid	$ 5,214	$ 5,569
Income taxes paid (refunds received), net	$ (383)	$ 1,992
Supplemental disclosures of non-cash investing and financing activities:		
Right-of-use assets obtained in exchange for lease obligations	$ 7,253	$ -
Amounts accrued for capital and patent expenditures	$ 145	$ 1,453

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
June 30, 2025
(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 June 30, 2025 and 2024 on the same basis as the audited financial statements for the year ended December 31, 2024. 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, 2024 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 operating decision maker, or CODM, reviews operating results on an aggregate basis and manages our operations as a single operating segment. Refer to Note 14, *Segment Information*, for further details on our segment information.

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

Below, we have included our accounting policies for revenue recognition related to product sales, net and cost of sales as a result of our launch of TRYNGOLZA in the U.S. Our other significant accounting policies have not changed substantially from those included in our Annual Report on Form 10-K for the year ended December 31, 2024.

Revenue Recognition

Product Sales, Net

We recognize revenue from product sales when the customer obtains control of our product in the amount of the transaction price, which is the amount that reflects the consideration which we expect to receive. We estimate reserves for variable consideration related to applicable discounts, rebates, chargebacks and other allowances included in our agreements with customers, payors and other third parties. We include the amount of variable consideration in the transaction price to the extent that it is probable that a significant reversal in the amount of the cumulative revenue recognized will not occur in a future period. If actual results vary significantly from our estimates, we adjust our estimates in the period that we become aware of such variances.

Cost of Sales

Our cost of sales is comprised of costs related to our commercial revenue, including manufacturing costs, transportation and freight costs and indirect overhead costs associated with the manufacturing and distribution of our products. We also may include certain period costs related to manufacturing services and inventory adjustments in cost of sales.

Cost of sales for a newly launched product, such as TRYNGOLZA, does not include the full cost of manufacturing until we manufacture and sell additional inventory after exhausting pre-launch inventory, which we previously recorded as research and development, or R&D, expense.

Recent Accounting Standards

In November 2023, the Financial Accounting Standards Board, or FASB, issued Accounting Standard Update, or ASU, 2023-07, which provides updated guidance on segment reporting. The guidance requires public companies to disclose significant expenses that are regularly provided to the CODM, other segment items for each reportable segment and measures of segment profit or loss used by the CODM for allocating resources. In addition, the updated guidance requires public companies with a single reportable segment to provide all disclosures required under Accounting Standards Codification, or ASC, Topic 280, *Segment Reporting*, and public companies to include in interim reports all disclosures related to a reportable segment's profit or loss and assets that are currently required in annual reports. We adopted the reporting requirements in our 2024 Annual Report on Form 10-K and began providing the interim reporting requirements in our Quarterly Report on Form 10-Q for the first quarter of 2025. Refer to Note 14, *Segment Information*, for further details on our segment information.

We do not expect any recently issued accounting standards other than those included in our Annual Report on Form 10-K for the year ended December 31, 2024 to have a material impact to our financial results.

3. Supplemental Financial Data

Inventories

Our inventories consisted of the following (in thousands):

	June 30, 2025	December 31, 2024
Raw materials	$ 706	$ 5,557
Work in process	24,114	6,679
Finished goods	157	$ 276
Total	$ 24,977	12,512
Reported as:		
Inventories	$ 8,481	$ 12,512
Deposits and other assets	16,496	-
Total	$ 24,977	$ 12,512

We classify inventories as non-current assets when we expect the inventories to remain on hand beyond one year. We include non-current inventories in deposits and other assets in our condensed consolidated balance sheets. The amount reported as deposits and other assets as of June 30, 2025 consists of work in process.

Accrued Liabilities

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

	June 30, 2025	December 31, 2024
Clinical expenses	$ 59,573	$ 77,436
In-licensing expenses	7,243	7,951
Commercial expenses	12,364	3,589
Other miscellaneous expenses	19,777	19,462
Total accrued liabilities	$ 98,957	$ 108,438

4. Revenues

During the three and six months ended June 30, 2025 and 2024, our revenues consisted of the following (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2025	2024	2025	2024
Revenue:				
Commercial revenue:				
Product sales, net:				
TRYNGOLZA sales, net	$ 19,273	$ -	$ 25,561	$ -
Total product sales, net	19,273	-	25,561	-
Royalty revenue:				
SPINRAZA royalties	54,337	56,743	102,347	95,198
WAINUA royalties	10,415	3,781	19,787	4,907
Other royalties	5,200	3,320	11,983	13,124
Total royalty revenue	69,952	63,844	134,117	113,229
Other commercial revenue:				
TEGSEDI and WAYLIVRA revenue, net	13,531	8,192	19,246	16,820
Other revenue	-	-	-	1,580
Total other commercial revenue	13,531	8,192	19,246	18,400
Total commercial revenue	102,756	72,036	178,924	131,629
Research and development revenue:				
Collaborative agreement revenue	336,921	141,524	381,951	190,870
WAINUA joint development revenue	12,372	11,690	22,785	22,249
Total research and development revenue	349,293	153,214	404,736	213,119
Total revenue	$ 452,049	$ 225,250	$ 583,660	$ 344,748

Revenue Sources

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

Commercial Revenue

In December 2024, the U.S. Food and Drug Administration, or FDA, approved TRYNGOLZA (olezarsen) for the treatment of familial chylomicronemia syndrome, or FCS. Following the approval, we launched TRYNGOLZA and began earning revenue from TRYNGOLZA sales. We recognize product sales, net of variable considerations related to applicable discounts and allowances, when the customer obtains control of our product.

We earn royalty payments primarily on net sales of SPINRAZA, WAINUA and QALSODY.

We earn commercial revenue from TEGSEDI and WAYLIVRA sales under our distribution agreements with Swedish Orphan Biovitrum AB, or Sobi. In addition, we receive royalties from PTC Therapeutics International Limited, or PTC, for TEGSEDI and WAYLIVRA sales. Refer to 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, 2024 for details on our commercialization partnerships with Sobi and PTC.

Under our distribution agreements with Sobi, we concluded that our performance obligation is to provide services to Sobi over the term of the agreement, which includes supplying finished goods inventory to Sobi. We are also responsible for maintaining the marketing authorization for TEGSEDI and WAYLIVRA in major markets and for leading the global commercial strategy for each medicine. We view this performance obligation as a series of distinct activities that are substantially the same. Therefore, we recognize as revenue the price Sobi pays us for the inventory when we deliver the finished goods inventory to Sobi. We also recognize distribution fee revenue based on Sobi's net sales of TEGSEDI and WAYLIVRA. Under our agreements with Sobi, Sobi does not generally have a right of return.

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, R&D services and manufacturing services.

For R&D services that we recognize over time, we measure our progress using an input method. The input methods we use are based on the effort we expend or costs we incur toward the satisfaction of our performance obligation. We estimate the amount of effort we expend, including the time we estimate it will take us to complete the activities, or costs we incur in a given period, relative to the estimated total effort or costs to satisfy the performance obligation. This results in a percentage that we multiply by the transaction price to determine the amount of revenue we recognize each period. This approach requires us to make numerous estimates that may involve judgement. If our estimates or judgements change over the course of the collaboration, they may affect the timing and amount of revenue that we recognize in the current and future periods.

Upfront payments: When we enter into a collaboration agreement and receive an upfront payment, we 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 consider milestone payments to be variable consideration and include them in the transaction price when it is probable. We typically include milestone payments for R&D services in the transaction price when they are achieved. We include these milestone payments when they are achieved because there is considerable uncertainty in the research and development processes that trigger these payments. Similarly, we include regulatory 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 remaining 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. Under the terms of the agreement, we received a $200 million upfront payment in 2021.

We evaluated our WAINUA collaboration under ASC Topic 808, *Collaborative Arrangements*, or 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 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 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 and Ono collaborations, which were the only collaborations that had either substantive changes or were new 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, 2024.

AstraZeneca

We have two collaborations with AstraZeneca: one focused on the joint development and commercialization of WAINUA and one focused on the treatment of cardiovascular, renal and metabolic diseases. From inception through June 30, 2025, we have received more than $905 million from these collaborations.

In the second quarter of 2025, we earned a $30 million milestone payment under our cardiovascular, renal and metabolic diseases collaboration when AstraZeneca initiated the Phase 2b study of opemalirsen (formerly ION532), an investigational medicine designed to reduce the production of apolipoprotein L1, or APOL1, for the treatment of APOL1-mediated kidney disease. We recognized this milestone payment as R&D revenue in full in the second quarter of 2025 because we did not have any remaining performance obligations related to the milestone payment. We will achieve the next payment of $20 million if AstraZeneca advances a medicine under this collaboration.

During the three and six months ended June 30, 2025 and 2024, we earned the following revenue from our relationship with AstraZeneca (in thousands, except percentage amounts):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2025	2024	2025	2024
Revenue from our relationship with AstraZeneca	$ 54,288	$ 15,960	$ 74,577	$ 27,645
Percentage of total revenue	12%	7%	13%	8%

We did not have any deferred revenue from our relationship with AstraZeneca at June 30, 2025 and December 31, 2024.

Ono

In March 2025, we entered into an agreement with Ono Pharmaceutical Co., Ltd., or Ono, to develop and commercialize sapablursen, an investigational RNA-targeted medicine for the potential treatment of polycythemia vera, or PV, a rare and potentially life-threatening hematologic disease. We are responsible for completing the ongoing Phase 2 IMPRSSION study, while Ono will be solely responsible for subsequent development, regulatory filings and commercialization of sapablursen.

Over the term of this collaboration, we are eligible to receive up to $940 million, which is comprised of a $280 million upfront payment, a $20 million development milestone payment, up to $20 million in regulatory milestone payments and up to $620 million in sales milestone payments. In addition, we are eligible to receive royalties in the mid-teen percentage range on net sales. From inception through June 30, 2025, we received the $280 million upfront payment under this collaboration. We achieved the upfront payment when this transaction received clearance under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, or HSR Act, in April 2025. We will achieve the next payment of $20 million if Ono initiates a pivotal clinical trial under this collaboration.

At inception, we identified two performance obligations under this agreement, comprised of our license of sapablursen to Ono and R&D services for sapablursen. We determined the transaction price to be the $280 million upfront payment we received in the second quarter of 2025. We allocated the transaction price based on the estimated stand-alone selling price of each performance obligation as follows:

- $278 million for the license of sapablursen; and
- $2 million for the R&D services for sapablursen.

We recognized $278 million of R&D revenue for the license of sapablursen in the second quarter of 2025 because we completed the performance obligation when we delivered the license to Ono. We recognized revenue for our R&D services performance obligation as we performed services based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. In the second quarter of 2025, we completed our R&D services performance obligation and recognized $2 million of R&D revenue.

During the three and six months ended June 30, 2025 and 2024, we earned the following revenue from our relationship with Ono (in thousands, except percentage amounts):

	Three Months Ended June 30, 2025	Six Months Ended June 30, 2025
Revenue from our relationship with Ono	$ 280,000	$ 280,000
Percentage of total revenue	62%	48%

We did not have any deferred revenue from our relationship with Ono at June 30, 2025 and December 31, 2024.

6. Basic and Diluted Net Income (Loss) Per Share

Basic net income (loss) per share

We calculated our basic net income (loss) per share for the three and six months ended June 30, 2025 and 2024 by dividing our net income (loss) by our weighted-average number of common shares outstanding during the period.

Diluted net income (loss) per share

For the three months ended June 30, 2025, we recorded net income. As a result, we computed diluted net income per share using the weighted-average number of common shares and dilutive common equivalent shares outstanding during the period. We calculated our diluted net income per share as follows (in thousands, except per share amounts):

Three Months Ended June 30, 2025	Income (Numerator)	Shares (Denominator)	Amount Per Share
Net income	$ 123,551	159,137	$ 0.78
Effect of dilutive securities:			
Shares issuable upon exercise of stock options	-	21	
Shares issuable upon vesting of restricted stock awards	-	1,449	
Shares issuable related to our Employee Stock Purchase Plan	-	86	
Shares issuable related to 1.75 percent convertible senior notes	3,215	10,702	
Shares issuable related to 0 percent convertible senior notes	792	10,936	
Diluted net income	$ 127,558	182,331	$ 0.70

For the six months ended June 30, 2025 and three and six months ended June 30, 2024, 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;
- 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 and six months ended June 30, 2024, common stock underlying the 0.125 percent convertible senior notes, or 0.125% Notes, and note hedges related to the 0.125% Notes would also have had an anti-dilutive effect on net loss per share.

As of June 30, 2025, we had warrants related to our 0% Notes outstanding. As of June 30, 2024, 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 June 30, 2025:

One year or less	66%
After one year but within two years	29%
After two years but within three and a half years	5%
Total	100%

As illustrated above, at June 30, 2025, 95 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 June 30, 2025, 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):

June 30, 2025	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale debt securities:				
Corporate debt securities (1)	$ 607,088	$ 242	$ (373)	$ 606,957
Debt securities issued by U.S. government agencies	122,690	66	(53)	122,703
Debt securities issued by the U.S. Treasury (1)	593,378	168	(449)	593,097
Debt securities issued by states of the U.S. and political subdivisions of the states	6,851	2	(1)	6,852
Total debt securities with a maturity of one year or less	1,330,007	478	(876)	1,329,609
Corporate debt securities	458,306	1,484	(361)	459,429
Debt securities issued by U.S. government agencies	71,028	178	(87)	71,119
Debt securities issued by the U.S. Treasury	184,559	366	(41)	184,884
Debt securities issued by states of the U.S. and political subdivisions of the states	2,216	1	-	2,217
Other municipal debt securities	698	-	(1)	697
Total debt securities with a maturity of more than one year	716,807	2,029	(490)	718,346
Total available-for-sale debt securities	$ 2,046,814	$ 2,507	$ (1,366)	$ 2,047,955
Equity securities:				
Publicly traded equity securities included in other current assets (2)	$ 11,897	$ 38	$ (8,946)	$ 2,989
Privately held equity securities included in deposits and other assets (3)	4,905	25,001	(7,090)	22,816
Total equity securities	16,802	25,039	(16,036)	25,805
Total available-for-sale debt and equity securities	$ 2,063,616	$ 27,546	$ (17,402)	$ 2,073,760

December 31, 2024	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale debt securities:				
Corporate debt securities (1)	$ 593,810	$ 487	$ (240)	$ 594,057
Debt securities issued by U.S. government agencies	143,647	287	(39)	143,895
Debt securities issued by the U.S. Treasury (1)	657,285	825	(120)	657,990
Debt securities issued by states of the U.S. and political subdivisions of the states	7,516	8	-	7,524
Total debt securities with a maturity of one year or less	1,402,258	1,607	(399)	1,403,466
Corporate debt securities	439,561	723	(2,275)	438,009
Debt securities issued by U.S. government agencies	65,255	137	(289)	65,103
Debt securities issued by the U.S. Treasury	149,086	124	(476)	148,734
Other municipal debt securities	698	-	(2)	696
Total debt securities with a maturity of more than one year	654,600	984	(3,042)	652,542
Total available-for-sale debt securities	$ 2,056,858	$ 2,591	$ (3,441)	$ 2,056,008
Equity securities:				
Publicly traded equity securities included in other current assets (2)	$ 11,897	$ 26	$ (6,660)	$ 5,263
Privately held equity securities included in deposits and other assets (3)	23,115	25,001	(7,093)	41,023
Total equity securities	35,012	25,027	(13,753)	46,286
Total available-for-sale debt and equity securities	$ 2,091,870	$ 27,618	$ (17,194)	$ 2,102,294

(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 six months ended June 30, 2025, we recorded a $2.3 million net unrealized loss 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 six months ended June 30, 2025, the amortized cost of our privately held equity securities decreased because we recorded a loss of $18.2 million in our condensed consolidated statements of operations related to an impairment of our investment in a privately held company.

The following is a summary of our investments we consider to be temporarily impaired at June 30, 2025 (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	
		Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses
Corporate debt securities	252	$ 544,205	$ (728)	$ 1,958	$ (6)	$ 546,163	$ (734)
Debt securities issued by U.S. government agencies	44	87,403	(140)	-	-	87,403	(140)
Debt securities issued by the U.S. Treasury	76	488,942	(440)	13,040	(50)	501,982	(490)
Debt securities issued by states of the U.S. and political subdivisions of the states	6	3,677	(1)	-	-	3,677	(1)
Other municipal debt securities	1	697	(1)	-	-	697	(1)
Total temporarily impaired debt securities	379	$ 1,124,924	$ (1,310)	$ 14,998	$ (56)	$ 1,139,922	$ (1,366)

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 June 30, 2025 and December 31, 2024 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 June 30, 2025	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents (1)	$ 176,462	$ 176,462	$ -
Corporate debt securities (2)	1,066,386	-	1,066,386
Debt securities issued by U.S. government agencies (3)	193,822	-	193,822
Debt securities issued by the U.S. Treasury (4)	777,981	777,981	-
Debt securities issued by states of the U.S. and political subdivisions of the states (3)	9,069	-	9,069
Other municipal debt securities (3)	697	-	697
Publicly traded equity securities included in other current assets (5)	2,989	2,989	-
Total	$ 2,227,406	$ 957,432	$ 1,269,974

	At December 31, 2024	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents (1)	$ 180,445	$ 180,445	$ -
Corporate debt securities (3)	1,032,066	-	1,032,066
Debt securities issued by U.S. government agencies (3)	208,998	-	208,998
Debt securities issued by the U.S. Treasury (3)	806,724	806,724	-
Debt securities issued by states of the U.S. and political subdivisions of the states (3)	7,524	-	7,524
Other municipal debt securities (3)	696	-	696
Publicly traded equity securities included in other current assets (5)	5,263	5,263	-
Total	$ 2,241,716	$ 992,432	$ 1,249,284

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

(1) Included in cash and cash equivalents.

(2) $29.9 million was included in cash and cash equivalents, with the difference included in short-term investments.

(3) Included in short-term investments.

(4) $24.4 million was included in cash and cash equivalents, with the difference included in short-term investments.

(5) Included in other current assets.

Convertible Notes

Our 1.75% Notes and 0% Notes had a fair value of $604.2 million and $640.7 million at June 30, 2025, respectively. Our 1.75% Notes and 0% Notes had a fair value of $569.3 million and $612.8 million at December 31, 2024, 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 June 30, 2025 and 2024 (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2025	2024	2025	2024
Cost of sales	$ 610	$ 246	$ 710	$ 450
Research, development and patent expense	19,542	22,766	39,840	44,991
Selling, general and administrative expense	9,538	7,716	18,858	16,627
Stock-based compensation expense, net of amounts capitalized	29,690	30,728	59,408	62,068
Capitalized stock-based compensation expense	509	-	1,000	-
Total stock-based compensation expense	$ 30,199	$ 30,728	$ 60,408	$ 62,068

As of June 30, 2025, total unrecognized estimated stock-based compensation expense related to non-vested stock options, RSUs and PRSUs was $42.3 million, $98.7 million and $15.4 million, respectively. Our actual expenses will likely 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 1.3 years, 1.6 years and 1.7 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, 2024 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 six months ended June 30, 2025 and 2024, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	Six Months Ended June 30,	
	2025	2024
Risk-free interest rate	4.5%	4.1%
Dividend yield	0.0%	0.0%
Volatility	42.0%	43.9%
Expected life	6.3 years	6.3 years

ESPP:

	Six Months Ended June 30,	
	2025	2024
Risk-free interest rate	4.3%	5.3%
Dividend yield	0.0%	0.0%
Volatility	41.3%	38.4%
Expected life	6 months	6 months

RSUs:

The weighted-average grant date fair value of RSUs granted to employees for the six months ended June 30, 2025 and 2024 was $32.97 and $52.60 per share, respectively.

PRSUs:

Under the terms of the PRSUs we granted in 2025 and 2024, the PRSUs may vest at the end of the three-year performance period based on our relative total shareholder return, or 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 six months ended June 30, 2025 and 2024 was $48.81 and $78.41 per share, respectively.

10. Income Taxes

We recorded nominal income tax provisions for the three and six months ended June 30, 2025 and 2024.

In July 2025, the One Big Beautiful Bill Act, or OBBBA, was signed into law, introducing significant changes to U.S. federal tax law. The new law restores current expensing of domestic R&D costs and allows us to accelerate the deduction for a significant amount of such costs capitalized since 2022. The law also permanently allows one hundred percent bonus depreciation for qualified business property, including machinery, equipment and certain improvements to nonresidential real property. The impact of the tax law changes from the OBBBA, which we do not anticipate will have a material effect on our 2025 effective tax rate, will be included in our financial statements beginning in the third quarter of 2025.

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 2023, we entered into a royalty purchase agreement with Royalty Pharma Investments, or 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 June 30, 2025 and 2024, the estimated effective interest rate under the agreement was 12.7 percent and 13.5 percent, respectively.

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

Liability related to sale of future royalties, net as of December 31, 2024	$	542,212
Royalty payments to Royalty Pharma		(24,894)
Interest expense related to sale of future royalties		37,165
Amortization of issuance costs related to sale of future royalties		305
Liability related to sale of future royalties, net as of June 30, 2025	$	554,788
Less: Current portion (1)		(13,583)
Liability related to sale of future royalties, net as of June 30, 2025 – Non-current	$	541,205

(1) Included in other current liabilities in our condensed consolidated balance sheet.

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.

12. Convertible Debt

1.75 Percent Convertible Senior Notes

In 2023, we completed a $575.0 million offering of our 1.75% Notes. We used $532.7 million of the net proceeds from the issuance of our 1.75% Notes to repurchase and settle our 0.125% Notes, which matured in December 2024.

At June 30, 2025, we had the following 1.75% Notes outstanding (in millions except interest rate and price per share data):

		1.75% Notes
Outstanding principal balance	$	575.0
Unamortized debt issuance costs	$	8.6
Maturity date		June 2028
Interest rate		1.75%
Effective interest rate	$	2.3%
Conversion price per share		53.73
Total shares of common stock subject to conversion		10.7

0 Percent Convertible Senior Notes and Call Spread

In 2021, we completed a $632.5 million offering of our 0% Notes. We used $319.0 million of the net proceeds from the issuance of our 0% Notes to pay the remaining $309.9 million principal balance of our 1 percent convertible senior notes, or 1% Notes, in 2021.

At June 30, 2025, we had the following 0% Notes outstanding (in millions except interest rate and price per share data):

		0% Notes
Outstanding principal balance	$	632.5
Unamortized debt issuance costs	$	2.4
Maturity date		April 2026
Interest rate		0%
Effective interest rate		0.5%
Conversion price per share	$	57.84
Effective conversion price per share with call spread	$	76.39
Total shares of common stock subject to conversion		10.9

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 warrants will expire in July 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, 2024 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.

Other Terms of Convertible Senior Notes

The 1.75% and 0% 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.

14. Segment Information

We operate as a single operating segment, Ionis operations, focused on the research, development and commercialization of our RNA-targeted medicines to bring better futures to people with serious diseases. As the CODM, our Chief Executive Officer manages our company, reviews operating results, assesses performance and allocates resources on an aggregate basis using consolidated net income or loss as the key measure of segment profit or loss. As such, results of our operations are reported on a consolidated basis for purposes of management and segment reporting.

Ionis operations derives its revenues from commercial and R&D revenue sources. Refer to Note 4, *Revenues*, for further details on our sources of revenue.

The following table sets forth information on segment profit or loss, including significant segment expenses (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2025	2024	2025	2024
Revenue	$ 452,049	$ 225,250	$ 583,660	$ 344,748
Less:				
Cost of sales	3,541	3,951	4,904	5,903
Drug discovery	30,255	26,691	57,244	54,862
Drug development	117,689	134,199	230,635	259,951
Medical affairs	7,826	7,092	13,468	11,768
Manufacturing and development chemistry	21,545	14,195	35,826	25,636
R&D support	20,607	17,067	41,159	39,013
Selling, general and administrative	81,081	57,418	148,061	101,151
Other segment items (1)	45,954	30,902	75,750	55,532
Consolidated net income (loss)	$ 123,551	$ (66,265)	$ (23,387)	$ (209,068)

(1) Other segment items include stock-based compensation expense, investment income, interest expense, gain or loss on investments, other income or expense and income tax expense or benefit.

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," the "Company," "we," "our," and "us," means Ionis Pharmaceuticals, Inc. and its subsidiaries.

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, 2024, 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, we have invented medicines that bring better futures to people with serious diseases. As a pioneer in RNA-targeted medicines with a deep understanding of disease biology and an industry-leading drug discovery technology, we are driven to deliver innovative, life-changing advances for patients.

With our commercial launch of TRYNGOLZA (olezarsen) in the United States, or U.S., following its approval by the U.S. Food and Drug Administration, or FDA, we began a new chapter as a fully integrated commercial-stage biotechnology company. We currently have six marketed medicines to treat serious diseases: TRYNGOLZA, WAINUA (eplontersen), SPINRAZA (nusinersen), QALSODY (tofersen), TEGSEDI (inotersen) and WAYLIVRA (volanesorsen). In addition, we are positioned to independently launch multiple medicines by the end of 2026, including donidalorsen for the treatment of hereditary angioedema, or HAE. Donidalorsen is currently under regulatory review in the U.S., positioning us for our second independent commercial launch in the second half of this year. We are also on track for Phase 3 readouts later this year, which include olezarsen for severe hypertriglyceridemia, or sHTG, and zilganersen for Alexander disease, or AxD. We also have a rich innovative pipeline across our focus areas of neurology, cardiology and select areas of high patient need. We currently have four wholly owned medicines and six partnered medicines in Phase 3 development, including ION528 for Angelman syndrome, or AS, which we advanced into a Phase 3 study in the second quarter of 2025. We also have additional medicines in early and mid-stage development.

Our multiple sources of revenue and strong financial foundation enable our continued investments to support ongoing and upcoming planned launches and to advance our wholly owned medicines in development. Our key recent achievements, combined with our independent and partnered product launches anticipated by the end of 2027, position us well to help patients with serious diseases and to deliver increasing product and royalty revenue.

Our Marketed Medicines

TRYNGOLZA is a once monthly, self-administered LIgand-Conjugated Antisense, or LICA, medicine approved in the U.S. as an adjunct to diet to reduce triglycerides in adults with familial chylomicronemia syndrome, or FCS. TRYNGOLZA is the first and only FDA-approved treatment that significantly and substantially reduces triglyceride levels in adults with FCS and provides a clinically meaningful reduction in acute pancreatitis, or AP, events. TRYNGOLZA is the first medicine we are commercializing independently in the U.S. In July 2025, TRYNGOLZA received a positive opinion from the Committee for Medicinal Products for Human Use, or CHMP, in Europe. Sobi has exclusive rights to commercialize TRYNGOLZA in countries outside of the U.S., Canada and China.

WAINUA (WAINZUA in Europe) is a once monthly, self-administered subcutaneous LICA medicine that is approved in the U.S., European Union, or EU, and numerous other countries for the treatment of adults with polyneuropathy of hereditary transthyretin-mediated amyloidosis, or ATTRv-PN, a debilitating, progressive, and fatal disease. In January 2024, we and AstraZeneca launched WAINUA in the U.S. for the treatment of adults with ATTRv-PN. The launch of WAINUA is underway in numerous countries, including the EU, following the approval by the European Commission, or EC, in March 2025. We and AstraZeneca are co-commercializing WAINUA in the U.S. AstraZeneca has exclusive rights to commercialize WAINUA outside of the U.S. From inception through June 30, 2025, we have earned more than $565 million in revenues from our WAINUA collaboration, including approximately $40 million in royalties on sales of WAINUA.

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 June 30, 2025, we have earned more than $2.4 billion in revenues from our SPINRAZA collaboration, including more than $1.9 billion in royalties on sales of SPINRAZA.

QALSODY is an antisense medicine that received accelerated approval from the 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. QALSODY was the first treatment approved to target a genetic cause of ALS. Our partner, Biogen, is responsible for commercializing QALSODY worldwide. Biogen is also evaluating QALSODY as a potential treatment for presymptomatic SOD1-ALS patients in the ongoing ATLAS study. QALSODY was granted Orphan Drug designation by the FDA and EMA.

TEGSEDI is a once weekly, self-administered subcutaneous medicine approved in Europe and Brazil for the treatment of patients with ATTRv-PN. We currently sell TEGSEDI in Europe through our distribution agreement with Swedish Orphan Biovitrum AB, or Sobi. 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 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.

Our Innovative Late-Stage Pipeline of Ionis-Owned Investigational Medicines

Olezarsen is our medicine in development for sHTG, a second potential indication which has a large patient population. 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), which achieved full enrollment in 2024. In March 2025, we published the Phase 3 study design and baseline characteristics for the CORE, CORE2 and ESSENCE studies in the *American Heart Journal*. In May 2025, we announced positive topline results from the ESSENCE study in people with moderate hypertriglyceridemia with or at risk for atherosclerotic cardiovascular disease. We licensed commercialization rights for olezarsen in most countries outside of the U.S., Canada and China to Sobi, and commercialization rights for olezarsen in Canada to Theratechnologies.

Donidalorsen is our medicine in development for the prophylactic treatment of HAE. Donidalorsen is currently under regulatory review in the U.S. with a Prescription Drug User Fee Act, or PDUFA, action date of August 21, 2025. Donidalorsen is also under regulatory review in the EU. Our regulatory submissions are based on the positive results from our comprehensive Phase 2 and Phase 3 development programs for donidalorsen. This included the positive results from the Phase 3 OASIS-HAE study in patients treated every four weeks and every eight weeks that were published in *The New England Journal of Medicine*, or *NEJM*, and positive results from OASISplus, our trial that includes an open-label, or OLE, cohort for patients rolling over from the Phase 3 study and a separate cohort for patients who have transitioned to donidalorsen from other prophylactic HAE medications that we refer to as the "switch study." We licensed commercialization rights for donidalorsen in Europe and the Asia-Pacific region to Otsuka Pharmaceutical Co., Ltd., or Otsuka. In addition, we licensed commercialization rights for donidalorsen in Canada to Theratechnologies. The FDA and EMA granted Orphan Drug designation to donidalorsen.

Zilganersen is our medicine in development for AxD. We completed enrollment in the Phase 3 portion of the ongoing study for patients with AxD in July 2024. Zilganersen was granted Fast Track designation for the treatment of AxD and Rare Pediatric designation by the FDA. Additionally, zilganersen was granted Orphan Drug designation by the FDA and EMA.

ION582 is our medicine in development for AS. In June 2025, we initiated the Phase 3 study, REVEAL, which we designed to evaluate the efficacy and safety of ION582. In addition, we are continuing to conduct the open label Phase 1/2 study, HALOS, of ION582 in patients with AS designed to assess the safety, tolerability and activity of multiple ascending doses of ION582 administered intrathecally. In 2024, we presented positive results from the completed multiple ascending dose, or MAD, portion of the study in people with AS. The FDA and EMA granted Orphan Drug designation to ION582. Additionally, the FDA granted Fast Track and Rare Pediatric designations to ION582.

Our Innovative Late-Stage Pipeline of Partnered Investigational Medicines

Eplontersen is our medicine in development to treat patients with transthyretin amyloidosis cardiomyopathy, or ATTR-CM. We completed enrollment in the Phase 3 CARDIO-TTRansform study in July 2023. The FDA granted Fast Track designation to eplontersen for the treatment of patients with ATTR-CM. Additionally, the FDA and EMA granted Orphan Drug designation to eplontersen for the treatment of ATTR.

Pelacarsen is our medicine in development to treat patients with elevated lipoprotein(a)-driven cardiovascular disease, or Lp(a)-driven CVD. Novartis is developing pelacarsen, including conducting the ongoing Phase 3 Lp(a) HORIZON cardiovascular outcome study in patients with elevated Lp(a)-driven CVD, which achieved full enrollment in July 2022 with more than 8,000 patients. The study design and baseline characteristics of the Phase 3 Lp(a) HORIZON study were published in the *American Heart Journal* in April 2025. The FDA granted Fast Track designation and the Center for Drug Evaluation of China National Medical Products Administration granted Breakthrough Therapy designation to pelacarsen for the treatment of patients with elevated Lp(a) and established CVD.

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, which achieved full enrollment in June 2024. The FDA granted Fast Track designation and the Japanese Ministry of Health, Labour and Welfare granted SENKU designation to bepirovirsen for the treatment of patients with HBV.

Sefaxersen is our medicine in development for immunoglobulin A, or IgA, nephropathy, or IgAN. In the second quarter of 2023, Roche advanced sefaxersen into Phase 3 development in patients with IgAN based on interim Phase 2 data.

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. We licensed global commercialization rights for ulefnersen to Otsuka. The FDA and EMA granted Orphan Drug designation to ulefnersen.

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 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, 2024.

Results of Operations

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2025	2024	2025	2024
Total revenue	$ 452.0	$ 225.3	$ 583.7	$ 344.7
Total operating expenses	$ 312.2	$ 291.3	$ 590.7	$ 560.4
Income (loss) from operations	$ 139.8	$ (66.1)	$ (7.0)	$ (215.6)
Net income (loss)	$ 123.6	$ (66.3)	$ (23.4)	$ (209.1)

Revenue

Total revenue for the three and six months ended June 30, 2025 were $452.0 million and $583.7 million, respectively, compared to $225.3 million and $344.7 million for the same periods in 2024 and was comprised of the following (in millions):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2025	2024	2025	2024
Revenue:				
Commercial revenue:				
Product sales, net:				
TRYNGOLZA sales, net	$ 19.3	$ -	$ 25.6	$ -
Total product sales, net	19.3	-	25.6	-
Royalty revenue:				
SPINRAZA royalties	54.3	56.7	102.3	95.2
WAINUA royalties	10.4	3.8	19.8	4.9
Other royalties	5.3	3.3	12.0	13.1
Total royalty revenue	70.0	63.8	134.1	113.2
Other commercial revenue:				
TEGSEDI and WAYLIVRA revenue, net	13.5	8.2	19.2	16.8
Other revenue	-	-	-	1.6
Total other commercial revenue	13.5	8.2	19.2	18.4
Total commercial revenue	102.8	72.0	178.9	131.6
Research and development revenue:				
Collaborative agreement revenue	336.8	141.6	382.0	190.9
WAINUA joint development revenue	12.4	11.7	22.8	22.2
Total research and development revenue	349.2	153.3	404.8	213.1
Total revenue	$ 452.0	$ 225.3	$ 583.7	$ 344.7

Commercial revenue for the three and six months ended June 30, 2025 increased 43% and 36%, respectively, compared to the same periods in 2024. This increase was driven by U.S. product sales from the launch of TRYNGOLZA. Higher royalties also contributed to the year over year increase.

The remainder of our revenue came from programs under our research and development, or R&D, collaborations, including revenue from the $280 million upfront payment for the license of sapablursen to Ono Pharmaceutical Co., Ltd., reflecting the value that our pipeline and technology continues to generate.

WAINUA (Eplontersen) Collaboration with AstraZeneca

Our financial results for the three and six months ended June 30, 2025 and 2024 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 as WAINUA advances toward the market for ATTR-CM under our collaboration with AstraZeneca.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2025	2024	2025	2024
WAINUA joint development revenue	$ 12.4	$ 11.7	$ 22.8	$ 22.2
Research and development expenses related to Phase 3 development of WAINUA	24.7	25.4	46.3	48.1
Medical affairs expenses for WAINUA	2.3	1.9	3.9	3.1
Commercialization expenses for WAINUA	6.8	6.6	14.5	12.6

Operating Expenses

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2025	2024	2025	2024
Operating expenses, excluding non-cash compensation expense related to equity awards	$ 282.5	$ 260.6	$ 531.3	$ 498.3
Non-cash compensation expense related to equity awards	29.7	30.7	59.4	62.1
Total operating expenses	$ 312.2	$ 291.3	$ 590.7	$ 560.4

Operating expenses, excluding non-cash compensation expense related to equity awards, for the three and six months ended June 30, 2025 increased compared to the same periods in 2024. SG&A expenses increased as anticipated year over year primarily due to the launches of WAINUA and TRYNGOLZA, and advancing launch preparation activities for donidalorsen. This increase was partially offset by a decrease in R&D expenses year over year as several late-stage studies ended. We expect our operating expenses, excluding non-cash compensation expense related to equity awards, to continue to increase during the remainder of 2025 as we advance our commercialization activities.

We believe non-cash compensation expense related to equity awards is not indicative of our operating results or cash flows from our operations.

Cost of Sales

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

Cost of sales for a newly launched product, such as TRYNGOLZA, does not include the full cost of manufacturing until we manufacture and sell additional inventory after exhausting pre-launch inventory, which we previously recorded as R&D expense.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2025	2024	2025	2024
Cost of sales, excluding non-cash compensation expense related to equity awards	$ 3.6	$ 4.0	$ 4.9	$ 5.9
Non-cash compensation expense related to equity awards	0.6	0.2	0.7	0.4
Total cost of sales	$ 4.2	$ 4.2	$ 5.6	$ 6.3

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 June 30,		Six Months Ended June 30,	
	2025	2024	2025	2024
Research, development and patent expenses, excluding non-cash compensation expense related to equity awards	$ 198.0	$ 199.3	$ 378.4	$ 391.3
Non-cash compensation expense related to equity awards	19.5	22.8	39.8	45.0
Total research, development and patent expenses	$ 217.5	$ 222.1	$ 418.2	$ 436.3

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 June 30,		Six Months Ended June 30,	
	2025	2024	2025	2024
Drug discovery expenses, excluding non-cash compensation expense related to equity awards	$ 30.3	$ 26.7	$ 57.3	$ 54.9
Non-cash compensation expense related to equity awards	3.6	4.6	7.7	8.9
Total drug discovery expenses	$ 33.9	$ 31.3	$ 65.0	$ 63.8

Drug discovery expenses, excluding non-cash compensation expense related to equity awards, increased in the three months and six months ended June 30, 2025 compared to the same periods in 2024 as we continued to advance our technologies discussed above.

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 June 30,		Six Months Ended June 30,	
	2025	2024	2025	2024
Eplontersen	$ 24.3	$ 24.3	$ 45.4	$ 46.0
Olezarsen	18.2	40.0	43.1	79.5
Donidalorsen	3.0	5.1	8.1	9.9
Zilganersen	2.3	1.6	7.5	3.7
Ulefnersen	2.2	3.4	5.2	6.9
ION582	11.7	2.4	17.5	6.8
Other development projects	19.3	23.5	35.7	44.2
Development overhead expenses	36.8	33.9	68.2	63.0
Total drug development expenses, excluding non-cash compensation expense related to equity awards	117.8	134.2	230.7	260.0
Non-cash compensation expense related to equity awards	8.7	10.3	16.9	20.7
Total drug development expenses	$ 126.5	144.5	$ 247.6	$ 280.7

Our development expenses, excluding non-cash compensation expense related to equity awards, decreased for the three and six months ended June 30, 2025 compared to the same periods in 2024 as several late-stage studies ended. We expect our development expenses will continue to stabilize as several late-stage studies end and we reallocate resources toward earlier stage programs.

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 June 30,		Six Months Ended June 30,	
	2025	2024	2025	2024
Medical affairs expenses, excluding non-cash compensation expense related to equity awards	$ 7.8	$ 7.1	$ 13.4	$ 11.8
Non-cash compensation expense related to equity awards	1.3	1.2	2.8	2.1
Total medical affairs expenses	$ 9.1	$ 8.3	$ 16.2	$ 13.9

Medical affairs expenses, excluding non-cash compensation expense related to equity awards, increased in the three and six months ended June 30, 2025 compared to the same periods in 2024 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 June 30,		Six Months Ended June 30,	
	2025	2024	2025	2024
Manufacturing and development chemistry expenses, excluding non-cash compensation expense related to equity awards	$ 21.5	$ 14.2	$ 35.8	$ 25.6
Non-cash compensation expense related to equity awards	1.6	2.3	3.7	4.6
Total manufacturing and development chemistry expenses	$ 23.1	$ 16.5	$ 39.5	$ 30.2

Manufacturing and development chemistry expenses, excluding non-cash compensation expense related to equity awards, increased in the three and six months ended June 30, 2025 compared to the same periods in 2024 due to the timing of manufacturing performed by our contract manufacturing organizations for drug product related to several late-stage programs.

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.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2025	2024	2025	2024
Personnel costs	$ 7.4	$ 7.2	$ 14.2	$ 15.0
Occupancy	6.5	6.7	13.8	13.8
Computer software and licenses	3.2	1.7	6.4	3.3
Insurance	0.7	0.8	1.7	1.7
Patent expenses	0.9	0.7	1.5	1.4
Other	1.9	-	3.6	3.8
Total R&D support expenses, excluding non-cash compensation expense related to equity awards	20.6	17.1	41.2	39.0
Non-cash compensation expense related to equity awards	4.3	4.3	8.7	8.6
Total R&D support expenses	$ 24.9	$ 21.4	$ 49.9	$ 47.6

R&D support expenses, excluding non-cash compensation expense related to equity awards, increased in the three and six months ended June 30, 2025 compared to the same periods in 2024 primarily due to increased costs relating to computer software and licenses.

Selling, General and Administrative Expenses

SG&A expenses include personnel, information technology systems and outside costs associated with the commercialization and pre-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 QALSODY and cost sharing payments associated with co-commercialization activities under our WAINUA collaboration with AstraZeneca.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2025	2024	2025	2024
Selling, general and administrative expenses, excluding non-cash compensation expense related to equity awards	$ 81.0	$ 57.4	$ 148.0	$ 101.2
Non-cash compensation expense related to equity awards	9.6	7.7	18.9	16.6
Total selling, general and administrative expenses	$ 90.6	$ 65.1	$ 166.9	$ 117.8

SG&A expenses, excluding non-cash compensation expense related to equity awards, increased in the three and six months ended June 30, 2025 compared to the same periods in 2024 primarily due to the launches of WAINUA and TRYNGOLZA, and advancing launch preparation activities for donidalorsen. We expect SG&A expenses to increase as we continue to invest in our independent commercial launches.

Investment Income

The following table sets forth information on investment income (in millions):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2025	2024	2025	2024
Investment income	$ 24.7	$ 25.6	$ 49.4	$ 51.9

Interest Expense

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2025	2024	2025	2024
Convertible notes:				
Non-cash amortization of debt issuance costs	$ 1.5	$ 1.5	$ 3.0	$ 3.0
Interest expense payable in cash	2.5	2.9	5.1	5.4
Interest on mortgage for manufacturing facility	0.1	0.1	0.1	0.2
Total interest expense	$ 4.1	$ 4.5	$ 8.2	$ 8.6

Interest Expense Related to Sale of Future Royalties

We recorded $18.6 million and $37.5 million of interest expense related to the sale of future royalties in the three and six months ended June 30, 2025, respectively, compared to $18.3 million and $36.3 million in the same periods in 2024, respectively. These amounts are related to the Royalty Pharma Investments, or Royalty Pharma, transaction, in which we sold a minority interest in our future SPINRAZA and pelacarsen 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.

Loss on Investments

The following table sets forth information on loss on investments (in millions):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2025	2024	2025	2024
Loss on investments	$ (18.3)	$ (3.5)	$ (20.5)	$ (1.2)

Loss on investments increased in the three and six months ended June 30, 2025 compared to the same periods in 2024 primarily due to a $18.2 million impairment of our investment in a privately held company that we recorded in the second quarter of 2025.

Income Tax Benefit (Expense)

We recorded nominal income tax provisions for the three and six months ended June 30, 2025 and 2024.

In July 2025, the One Big Beautiful Bill Act, or OBBBA, was signed into law, introducing significant changes to U.S. federal tax law. The new law restores current expensing of domestic R&D costs and allows us to accelerate the deduction for a significant amount of such costs capitalized since 2022. The law also permanently allows one hundred percent bonus depreciation for qualified business property, including machinery, equipment and certain improvements to nonresidential real property. The impact of the tax law changes from the OBBBA, which we do not anticipate will have a material effect on our 2025 effective tax rate, will be included in our financial statements beginning in the third quarter of 2025.

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

Net Income (Loss) and Net Income (Loss) per Share

The following table sets forth information on net income (loss) and net income (loss) per share (in millions, except per share amounts):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2025	2024	2025	2024
Net income (loss)	$ 123.6	$ (66.3)	$ (23.4)	$ (209.1)
Basic net income (loss) per share	$ 0.78	$ (0.45)	$ (0.15)	$ (1.43)
Diluted net income (loss) per share	$ 0.70	$ (0.45)	$ (0.15)	$ (1.43)

The period-over-period fluctuations in our net income (loss) were driven by factors discussed in the sections above.

Liquidity and Capital Resources

We have financed our operations primarily from research and development collaborative agreements. We also financed our operations from commercial revenue from SPINRAZA, WAINUA and QALSODY royalties and TEGSEDI and WAYLIVRA commercial revenue. In addition, we began earning commercial revenue from TRYNGOLZA product sales in late December 2024. From our inception through June 30, 2025, we have earned approximately $8.5 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 June 30, 2025, we have raised net proceeds of approximately $2.6 billion from the sale of our equity securities. Additionally, from our inception through June 30, 2025, 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.

From December 31, 2024 to June 30, 2025, our working capital and long-term obligations decreased as we reclassified our 0% Notes from non-current liabilities to current liabilities in the second quarter of 2025 because the notes are due in April 2026.

The following table summarizes our contractual obligations, excluding our liability related to the sale of future royalties, as of June 30, 2025. The table provides a breakdown of when obligations become due.

	Payments Due by Period (in millions)		
(selected balances described below)	Total	Less than 1 year	More than 1 year
1.75% Notes (principal and interest payable)	$ 605.2	$ 10.1	$ 595.1
0% Notes (principal payable)	632.5	632.5	-
Operating leases	261.9	21.0	240.9
Building mortgage payments (principal and interest payable)	9.4	0.5	8.9
Other obligations (principal and interest payable)	0.7	0.1	0.6
Total	$ 1,509.7	$ 664.2	$ 845.5

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 of our audited financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2024 for further details on our operating facilities.

Operating Leases

Refer to Part IV, Item 15, Note 7 of our audited financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2024 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.

Other Obligations

In addition to contractual obligations, we had outstanding purchase orders as of June 30, 2025 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.

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 June 30, 2025. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to June 30, 2025.

We also performed an evaluation of any changes in our internal controls over financial reporting that occurred during our last fiscal quarter and that have materially affected, or are reasonably likely to materially affect, our internal controls over financial reporting. We conducted this evaluation under the supervision of and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer. That evaluation did not identify any changes in our internal controls over financial reporting that occurred during our latest fiscal quarter and that have materially affected, or are reasonably likely to materially affect, our internal controls over financial reporting.

PART II — OTHER INFORMATION

ITEM 1. LEGAL PROCEEDINGS

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. 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, 2024.

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 events;
- Our dependence upon our own and third-party information technology systems; 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 continue to invest significant resources to develop our capabilities. If we are unable to effectively establish or maintain an effective commercialization infrastructure, or enter into agreements with third parties to commercialize our medicines, we may not be able to successfully commercialize our medicines.

We have historically relied on third parties to commercialize our marketed medicines and have limited experience as a company in commercializing medicines. TRYNGOLZA is our first independently launched medicine and we expect to independently launch additional medicines in the future. Any failure to effectively commercialize our medicines, including our failure to allocate resources to our commercial launches efficiently or timely, could adversely impact the revenue we generate from our medicines. If the commercialization of TRYNGOLZA and future sales are less successful than anticipated by us or our investors or securities analysts, our stock price could decline and our business may be harmed.

We will have to continue to invest significant financial and management resources to build and maintain the infrastructure required to successfully commercialize our medicines. We will need to establish and maintain effective sales teams for each of our independently launched medicines and there are significant risks involved in 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 must also continue to scale-up existing internal support functions to aid our commercialization efforts. Further, these existing support functions will need to work effectively in coordination with new commercial functional areas. Any failure to establish or maintain an effective commercialization infrastructure, including our sales, marketing, market access, distribution, and related capabilities, scale-up our existing support functions, or effectively integrate new functional areas, could adversely affect our ability to successfully commercialize our medicines.

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. In addition, 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.

The proximity of our planned upcoming independent launches could increase the likelihood that the risks set forth above will occur.

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 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 several 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, public perception regarding 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.

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, the product label for WAYLIVRA in the EU requires regular blood monitoring, which has negatively affected our ability to attract and retain patients for this medicine.

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.

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. For example, on May 12, 2025, President Trump issued an executive order implementing the concept of most-favored nation pricing. Under this order, HHS, in coordination with other federal agencies, is directed to take actions to ensure that the price of prescription drugs paid by federal health insurers, including Medicare and Medicaid, is in line with the prices paid in comparably developed nations.

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. The IRA, among other things, (1) directs HHS to negotiate the price of certain single-source drugs and biologics that have been on the market for at least seven years covered under Medicare, or the Medicare Drug Price Negotiation Program, and (2) imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation. These provisions began to take effect progressively starting in fiscal year 2023, although the Medicare Drug Price Negotiation Program is currently subject to legal challenges. Under this program, HHS has already announced the agreed-upon prices of the first drugs that were subject to price negotiations and will announce the agreed-upon prices of additional drugs in the coming years. In response to an October 2022 executive order, on February 14, 2023, HHS released a report outlining three new models for testing by the CMS Innovation Center that will be evaluated on their ability to lower the cost of drugs, promote accessibility, and improve quality of care. It is unclear whether or how these selected models or similar policy initiatives will impact prescription drug pricing in the future, particularly in light of the recent U.S. presidential and congressional elections.

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.

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 that our own 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 or of medicines we are commercializing. For example:

- Onasemnogene abeparvovec and risdiplam compete with SPINRAZA;
- Acoramidis, patisiran, tafamidis, tafamidis meglumine and vutrisiran compete with WAINUA;
- Nexiguran ziclumeran, ALXN2220 and NNC6019-0001 could compete with WAINUA;
- Plozasiran, pegozafermin and NST-1024 could compete with TRYNGOLZA and WAYLIVRA;
- Lanadelumab-flyo, C1 esterase inhibitor, berotralstat, C1 esterase inhibitor subcutaneous, garadacimab, deucrictibant, NTLA-2002 and STAR-0215 could compete with donidalorsen;
- Olpasiran, zerlasiran, lepodisiran and muvalaplin could compete with pelacarsen;
- NI-005/AP-101 could compete with QALSODY;
- VIR-2218, VIR-3434, BRII-179, AB-729, selgantolimod, bersacapavir, REP 2139-Mg and VTP-300 could complete with bepirovirsen;
- Budesonide, sparsentan, atrasentan, iptacopan, zigakibart, sibeprenlimab, atacicept, ravulizumab, vemircopan, felzartamab, telitacicept and povetacicept could compete with sefaxersen; and
- GTX-102, alogabat and NNZ-2591 could compete with ION582.

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.

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. The FDA and foreign regulatory bodies have the authority to impose significant restrictions on an approved medicine through the product label. 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.

Promotional communications regarding prescription medicines must be consistent with the information in the product's approved labeling. Additionally, 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 the 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.

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.

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 are co-developing and co-commercializing WAINUA in the U.S. and AstraZeneca has 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 (1) the amount and timing of resources that AstraZeneca devotes to our collaboration, particularly outside of the U.S; (2) the pricing and reimbursement strategies for WAINUA; and (3) whether AstraZeneca elects to terminate the collaborative arrangement. 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. We will also need to ensure that we have the manufacturing capabilities in place to support advances in our drug development activities, such as new chemistries. 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. If a supplier chooses to devote more resources to other products, especially products with higher manufacturing capacity needs, that could impact such supplier's capability to deliver our requirements timely. 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.

We rely on third-party manufacturers to supply the drug substance and drug product for TRYNGOLZA and WAINUA and drug product for WAYLIVRA. The operations of our suppliers, many of which are located outside of the United States, are subject to additional risks that are beyond our control. For example, tariffs on the raw materials, components, or equipment we use to manufacture our products, or on our drug substance or finished products, will increase our manufacturing costs. There have also been Congressional legislative proposals to discourage contracting with Chinese companies for the development or manufacturing of pharmaceutical products. In addition, merger and acquisition activity within the commercial manufacturing space could reduce the availability of resources from our third-party manufacturers. Delays or disruption to our own or third-party commercial manufacturing capabilities for any reason could limit the commercial success of our medicines.

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.

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. Similarly, topline, preliminary or interim data we release for any of our clinical studies may not be indicative of full or final results from such study.

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. In addition, we may release topline, preliminary or interim data for any of our clinical studies. The interim, topline or preliminary results we report may differ from future results of the same studies, or different conclusions or considerations may qualify such results, once additional data have been received and fully evaluated. As a result, such data should be viewed with caution until the final data are available.

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.

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 European Commission 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, zilganersen and ION582. 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.

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 Israel that may be materially impacted by the ongoing military conflicts in Israel and elsewhere in the Middle East and could result in difficulties enrolling or completing our clinical trials in such areas on schedule.

Since corporate partnering is part of our strategy to fund the advancement and commercialization of some 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 those 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. While we are now commercializing some of our medicines independently, we still 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 bepirovirsen; and
- Roche for development and funding of sefaxersen.

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 QALSODY, SPINRAZA, WAINUA, bepirovirsen, donidalorsen, sefaxersen and pelacarsen.

We may not be able to benefit from designations for our medicines from regulatory authorities that are intended to confer benefits such as financial incentives or an accelerated regulatory pathway.

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 TRYNGOLZA for the treatment of patients with FCS, to WAINUA for the treatment of patients with ATTR, to ulefnersen for the treatment of patients with FUS-ALS, to ION582 for the treatment of patients with Angelman syndrome, and to some of our earlier stage medicines. The FDA and EMA have granted Orphan Drug designation to donidalorsen for the treatment of patients with HAE, to WAYLIVRA for the treatment of patients with FCS, to tominersen for the treatment of patients with HD, and to some of our earlier stage medicines. 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.

We may also seek rare pediatric disease designation for some of our medicines. The FDA defines “rare pediatric disease” as a serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years or is a rare disease or condition within the meaning of the Orphan Drug Act. Designation of a medicine as a medicine for a rare pediatric disease does not guarantee that a marketing application for such medicine will meet the eligibility criteria for a rare pediatric disease priority review voucher, or PRV, at the time the application is approved. Under the FDCA, we will need to request a rare pediatric disease PRV in our original marketing application for any potential medicine for which we have received rare pediatric disease designation. The FDA may determine that a marketing application for any such medicine, if approved, does not meet the eligibility criteria for a PRV. Under the current statutory sunset provisions, after December 20, 2024, the FDA may only award a PRV for an approved rare pediatric disease application if the sponsor has rare pediatric disease designation for the drug or biologic that is the subject of such application, and that designation was granted by December 20, 2024. After September 30, 2026, the FDA may not award any rare pediatric disease PRVs. However, it is possible the authority for FDA to award rare pediatric disease PRV will be further extended by Congress.

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 building and maintaining new support functions and scaling up existing internal support functions and expanding our manufacturing capabilities. All of these activities will require significant cash. As of June 30, 2025, we had cash, cash equivalents and short-term investments equal to $2.3 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. For example, in September 2024, we completed an underwritten public offering of 11,500,000 shares of our common stock for total net proceeds, after deducting underwriting discounts and commissions and other offering expenses payable by us, of approximately $489.1 million. 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.

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 June 30, 2025, we had an accumulated deficit of approximately $2.3 billion and stockholders' equity of approximately $0.6 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 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.

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.

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 in the future or at all.

Our business exposes us to potential product liability risks that are inherent in the testing, manufacturing, marketing and sale of therapeutic products, including potential product liability claims related to 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, scientific and commercial staff. We do not have employment agreements with any of our employees that would prevent them from leaving us. The loss of our key management, 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, fires, earthquakes, war, civil or political unrest, terrorism or disruptions of the U.S. government.*

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 fires, hurricanes, tornadoes, droughts, floods, or other events that may result from the impact of climate change on the environment, any of which could impact our business and manufacturing operations. 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, and various regions within California have recently experienced numerous catastrophic wildfires. We manufacture the finished drug product for TRYNGOLZA, WAYLIVRA and eplontersen for ongoing clinical trials at third-party contract manufacturers. Biogen manufactures the finished drug product for SPINRAZA and QALSODY and AstraZeneca is responsible for WAINUA's commercial drug supply. 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.

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 staffing shortages or a shutdown or other significant disruption of the U.S. government, including the FDA or the U.S. PTO.

Risks related to personal information, cybersecurity, social media and artificial intelligence

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

We are dependent upon our own and third-party data as well as information technology systems and infrastructure, including mobile technologies, to operate our business. The personal information we process subjects us to stringent and evolving U.S. and foreign laws, rules and regulations, contractual obligations, industry standards and other obligations related to data privacy and security. Our personal information obligations require us to implement and maintain certain practices, including those in relation to cross-border transfers of personal information. The multitude and complexity of our information technology systems and infrastructure make them vulnerable to a variety of evolving threats that may result in systems or data interruption, corruption, destruction, disruption of data integrity, malicious intrusion, or random attacks or other compromise (such as due to malfunctions, software vulnerabilities, natural disasters, telecommunications failures, malicious actors and personnel error). Data privacy or security incidents or breaches 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. Cyber-attacks are increasing in their frequency, sophistication and intensity, particularly as companies (including us) continue to move to more remote work structures. 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 the Middle East and the surrounding areas, or collectively, conflicts in Eastern Europe and the Middle East, as well as related political or economic responses and counter-responses by various global actors.

Cybersecurity related events could include the deployment or use of harmful malware or malicious code, denial-of-service attacks, credential stuffing attacks, credential harvesting attacks, social engineering attacks (including deep fakes), ransomware and other means to affect the confidentiality, integrity or availability of our data as well as information systems and infrastructure. Our current, past and prospective business partners face similar risks and any security breaches of their systems could adversely affect our security posture. A security breach or privacy violation (including perceived breaches or violations) could result in any of the following, any of which could disrupt our business and result in increased costs or loss of revenue:

- harm our reputation;
- delay progress on the development of our medicines;
- compel us to comply with applicable security or data breach notification obligations (including laws);
- result in the diversion of monetary funds and other company resources;
- subject us to financial or other penalties, regulatory investigations or actions, including mandatory and costly corrective actions; and
- require us to verify the correctness of database contents and otherwise subject us to litigation or other liabilities.

Risk mitigation strategies such as liability limitations in our contracts and insurance coverage may prove inadequate if there is a security breach or privacy violation. While we have invested, and continue to invest, in the protection of our data and information technology systems and infrastructure, our efforts may not be successful. Non-compliance with relevant data protection obligations or a failure to secure our data, information technology systems or infrastructure 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, 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.

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 disclosing clinical data, when we anticipate completing a clinical study, 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. In addition, our share price may be dependent upon the valuations and recommendations of the analysts who cover our business. If our results do not meet these analysts' forecasts, the expectations of our investors or the financial guidance we provide to investors in any period, the market price of our common stock could decline. Our ability to meet analysts' forecasts, investors' expectations and our financial guidance is substantially dependent on our ability to maintain or increase sales of our commercial medicines, both partnered and unpartnered.

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 June 30, 2025, the closing market price of our common stock ranged from $51.86 to $25.51 per share. Many factors can affect the market price of our securities, including, for example, fluctuations in our operating results, financing transactions, 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, events such as recent tariffs announcements and the ongoing conflicts in Eastern Europe and the Middle East 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.

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 tariffs announcements and the ongoing conflicts in Eastern Europe and the Middle East. 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 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;
- the potential for a local seller, faced with higher local prices, importing medicines from an international market with lower prices rather than buying such medicines locally, which is referred to as parallel importation;
- 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.

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.

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 2024, we used $44.5 million of the net proceeds to settle the remaining principal balance of our 0.125% Notes upon maturity. In 2021, we completed a $632.5 million offering of 0% Notes and used $319.0 million of the net proceeds from the issuance of the 0% Notes to repurchase the remaining $309.9 million of our 1% Notes. 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. For our 0.125% Notes, the note hedges expired upon maturity of the 0.125% Notes and the warrants fully expired in June 2025. Terminating or unwinding the call spread transactions for our 0% Notes 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.

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 21.6 million shares of our common stock upon conversion of our 1.75% Notes and 0% Notes. In connection with the issuance of the 0% Notes, we entered into certain call spread transactions covering 10.9 million shares that we expect will offset the dilution to holders of common stock upon any conversion of those notes. 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. 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, 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 offset any cash payments we are required to make in excess of the principal amount of the converted 0% 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.

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.

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.

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.

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. For example, in June 2024, California enacted Senate Bill 167, or SB 167, which, with certain exceptions, suspends the ability to use California net operating losses to offset California income and limits the ability to use California business tax credits to offset California taxes, for taxable years beginning after 2023 and before 2027.

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 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. In particular, our tax obligations and effective tax rate in the jurisdictions in which we conduct business could increase in the future as a result of the base erosion and profit shifting, or BEPS, project led by the Organization for Economic Co-operation and Development, or OECD, and other initiatives led by the OECD or the European Commission. The OECD is leading work on an iteration of the BEPS project based on two "pillars" (subject to certain revenue thresholds), involving the reallocation of taxing rights in respect of certain multinational enterprises above a fixed profit margin to the jurisdictions in which they carry on business) (referred to as "Pillar One") and imposing a minimum effective corporate tax rate on certain multinational enterprises (referred to as "Pillar Two"). Based on the minimum revenue thresholds we do not expect to fall within the scope of these requirements in the near term.

We may be audited in various jurisdictions, and such jurisdictions may assess additional income, sales and value-added or other 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.

ITEM 5. OTHER INFORMATION

Trading Plans

During the quarter ended June 30, 2025, our directors and officers (as defined in Rule 16a-1(f) under the Exchange Act), or 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.

			Trading Arrangement			
	Action	Date	Rule 10b5-1*	Non-Rule 10b5-1**	Total Shares To Be Sold	Expiration Date
Frank Bennett, EVP, Chief Scientific Officer	Termination	May 6, 2025	X		104,079	Upon the execution of all instructions included in the plan
Joseph Baroldi, EVP, Chief Business Officer	Adoption	May 2, 2025	X		87,874	The earlier to occur of (i) August 3, 2026, and (ii) Upon the execution of all instructions provided in the plan
Patrick O' Neil, EVP, Chief Legal Officer and General Counsel	Adoption	May 2, 2025	X		237,477	The earlier to occur of (i) August 3, 2026, and (ii) Upon the execution of all instructions provided in the plan
Eugene Schneider, EVP, Chief Clinical Development and Operations Officer	Adoption	May 2, 2025	X		38,756	The earlier to occur of (i) August 3, 2026, and (ii) Upon the execution of all instructions provided in the plan
Richard Geary, EVP, Chief Development Officer	Adoption	May 6, 2025	X		220,870	The earlier to occur of (i) July 31, 2026, and (ii) Upon the execution of all instructions provided in the plan
B. Lynne Parshall, Board Member	Adoption	May 6, 2025	X		41,993	The earlier to occur of (i) May 31, 2026, and (ii) Upon the execution of all instructions provided in the plan
Frank Bennett, EVP, Chief Scientific Officer	Adoption	May 13, 2025	X		67,800	The earlier to occur of (i) August 17, 2026, and (ii) Upon the execution of all instructions provided in the plan

ITEM 6. EXHIBITS

a. Exhibits

Exhibit Number	Description of Document
10.1	Collaboration, License and Development Agreement between the Registrant and AstraZeneca AB dated December 7, 2012. 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.
10.2	Amendment #1 to Collaboration, License and Development Agreement between the Registrant and AstraZeneca AB dated August 13, 2013. 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.
10.3	Amendment No. 2 to the Collaboration, License and Development Agreement between the Registrant and AstraZeneca AB dated October 15, 2014. 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.
10.4	Amendment No. 3 to the Collaboration, License and Development Agreement between the Registrant and AstraZeneca AB dated January 18, 2016. 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.
10.5	Amendment No. 4 to the Collaboration, License and Development Agreement by and between the Registrant and AstraZeneca AB, dated October 18, 2018. 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.
10.6	Strategic Collaboration Agreement between the Registrant and AstraZeneca AB dated July 31, 2015. 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.
10.7	Amendment No. 1 to the Strategic Collaboration Agreement by and between the Registrant and AstraZeneca AB, dated October 18, 2018. 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 June 30, 2025, formatted in Inline Extensible Business Reporting Language (iXBRL): (i) condensed consolidated balance sheets, (ii) condensed consolidated statements of operations, (iii) condensed consolidated statements of comprehensive income (loss), (iv) condensed consolidated statements of stockholders' equity, (v) condensed consolidated statements of cash flows and (vi) notes to condensed consolidated financial statements (detail tagged).
104	Cover Page Interactive Data File (formatted in iXBRL and included in exhibit 101).

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

SIGNATURES

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

Signatures	Title	Date
/s/ BRETT P. MONIA Brett P. Monia, Ph.D.	Director and Chief Executive Officer (Principal executive officer)	July 30, 2025
/s/ ELIZABETH L. HOUGEN Elizabeth L. Hougen	Executive Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	July 30, 2025

Certain identified information in this exhibit, marked by [***], has been excluded because it is both (i) not material, and (ii) the type that the registrant treats as private or confidential.

COLLABORATION, LICENSE AND DEVELOPMENT AGREEMENT

BETWEEN

ISIS PHARMACEUTICALS, INC.,

AND

ASTRAZENECA AB

COLLABORATION, LICENSE AND DEVELOPMENT AGREEMENT

This COLLABORATION, LICENSE AND DEVELOPMENT AGREEMENT (the "***Agreement***") is entered into as of the 7th day of December, 2012 (the "***Effective Date***") by and between **Isis Pharmaceuticals, Inc.**, a Delaware corporation, having its principal place of business at 2855 Gazelle Court, Carlsbad, CA 92010 ("***Isis***"), and **AstraZeneca AB**, a company incorporated in Sweden under no. 556011-7482 with offices at SE-151 85 Södertälje, Sweden ("***AstraZeneca***"). AstraZeneca and Isis each may be referred to herein individually as a "***Party***" or 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. All attached appendices and schedules are a part of this Agreement.

RECITALS

WHEREAS, Isis has expertise in discovering and developing antisense drugs for cancer and is (i) developing ISIS-STAT3$_{Rx}$ in a Phase 1/2 Trial in patients with cancer, (ii) working to identify an antisense oligonucleotide targeting the gene target, [***] for the treatment of cancer, and (iii) conducting drug discovery efforts for numerous other cancer targets;

WHEREAS, AstraZeneca has expertise in developing and commercializing human therapeutics, and is interested in developing and commercializing ISIS-STAT3$_{Rx}$, and drugs targeting [***] and other cancer targets; and

WHEREAS, AstraZeneca desires Isis to (i) grant AstraZeneca an exclusive license to Isis' STAT3 Program and [***] Program, (ii) conduct research and development activities for the STAT3 Program and [***] Program, and (iii) collaborate with Isis to identify a development candidate for each of three separate cancer-related genes, and with respect to drugs targeting such genes, to grant an option to exclusively license the programs associated with such genes;

NOW, THEREFORE, in consideration of the respective covenants, representations, warranties and agreements set forth herein, the Parties hereto agree as follows:

ARTICLE 1.
STAT3 DEVELOPMENT PROGRAM

1.1. **STAT3 Program Overview**. The intent of the STAT3 Program is (i) for Isis to complete the ongoing Phase 1/2 Trial for ISIS-STAT3$_{Rx}$; and (ii) for AstraZeneca to perform all other preclinical, clinical (including conducting the [***]), regulatory and commercial activities related to STAT3 Products. The purpose of this Section 1.1 is to provide a high-level overview of the roles, responsibilities, rights and obligations of each Party under this Agreement with regard to ISIS-STAT3$_{Rx}$, and therefore this Section 1.1 is qualified in its entirety by the more detailed provisions of this Agreement set forth below.

1.2. STAT3 Research and Development Responsibilities.

1.2.1. STAT3 Research and Development Plan Activities; Timelines. Isis will use Commercially Reasonable Efforts to conduct the Isis Conducted Activities designated under the STAT3 Research and Development Plan in accordance with the timelines specified therein, and AstraZeneca will use Commercially Reasonable Efforts to conduct the AstraZeneca Conducted Activities designated under the STAT3 Research and Development Plan in accordance with the timelines specified therein.

1.2.2. STAT3 Research and Development Plan. The Parties will continue to develop and refine the STAT3 Research and Development Plan initially agreed at the Effective Date as needed and update it at least once each six months, and submit it to the JSC for its review and comment. Subject to Section 4.1.4, any material changes to the STAT3 Research and Development Plan must be mutually agreed to by the Parties in accordance with the provisions of Section 4.1.3. On a rolling basis, the STAT3 Research and Development Plan will contain activities for at least the next [***], including the key Development and regulatory decisions for ISIS-STAT3$_{Rx}$ and the key factors that will be considered when making such Development and regulatory decisions.

1.2.3. Phase 1/2 Trial.

(a) High Response Outcome Analysis. A "***High Response Outcome***" is achieved when the [***].

(b) Medium Response Outcome Analysis. A "***Medium Response Outcome***" is achieved if, [***]. If there has not been a [***] in at least [***] of the evaluable DLBCL Patients in the Phase 1/2 Trial, then there has been a "***Low Response Outcome.***"

For purposes of this Agreement, "***Durable Response***" means [***]. DLBCL Patients who achieve a Durable Response at [***] of treatment with ISIS-STAT3$_{Rx}$ but who are discontinued from the Phase 1/2 Trial before 24 weeks of treatment due to electing to receive a bone marrow transplant (a "***BMT Patient***") will be [***]; *provided, however*, that no more than [***] BMT Patients will be [***] for purposes of determining whether a High Response Outcome has been achieved and no more than [***] BMT Patient will be [***] for purposes of determining whether a Medium Response Outcome has been achieved.

(c) **Target Knock-Down**. "***Target Knock-Down***" means [***]. The [***] sample must contain [***]. The [***] sample will be taken within [***]. Analysis can be based on results from [***]. The JSC will unanimously decide on [***]. The selected pathology laboratory that conducts Target Knockdown analysis will report the results of this analysis to the JSC which will review whether the Target Knockdown criteria have been achieved. The success criteria for Target Knock-Down requires [***]. The JSC will review the [***] on an ongoing basis with respect to quality of samples, post-treatment sampling time point, and technical challenges associated with measuring the [***]. If the JSC unanimously agree to a change in the Target Knock-Down criteria based on this ongoing data review, the criteria to meet the Target Knock-Down component of the response outcome will be amended. If there is a High Response Outcome and at least [***], then Target Knock-Down will [***].

(d) **Safety Concern**. For purposes of this Agreement, "***Safety Concern***" means [***].

(e) **Notice of High Response Outcome, Medium Response Outcome or Low Response Outcome**. Promptly following Isis' determination that a High Response Outcome, Medium Response Outcome or Low Response Outcome has occurred, Isis will provide AstraZeneca with written notice (an "***Outcome Notice***") of whether (i) there is a High Response Outcome (and whether at least [***]), Medium Response Outcome or Low Response Outcome, (ii) there is a Safety Concern, and (iii) Target Knock-Down was achieved, and will include with such Outcome Notice the available components of the Phase 1/2 Trial Data Package. AstraZeneca may dispute Isis' determination regarding any of items (i), (ii) or (iii) described in this Section 1.2.3(e), by providing Isis written notice thereof within 30 days of AstraZeneca's receipt of the Outcome Notice (in which case Section 1.2.4 will apply); otherwise the determinations set forth in the Outcome Notice will be binding on the Parties.

(f) **AstraZeneca's Response to the Phase 1/2 Trial Data Package**.

(i) If either (a) Target Knock-Down was not achieved and there was [***]; or (b) there is a Low Response Outcome; or (c) there is a Safety Concern (in each case whether determined under Section 1.2.3(e) or the Third Party expert under Section 1.2.4), then within 10 Business Days of the Outcome Notice or determination of the Third Party expert under Section 1.2.4 (as applicable) if AstraZeneca either (x) provides Isis with a written notice that it wishes to terminate the license granted by Isis to AstraZeneca under Section 6.1.1, or (y) does not provide any written notice as to whether or not it wishes to terminate the license or continue with the license, the license granted by Isis to AstraZeneca under Section 6.1.1 will terminate and no milestone payment for ISIS-STAT3$_{Rx}$ will be payable.

(ii) If either (a) AstraZeneca provides Isis with a written notice that it wishes to continue with the license under Section 6.1.1 despite its option to terminate its license to STAT3 Products under Section 1.2.3(f)(i) within the timeline specified therein, or (b) if such Section 1.2.3(f)(i) does not apply, then in the case of a High Response Outcome, Medium Response Outcome or Low Response Outcome (in each case whether determined under Section 1.2.3(e) or the Third Party expert under Section 1.2.4), the applicable milestone payment under TABLE 1 in Section 8.4 will become due following such determination, and AstraZeneca will pay Isis such milestone payment within 30 days after receipt of an invoice from Isis. In addition, if there is a Medium Response Outcome, at the next meeting of the JSC, AstraZeneca will indicate whether it plans to [***].

(g) **AstraZeneca's Continued Development Following Phase 1/2 Trial Data Package**. Without limiting Section 1.2.1 or Section 7.1:

(i) If the license granted by Isis to AstraZeneca under Section 6.1.1 is not terminated under Section 1.2.3(f)(i) and there is a High Response Outcome (or there is a Medium Response Outcome *but* AstraZeneca plans to [***]), then *provided* Isis has supplied the API to AstraZeneca in accordance with Section 4.6.1(b)(i), AstraZeneca will initiate a clinical study for ISIS-STAT3$_{Rx}$ in accordance with the STAT3 Research and Development Plan within [***] after AstraZeneca's receipt of such Phase 1/2 Trial Data Package; and

(ii) If the license granted by Isis to AstraZeneca under Section 6.1.1 is not terminated under Section 1.2.3(f)(i) and there is a Medium Response Outcome (and AstraZeneca does not plan to [***]), *provided* Isis has supplied the API to AstraZeneca in accordance with Section 4.6.1(b)(i), AstraZeneca will initiate a Clinical Study within [***] after AstraZeneca's receipt of such Phase 1/2 Trial Data Package.

(h) **Subsequent [***] Development within [***] after a Medium Response Outcome**. If AstraZeneca pays Isis the milestone payment under Column 2 of TABLE 1 in Section 8.4 for a Medium Response Outcome, but initiates a Clinical Study to evaluate ISIS-STAT3$_{Rx}$ as a [***] in DLBCL Patients within [***] after AstraZeneca's Initiation of a Clinical Study to evaluate ISIS-STAT3 $_{Rx}$ as a [***] in DLBCL Patients, then (A) within 30 days after AstraZeneca's receipt of an invoice from Isis, AstraZeneca will pay Isis an amount equal to $[***] ([***]), and (B) *so long as* AstraZeneca is developing or commercializing ISIS-STAT3$_{Rx}$ as a [***] in DLBCL Patients (i) with respect to any unachieved milestone events, in lieu of paying Isis the milestone payments under Column 2 of TABLE 1 in Section 8.4, AstraZeneca will pay to Isis the milestone payments as set forth in Column 1 of TABLE 1 in Section 8.4 when a milestone event listed in TABLE 1 is achieved by a STAT3 Product, and (ii) the High Response Outcome royalty rates set forth in Section 8.8 will apply to STAT3 Products.

(i) **Subsequent [***] Development more than [***] after a Medium Response Outcome**. If AstraZeneca pays Isis the milestone payment under Column 2 of TABLE 1 in Section 8.4 for a Medium Response Outcome but subsequently Initiates a Clinical Study to evaluate ISIS-STAT3$_{Rx}$ as a [***] in DLBCL Patients *more than* [***] after AstraZeneca's Initiation of a Clinical Study to evaluate ISIS-STAT3$_{Rx}$ as a [***] in DLBCL Patients, then AstraZeneca will continue to pay Isis the milestone payments under Column 2 of TABLE 1 in Section 8.4, AstraZeneca will have no obligation to pay Isis such $[***] payment or the milestone payments as set forth in Column 1 of TABLE 1 in Section 8.4, and the High Response Outcome royalty rates set forth in Section 8.8 will not apply to STAT3 Products.

1.2.4. Disputes Regarding High Response Outcome, Medium Response Outcome, Low Response Outcome, Safety Concern or Target Knock-Down. If under Section 1.2.3(e) AstraZeneca timely disputes whether (i) a High Response Outcome, Medium Response Outcome or Low Response Outcome has been achieved (including whether the [***]), (ii) there is a Safety Concern, or (iii) Target Knock-Down was achieved, then the Parties will promptly (but no later than 15 days after the dispute arises) engage and refer such dispute to a mutually agreed upon single, independent Third Party oncologist with expertise in the area and appropriate professional credentials. Within 30 days of receiving the Phase 1/2 Trial Data Package, to the extent disputed by the Parties, such Third Party expert will determine whether there is a High Response Outcome, Medium Response Outcome, or Low Response Outcome and whether there is a Safety Concern, and/or if there is Target Knock-Down. The determination of the Third Party expert engaged under the preceding sentence will be final and binding on the Parties. The costs of any Third Party expert engaged under this Section 1.2.4 will be paid by the Party against whose position the Third Party expert's determination is made.

ARTICLE 2.
[***] RESEARCH AND DEVELOPMENT PROGRAM

2.1. **[***] Program Overview**. The intent of the [***] Program is (i) for Isis to discover a development candidate for [***] and complete IND-Enabling Toxicology Studies with such development candidate, and (ii) for AstraZeneca to perform, among other activities, *in vitro* and *in vivo* experiments to support the selection of the [***] Development Candidate, and all other preclinical, clinical, regulatory and commercial activities related to [***] Products. The purpose of this Section 2.1 is to provide a high-level overview of the roles, responsibilities, rights and obligations of each Party under this Agreement with regard to the [***] Research and Development Plan, and therefore this Section 2.1 is qualified in its entirety by the more detailed provisions of this Agreement set forth below.

2.2. [***] Research and Development Responsibilities.

2.2.1. [***] Research and Development Plan Activities; Timelines. Isis will use Commercially Reasonable Efforts to conduct the Isis Conducted Activities designated under the [***] Research and Development Plan (which is attached hereto as Appendix 2) in accordance with the timelines specified therein, and AstraZeneca will use Commercially Reasonable Efforts to conduct the AstraZeneca Conducted Activities designated under the [***] Research and Development Plan in accordance with the timelines specified therein. In addition, with respect to the [***] Program:

(a) Isis will use Commercially Reasonable Efforts to designate an [***] Lead Candidate by [***]; and

(b) subject to Section 2.2.3 and Section 2.2.4, Isis will initiate IND-Enabling Toxicology Studies no later than [***] after AstraZeneca notifies Isis of the Selection of the [***] Development Candidate under Section 2.2.3.

2.2.2. [***] Research and Development Plan. The Parties will continue to develop and refine the [***] Research and Development Plan initially agreed at the Effective Date as needed, and update it at least once each six months, and submit it to the JSC for its review and comment. Subject to Section 4.1.4, any material changes to the [***] Research and Development Plan must be mutually agreed to by the Parties in accordance with the provisions of Section 4.1.3. On a rolling basis, the [***] Research and Development Plan will contain activities for at least the next [***], including the key Development and regulatory decisions for the [***] Development Candidate and the key factors that will be considered when making such Development and regulatory decisions. In addition, once the [***] Development Candidate is selected under Section 2.2.3, the JSC will work to establish a plan for IND filing support and activities, which plan will include a timeline and responsibilities for filing the IND and will specify that AstraZeneca will [***]. To the extent that AstraZeneca has not fully used the [***] available to it pursuant to Section 6.5.1 or Section 7.1.5, then AstraZeneca shall be entitled to allocate such [***] to the activities to be performed by Isis pursuant to this Section 2.2.2.

2.2.3. **[***] Development Candidate**. Isis will use Commercially Reasonable Efforts to designate an [***] Lead Candidate by [***]. AstraZeneca shall be entitled to participate with Isis in the identification of an [***] Lead Candidate and a back-up and Isis will notify AstraZeneca in writing promptly after designating an [***] Lead Candidate and, together with such notice, Isis will provide AstraZeneca the applicable Lead Candidate Data Package. As promptly as possible (but no later than [***] after AstraZeneca receives such Lead Candidate Data Package) (such [***] deadline, which AstraZeneca has determined is sufficient for AstraZeneca to complete its candidate selection identification criteria analysis, the "[***] ***Development Candidate Decision Deadline***"), AstraZeneca will determine whether to select the [***] Lead Candidate (or another [***] Compound) as the [***] Development Candidate. In addition, during such [***] period, AstraZeneca will keep the JSC apprised of AstraZeneca's progress in making a decision regarding which [***] Compound AstraZeneca may select as the [***] Development Candidate to enable Isis to plan as early as possible for manufacturing of the [***] Development Candidate for IND-Enabling Toxicology Studies. If the JSC determines that any back up [***] Compound(s) to the proposed [***] Lead Candidate should be considered alongside the proposed [***] Lead Candidate, then the JSC may unanimously agree to extend the [***] Development Candidate Decision Deadline if the JSC determines AstraZeneca should have additional time to consider both candidates before making a decision as to which may be selected as the [***] Development Candidate. If AstraZeneca selects the [***] Lead Candidate or any other [***] Compound as the [***] Development Candidate, then AstraZeneca will notify Isis of such selection by the [***] Development Candidate Decision Deadline, and will pay Isis the [***] Development Candidate milestone payment under Section 8.5 within 30 days after AstraZeneca's receipt of an invoice from Isis. Subject to Section 2.2.4, if AstraZeneca either (i) provides a written notice that it has not selected the [***] Lead Candidate or any other [***] Compound as the [***] Development Candidate by the [***] Development Candidate Decision Deadline or (ii) does not provide Isis any written notice as to whether or not AstraZeneca has selected the [***] Lead Candidate or any other [***] Compound as the [***] Development Candidate by the [***] Development Candidate Decision Deadline, then the license granted by Isis to AstraZeneca under Section 6.1.2 will terminate and no milestone payment for such [***] Development Candidate will be payable.

2.2.4. **Failure to Designate an [***] Lead Candidate or Select an [***] Development Candidate**.

(a) ***JSC Decides to Perform Additional Work***. If AstraZeneca has not selected the [***] Lead Candidate or any other [***] Compound as the [***] Development Candidate by the [***] Development Candidate Decision Deadline but AstraZeneca informs Isis that it believes further work to pursue an [***] Development Candidate should be pursued, then, within 30 days after the [***] Development Candidate Decision Deadline, the JSC may unanimously decide to pursue further work to identify other [***] Compounds for consideration as the [***] Development Candidate under a mutually agreed amended [***] Research and Development Plan, in which case the license granted by Isis to AstraZeneca under Section 6.1.2 will not terminate as provided in Section 2.2.3.

(b) ***Isis Fails to Designate an [***] Lead Candidate by [***]; the JSC Decides Not to Perform Additional Work***. If (A) Isis, having used Commercially Reasonable Efforts, does not designate an [***] Lead Candidate by [***], or (B) Isis has designated an [***] Lead Candidate by [***], but AstraZeneca has not selected the [***] Lead Candidate or any other [***] Compound as the [***] Development Candidate by the [***] Development Candidate Decision Deadline and the JSC has not unanimously decided to pursue further work to identify other [***] Compounds for consideration as the [***] Development Candidate under a mutually agreed amended [***] Research and Development Plan, then, if AstraZeneca elects to abandon its rights to [***] and terminate the license granted by Isis to AstraZeneca under Section 6.1.2, no [***] milestone payment will be payable but AstraZeneca may elect to add an additional Oncology Target to the Oncology Collaboration by providing Isis written notice of such election (together with the gene target AstraZeneca proposes to add to the Oncology Collaboration, including the gene name and the NCBI accession number or nucleic acid sequence for such gene target, and any Patent Rights comprised in AstraZeneca Background IP consistent with the process described in Section 3.3.5 below) on or before (X) [***], in the case of item (A) above, or (Y) within [***] after the last to occur in item (B) above, as applicable. If AstraZeneca timely provides Isis with such an election notice, and Isis and AstraZeneca mutually agree on the proposed target, then, upon Isis' receipt of AstraZeneca's written agreement to be responsible for any Target Encumbrances that Isis notifies AstraZeneca as being applicable to such proposed target and related Products, (i) such proposed target will be an Oncology Target and the Oncology Collaboration will be expanded to a total of four Oncology Targets, (ii) Isis' obligations and AstraZeneca's rights under this Agreement with respect to the [***] Research and Development Plan (including the [***] Development Candidate and all other [***] Compounds) will terminate, and (iii) the license granted by Isis to AstraZeneca under Section 6.1.2 will terminate and no [***] milestone payment will be payable.

2.2.5. **Notice of Completion of IND-Enabling Toxicology Studies; IND Support Package**. Isis will notify AstraZeneca in writing within 30 days after Isis achieves Completion of the IND-Enabling Toxicology Studies under the [***] Research and Development Plan and, together with such notice, will deliver to AstraZeneca the IND Support Package.

ARTICLE 3.
ONCOLOGY COLLABORATION; OPTIONS

3.1. **Oncology Collaboration Overview**. The intent of the Oncology Collaboration is (i) for Isis to generate an Oncology Lead Candidate for each of the Oncology Collaboration Programs, (ii) with respect to each such Oncology Lead Candidate, for AstraZeneca to perform certain *in vitro* and *in vivo* (animal) experiments to support their designation, and (iii) for AstraZeneca to conduct IND-Enabling Toxicology Studies with the Oncology Development Candidate. For each Oncology Collaboration Program, AstraZeneca will have an exclusive option to further develop and commercialize Products under an exclusive license from Isis. The purpose of this Section 3.1 is to provide a high-level overview of the roles, responsibilities, rights and obligations of each Party under this Agreement with regard to the Oncology Collaboration Programs, and therefore this Section 3.1 is qualified in its entirety by the more detailed provisions of this Agreement set forth below. Both Parties agree that while the primary focus of the collaboration is oncology, if the JSC unanimously agrees, then targets outside oncology could be included in this Agreement either during the selection process described below or as Substituted Targets.

3.2. **Oncology Research and Development Plan Activities and Term**.

3.2.1. **Oncology Research and Development Plan Activities; Timelines**. Each Oncology Research and Development Plan will be mutually agreed to by the Parties, and subject to Section 4.1.4 any material changes to a Collaboration Plan will be mutually agreed to by the Parties in accordance with the provisions of Section 4.1.3. Isis will use Commercially Reasonable Efforts to conduct the Isis Conducted Activities designated under each Oncology Research and Development Plan in accordance with the timelines specified therein, and AstraZeneca will use Commercially Reasonable Efforts to conduct the AstraZeneca Conducted Activities designated under each Oncology Research and Development Plan in accordance with the timelines specified therein. In addition Isis will use Commercially Reasonable Efforts to designate an Oncology Lead Candidate with respect to a particular Oncology Target. Both Parties will use their Commercially Reasonable Efforts to agree to the Reserved Targets in accordance with the timelines in Section 3.3.5 and to designate the Oncology Targets in accordance with the timelines in Section 3.3.6.

3.2.2. **Oncology Collaboration Term**. The period during which the Parties will conduct the Oncology Collaboration (such period, the "***Oncology Collaboration Term***") will begin on the Effective Date and will end on the [***] anniversary of the Effective Date; *provided that* if one or both Substitute Targets are substituted into the Oncology Collaboration in accordance with Section 3.3.7 below or an additional Oncology Target is added to the Oncology Collaboration in accordance with Section 2.2.4, then, in order to provide sufficient time to perform such additional activities with respect to such Substitute Target or additional Oncology Target, the Oncology Collaboration Term for all Oncology Collaboration Programs will be extended for an additional [***] from the date the last Substitute Target or additional Oncology Target was included in the Oncology Collaboration.

3.3. Oncology Collaboration.

3.3.1. Oncology Research and Development Plans. The Oncology Collaboration will be carried out in accordance with a written research and development plan that sets forth all research and development activities of the Parties with respect to each Oncology Target through AstraZeneca's Completion of the IND-Enabling Toxicology Studies (each such plan, an "***Oncology Research and Development Plan***"). Each time the Parties have designated one of the three Oncology Targets in accordance with Section 3.3.6, the JSC will unanimously agree on an Oncology Research and Development Plan for each such Oncology Target. Each Oncology Research and Development Plan will include a description of the specific activities to be performed by the Parties in support of the Oncology Collaboration Program, the specific criteria to achieve Target Sanction status for the Oncology Target, the specific activities to be performed to achieve an Oncology Development Candidate and projected timelines for completion of such activities. A template Oncology Research and Development Plan for guidance on the expected activities of each Party is attached hereto as APPENDIX 3, which will be used by the JSC as a starting point when creating each Oncology Research and Development Plan. The Parties will continue to develop and refine each Oncology Research and Development Plan initially agreed as needed, and update it at least once every six months, and submit it to the JSC for its review and comment. AstraZeneca will ensure on a rolling basis that each Oncology Research and Development Plan contains activities for at least the next [***], including the key Development and regulatory decisions for the Oncology Development Candidate and the key factors that will be considered when making such Development and regulatory decisions, and will be consistent in scope with the STAT3 Research and Development Plan and [***] Research and Development Plan. For clarity, Isis will not be obligated to initiate work on more than [***] Oncology Targets (excluding a Substitute Target) in any rolling [***] period during the Oncology Collaboration Term to ensure even utilization of resources unless agreed otherwise unanimously by the JSC. Lastly, once an Oncology Development Candidate is selected under Section 3.3.3, the JSC will work to establish a plan for IND filing support and activities, which plan will include a timeline and responsibilities for filing the IND and will specify that AstraZeneca will reimburse Isis for its time incurred in performing Isis' designated responsibilities in connection with the IND filing to the extent those responsibilities are not Isis Conducted Activities, at the FTE rate, and any of Isis' reasonable travel expenses for travel requested by AstraZeneca, and its outside consultants' costs and consultants' reasonable travel expenses incurred by Isis in performing such activities agreed in advance by AstraZeneca. To the extent that AstraZeneca has not fully used the [***] available to it pursuant to Section 6.5.1 or Section 7.1.5, then AstraZeneca shall be entitled to allocate such [***] to the activities to be performed by Isis pursuant to this Section 3.3.1.

3.3.2. Target Sanction. The JSC will determine if an Oncology Target has achieved Target Sanction status based on the specific criteria determined by the JSC. The JSC will record in the minutes of the JSC each time an Oncology Target has achieved Target Sanction status.

3.3.3. **Oncology Development Candidate Selection**. Isis will notify AstraZeneca in writing promptly after designating an Oncology Lead Candidate and, together with such notice, Isis will provide AstraZeneca the applicable Lead Candidate Data Package. As promptly as possible (but no later than [***] after AstraZeneca receives such Lead Candidate Data Package) (each such [***] deadline, which AstraZeneca has determined is sufficient for AstraZeneca to complete its candidate selection identification criteria analysis, an "***Oncology Development Candidate Decision Deadline***"), AstraZeneca will determine whether to select the Oncology Lead Candidate (or another Oncology Compound) as an Oncology Development Candidate. In addition, during such [***] period, AstraZeneca will keep the JSC apprised of AstraZeneca's progress in making a decision regarding which Oncology Compound AstraZeneca may select as the Oncology Development Candidate to enable Isis to plan as early as possible for manufacturing of the Oncology Development Candidate for IND-Enabling Toxicology Studies. If the JSC determines that any back up Oncology Compound to the proposed Oncology Lead Candidate should be considered alongside the proposed Oncology Lead Candidate, then the JSC may unanimously agree to extend the Oncology Development Candidate Decision Deadline if the JSC determines AstraZeneca should have additional time to consider both candidates before making a decision as to which may be selected as the Oncology Development Candidate. If AstraZeneca selects the Oncology Lead Candidate or any other Oncology Compound as an Oncology Development Candidate, then AstraZeneca will notify Isis of such selection by the Oncology Development Candidate Decision Deadline, and will pay Isis the Designation of Oncology Development Candidate milestone payment under Section 8.6 within 30 days after AstraZeneca's receipt of an invoice from Isis. In addition, provided Isis has supplied the API to AstraZeneca in accordance with Section 4.6.1(b)(iii), AstraZeneca will initiate IND-Enabling Toxicology Studies under the applicable Oncology Research and Development Plan no later than [***] days after AstraZeneca pays Isis the Designation of Oncology Development Candidate milestone payment under Section 8.6.

If AstraZeneca either (i) does not provide Isis written notice that AstraZeneca has selected the Oncology Lead Candidate or any other Oncology Compound as the Oncology Development Candidate by the Oncology Development Candidate Decision Deadline, or (ii), provides Isis written notice that AstraZeneca has not selected the Oncology Lead Candidate or any other Oncology Compound as the Oncology Development Candidate by the Oncology Development Candidate Decision Deadline, then such Oncology Collaboration Program will no longer be a part of this Agreement and AstraZeneca's Option for (and Isis' obligations with respect to) such Oncology Collaboration Program will terminate and no milestone payments for such Oncology Collaboration Program will be payable.

3.3.4. **Notice of Completion of IND-Enabling Studies; IND Support Package**. AstraZeneca will notify Isis in writing within 30 days after each time Completion of the IND-Enabling Toxicology Studies is achieved under an applicable Oncology Research and Development Plan and, together with such notice, will deliver to Isis the applicable IND Support Package, always provided that the Parties may mutually agree that an IND-Enabling Toxicology Study should not be completed (for example if there is an unacceptable toxicity in the study).

3.3.5. **Reserved Targets**. The Parties will select certain gene targets to be reserved (each such reserved gene target, a "***Reserved Target***") for potential selection as Oncology Targets under this Agreement according to the following schedule:

(a) Within [***] after the Effective Date, Isis and AstraZeneca will mutually agree on a pool of [***] oncology gene targets to be reserved for selection of the first Oncology Target under this Agreement;

(b) Within [***] after the Effective Date, Isis and AstraZeneca will mutually agree on a second pool of [***] oncology gene targets to be reserved for selection of the second Oncology Target under this Agreement; and

(c) Within [***] after the Effective Date, Isis and AstraZeneca will mutually agree on a third pool of [***] oncology gene targets to be reserved for selection of the third Oncology Target under this Agreement.

As part of the process for determining which gene targets will be reserved as Reserved Targets for potential selection as Oncology Targets, during the relevant time periods described above during which the Parties will consider gene targets to be Reserved Targets, AstraZeneca will inform Isis (A) if any of AstraZeneca's JSC or JPC members have knowledge (without conducting any additional investigation) of any additional Third Party licenses or other intellectual property rights that AstraZeneca requires in order for AstraZeneca to conduct its obligations under the Collaboration Plans if such Reserved Target was selected as an Oncology Target, and (B) if any Patent Rights comprised in AstraZeneca Background IP relate to any proposed gene targets, and whether AstraZeneca has the ability to grant a license or sublicense hereunder to such Patent Rights without violating the terms of any agreement with any Third Party. If AstraZeneca reports any of the conditions set forth in (A) or (B) of this Section 3.3.5(c) exist, then unless otherwise agreed by the Parties, such gene target will not be reserved as a Reserved Target for potential selection as an Oncology Target. Within [***] days after the Parties agree upon each pool of [***] Reserved Targets, Isis will inform AstraZeneca of any known encumbrances related to the Reserved Targets under any Third Party agreement to which Isis or its Affiliate is a party, including any payment obligations such as milestone and royalty payments (such encumbrances for which AstraZeneca is so notified, the "***Target Encumbrances***"). The JSC will maintain the list of Reserved Targets and will attach to the minutes of the JSC meeting any changes to such list of Reserved Targets.

3.3.6. **Selection of the Three Oncology Targets**. Within [***] after a designation of a pool of [***] Reserved Targets under Section 3.3.5, Isis and AstraZeneca will mutually agree on and designate one Reserved Target to be an Oncology Target that is the subject of an Oncology Collaboration Program. After selecting the Oncology Target, the remaining [***] unselected Reserved Targets will no longer be Reserved Targets, and Isis' obligations and AstraZeneca's rights under this Agreement with respect to such Reserved Targets (including but not limited to Section 5.1) will terminate. AstraZeneca will be responsible for any payment obligations arising from the Target Encumbrances identified in accordance with Section 2.2.4(b), Section 3.3.5 or Section 3.3.7 (other than Isis Supported Pass-Through Costs) applicable to such Oncology Targets and related Products. If Isis fails to notify AstraZeneca of a Target Encumbrance in accordance with Section 2.2.4(b), Section 3.3.5 or Section 3.3.7, such un-notified Target Encumbrance shall remain the responsibility of Isis. For clarity, this process will occur [***] times to nominate the [***] Oncology Targets and be complete no later than [***] from the Effective Date, and is illustrated in SCHEDULE 3.3.6, after which any remaining Reserved Targets will no longer be Reserved Targets.

3.3.7. **Rights of Substitution**.

(a) **Generally**. At any time during the first [***] years of the Oncology Collaboration Term, AstraZeneca will have the right, subject to the limits set forth below, to propose that research and development activities be discontinued with respect to an Oncology Target for which [***] (a "***Discontinued Target***"), and to propose that a new oncology target be substituted for such Discontinued Target in accordance with the procedures set out below in Section 3.3.7(b) (such notice, a "***Substitute Notice***" and such newly proposed oncology target, a "***Proposed Substitute Target***").

(b) **Proposing the Substitute Target**. Within 30 days after Isis' receipt of a Substitute Notice, Isis and AstraZeneca will discuss and mutually agree whether such Proposed Substitute Target will become an Oncology Target. Isis will, within [***] days after Isis' receipt of any Substitute Notice, inform AstraZeneca of any Target Encumbrances applicable to the Proposed Substitute Target. If Isis and AstraZeneca mutually agree that the Proposed Substitute Target will become an Oncology Target, then such Proposed Substitute Target (a "***Substitute Target***") will become an Oncology Target upon (i) Isis' receipt of AstraZeneca's written agreement to be responsible for any payment obligations arising from the Target Encumbrances identified in accordance with this Section 3.3.7(b) (other than Isis Supported Pass-Through Costs) applicable to such Substitute Target and related Products, and (ii) if the Substitute Target is substituted in as an Oncology Target after the Discontinued Target achieved Target Sanction status, Isis' receipt of the payment in accordance with Section 3.3.7(d) below. For clarity, any Discontinued Target will no longer be an Oncology Target and will therefore no longer be a part of the Oncology Collaboration under this Agreement, and Isis' obligations and AstraZeneca's rights under this Agreement with respect to such Discontinued Target (including but not limited to Section 5.1.1) will terminate.

(c) **Number of Substitute Targets**. Notwithstanding anything to the contrary contained in this Agreement, in no event will AstraZeneca have the right to designate more than [***] Substitute Targets under this Section 3.3.7; *provided that* no more than [***] of such [***] Substitute Targets can be substituted in for an Oncology Target that has reached [***] status.

(d) **Payment for the Substitute Target**. If a Substitute Target is substituted in as an Oncology Target after [***] status for a Discontinued Target under this Section 3.3.7, AstraZeneca will pay Isis $[***] within 30 days after such Substitute Target is substituted in as an Oncology Target.

3.3.8. **Oncology Research and Development Plans**. If a Substitute Target is substituted in under Section 3.3.7, within 30 days after such substitution the Parties will mutually agree on an Oncology Research and Development Plan for such new Oncology Target using the template Oncology Research and Development Plan attached hereto as APPENDIX 3 as a starting point, subject to review and comment by the JSC, and remove any Oncology Research and Development Plan with respect to the Discontinued Target.

3.4. **Expiration of Oncology Collaboration Term**. On an Oncology Collaboration Program-by-Oncology Collaboration Program basis, if, despite the Parties' Commercially Reasonable Efforts, by the expiration of the Oncology Collaboration Term, Isis has not designated an Oncology Lead Candidate with respect to a particular Oncology Target, then (i) the Parties' will no longer have an obligation to perform any activities under this ARTICLE 3 with respect to such Oncology Collaboration Program; (ii) any Oncology Collaboration Program that has not reached the Development Candidate stage will no longer be considered an Oncology Collaboration Program and the applicable gene target associated therewith will no longer be an Oncology Target under this Agreement; (iii) the Parties' respective obligations and AstraZeneca's rights under this Agreement with respect to such Oncology Target and any Compounds targeting such Oncology Target will then terminate, and Isis will be free to Develop and Commercialize on its own or with a Third Party such Oncology Target and any ASOs targeting such Oncology Target; (iv) Isis will have exclusive rights (and AstraZeneca will, and hereby does grant Isis an exclusive license) to all data, results and information generated under the Oncology Collaboration Program for such Oncology Target to research, develop, manufacture and commercialize ASOs targeting such Oncology Target and AstraZeneca will promptly transfer to Isis copies of all such data, results and information in AstraZeneca's possession, provided that if within five years after the expiration of the Oncology Collaboration Term for such Oncology Target, Isis is not Developing ASOs for such Oncology Target, such rights and license shall become non-exclusive and (v) AstraZeneca will and hereby does grant Isis an irrevocable, royalty free non exclusive license to any Know-How and/or Patent Rights generated by AstraZeneca under the Oncology Collaboration Program for such Oncology Target to research, develop, manufacture and commercialize ASOs targeting such Oncology Target. With regard to the Jointly-Owned Collaboration Technology for such Oncology Collaboration Program, Isis will control the Jointly-Owned Patents that result, and AstraZeneca will assign ownership to Isis on condition that Isis grants AstraZeneca an irrevocable, royalty-free, non-exclusive license for any purpose. For clarity, except to the extent expressly set forth in the foregoing, the expiration of the Oncology Collaboration Term will not affect the Parties' respective rights and obligations with respect to any Oncology Collaboration Program that has reached the Development Candidate stage by the end of the Oncology Collaboration Term and for which AstraZeneca has timely exercised its Option under Section 3.5.

3.5. **Options**. On an Oncology Target-by-Oncology Target basis, AstraZeneca has an exclusive option which it may exercise at any time on or before 5:00 p.m. (Pacific time) on the [***] day (each, an "***Option Deadline***") following the earlier of (i) [***], or (ii) [***] (each, an "***Option***") to obtain from Isis the license set forth in Section 6.1.3 below. AstraZeneca will notify Isis whether AstraZeneca is exercising its Option to license the applicable Oncology Target (and all Products included in the applicable Oncology Collaboration Program) by notifying Isis in writing on or before the applicable Option Deadline.

3.5.1. If AstraZeneca notifies Isis in writing by the Option Deadline that AstraZeneca is exercising the Option, AstraZeneca shall pay Isis the license fee set forth in Section 8.2 within 30 days after AstraZeneca's receipt of an invoice from Isis for such license fee, and Isis will, and hereby does, grant to AstraZeneca the license set forth in Section 6.1.3 below.

3.5.2. If AstraZeneca either (i) notifies Isis in writing by the Option Deadline that AstraZeneca is not exercising the Option, or (ii) does not provide any written notice to Isis by the Option Deadline as to whether or not AstraZeneca is exercising the Option, then AstraZeneca's Option will expire and no license fee is payable under Section 8.2 with respect to such Option. In such a case, AstraZeneca will have no further rights to (and Isis will have no further obligations with respect to) such Oncology Target (including all Compounds included in the applicable Oncology Collaboration Program) and the gene target to which such Compounds are directed will no longer be an Oncology Target. Following any expiration of an Option under this Section 3.5.2, subject to agreeing otherwise as provided in Section 3.3.4, AstraZeneca will [***] and, upon [***], will promptly transfer to Isis all data, results and information related to the testing and studies with respect to the applicable Oncology Target in the possession of AstraZeneca and its contractors.

ARTICLE 4.
COLLABORATION MANAGEMENT; ADMINISTRATION; COSTS AND EXPENSES AND MANUFACTURING

4.1. Collaboration Management.

4.1.1. **JSC**. The Parties will establish a joint steering committee ("***JSC***") for the STAT3 Program, [***] Program, and the Oncology Collaboration Programs, to provide advice and make recommendations on the conduct of activities under the respective Collaboration Plans, which advice and recommendations will be consistent with each Collaboration Plan. The JSC will consist of three representatives appointed by Isis and three representatives appointed by AstraZeneca. Each JSC member will be a senior development leader or have similar experience and expertise as a senior development leader. Each Party will designate one of its three representatives who is empowered by such Party to make decisions related to the performance of such Party's obligations under this Agreement to act as the co-chair of each JSC. The co-chairs will be responsible for overseeing the activities of its JSC consistent with the responsibilities set forth in Section 4.1.2. SCHEDULE 4.1.1 sets forth certain JSC governance matters agreed to as of the Effective Date. The JSC will determine the JSC operating procedures at its first meeting, including the JSC's policies for replacement of JSC members, policies for participation by additional representatives or consultants invited to attend JSC meetings, and the location of meetings, which will be codified in the written minutes of the first JSC meeting. Each Party will be responsible for the costs and expenses of its own employees or consultants attending JSC meetings.

4.1.2. **Role of the JSC**. Without limiting any of the foregoing, the JSC will perform the following functions, some or all of which may be addressed directly at any given JSC meeting:

(a) Maintain the list of Reserved Targets;

(b) Maintain the list of Oncology Targets that are the subject of the Oncology Collaboration Programs;

(c) Set the Target Sanction criteria for each Oncology Target;

(d) Consider whether and for how long a back up candidate for the [***] Lead Candidate or the Oncology Lead Candidate shall be considered in parallel with the [***] Lead Candidate or Oncology Lead Candidate (as applicable).

(e) Create each Oncology Research and Development Plan using the template attached hereto as APPENDIX 3 as a starting point;

(f) review the overall progress of the activities under the applicable Collaboration Plan, including forecasts of costs associated with supplies of API/finished Product;

(g) review and provide advice on the applicable Collaboration Plan;

(h) subject to Section 4.1.3(a), materially amend the applicable Collaboration Plan upon unanimous consent; and

(i) such other review and advisory responsibilities as may be assigned to the JSC pursuant to this Agreement.

4.1.3. Collaboration Program Decision Making.

(a) AstraZeneca shall have the final decision making authority with respect to amendments to a Collaboration Plan which are not material as provided in Section 4.1.3(b).

(b) A proposed amendment to a Collaboration Plan shall be regarded as material for the purposes of this Section 4.1.3 if it would result in either (i) [***], or (ii) [***].

(c) If a proposed material amendment to a Collaboration Plan cannot be unanimously agreed to by the JSC or the Parties and the change could be materially detrimental to the further development of a Product then the co-chairs shall continue to revise the Collaboration Plan until such time as a unanimous decision can be reached, and at any time either Party may refer the matter to the Senior Representatives in accordance with Section 14.1, which Senior Representatives shall be asked to use their good faith efforts to mutually agree on an acceptable way forward. Once the matter has been referred to the Senior Representatives, if after negotiating in good faith pursuant to Section 14.1.1, undertaken with reasonable promptness and including a detailed comparison of the proposed amendment to the Collaboration Plan against the AstraZeneca performance metrics described in the document provided by AstraZeneca to Isis entitled [***] attached hereto as SCHEDULE 4.1.3(c), the Senior Representatives fail to reach an amicable agreement within 90 days, then AstraZeneca shall have the final decision making authority (1) if [***], or (2) if [***], or (3) if [***].

(d) ***"Initial Research and Development Plan"*** means, as applicable (i) the STAT3 Research and Development Plan or [***] Research and Development Plan (as each such plan is attached to this Agreement on the Effective Date) or (ii) with respect to each Oncology Development Candidate, the first Oncology Research and Development Plan agreed to by the Parties following designation of such Oncology Development Candidate.

(e) Isis and AstraZeneca will conduct the Collaboration Plans giving due consideration to the recommendations and advice of the JSC, in accordance with their obligations under Section 1.2.1, Section 2.2.1 and Section 3.3.1. With respect to the STAT3 Research and Development Plan, [***] Research and Development Plan and each Oncology Research and Development Plan agreed to by the Parties following designation of the applicable Oncology Development Candidate, AstraZeneca will have the final decision-making authority regarding the [***], and [***].

(f) Notwithstanding the foregoing, in all cases where AstraZeneca has final decision making authority Isis will have no obligation to perform any activity that (A) [***], (B) [***], or (C) [***].

4.1.4. **Term of the JSC**. Isis' obligation to participate in relation to a Collaboration Plan in the JSC will terminate on the date Isis completes all the Isis Conducted Activities under such Collaboration Plan. Thereafter, Isis will have the right, but not the obligation, to participate in the JSC meetings in relation to such Collaboration Plan upon Isis' request. After the [***] for a Product specified in the Collaboration Plan, in respect of such Collaboration Plan, the JSC shall cease to be responsible for making decisions (and for the avoidance of doubt, without limiting the foregoing, the provisions of Section 4.1.3 shall cease to apply) and AstraZeneca shall have full decision making authority and may make amendments to such Collaboration Plan (including with respect to the [***] program under such Collaboration Plan), subject to AstraZeneca's continuing obligation to use Commercially Reasonable Efforts under this Agreement; *provided, however*, that, with respect to the [***] for such Product, AstraZeneca's decision making will be consistent with the Collaboration Plan approved by the JSC at the time such [***] (taking into consideration [***]). The JSC shall become a forum for the Parties to share information regarding the Collaboration Plan and the Product, and the Parties shall decide on the number and frequency of meetings required of the JSC in respect of such Collaboration Plan in its new role.

4.2. **Alliance Managers**. Each Party will appoint a representative to act as its alliance manager (each, an "***Alliance Manager***"). Each Alliance Manager will be responsible for supporting the JSC and performing the activities listed in SCHEDULE 4.2.

4.3. **Disclosure of Results**. Each Party will promptly disclose to the other Party the results of all work performed by the Parties under the Collaboration Plans in a reasonable manner as such results are obtained. Isis and AstraZeneca will provide reports and analyses at each JSC meeting, and more frequently on reasonable request by the JSC, detailing the current status of each Collaboration Plan. The results, reports, analyses and other information regarding the Collaboration Plans disclosed by one Party to the other Party pursuant hereto may be used only in accordance with the rights granted and other terms and conditions under this Agreement. Any reports required, excluding reports needed for submission to a Regulatory Agency, under this Section 4.3 may take the form of and be recorded in minutes of the JSC that will contain copies of any slides relating to the results and presented to the JSC. Reports needed to support regulatory submissions and updates to a Regulatory Agency will be provided in a timely manner and in a format consistent with industry practice as agreed upon by the JSC.

4.4. **Materials Transfer**. In order to facilitate the activities under the Collaboration Plans, either Party may provide to the other Party certain materials for use by the other Party in furtherance of the Collaboration Plans. All such materials will be used by the receiving Party in accordance with the terms and conditions of this Agreement solely for purposes of exercising its rights and performing its obligations under this Agreement, and the receiving Party will not transfer such materials to any Third Party unless expressly contemplated by this Agreement or upon the written consent of the supplying Party. Except as expressly set forth herein, THE MATERIALS ARE PROVIDED "AS IS" AND WITHOUT ANY REPRESENTATION OR WARRANTY, EXPRESS OR IMPLIED, INCLUDING ANY IMPLIED WARRANTY OF MERCHANTABILITY OR OF FITNESS FOR ANY PARTICULAR PURPOSE OR ANY WARRANTY THAT THE USE OF THE MATERIALS WILL NOT INFRINGE OR VIOLATE ANY PATENT OR OTHER PROPRIETARY RIGHTS OF ANY THIRD PARTY.

4.5. **Collaboration Costs and Expenses**.

4.5.1. **STAT3 Program and [***] Program.**

(a) **R&D Research and Development Plan Costs**. Except as otherwise provided below and under Section 4.5.1(b), Isis will be responsible for all costs and expenses associated with the Isis Conducted Activities designated under the R&D Research and Development Plan, and AstraZeneca will be responsible for all costs and expenses associated with any AstraZeneca Conducted Activities designated under the R&D Research and Development Plan. With respect to the [***] Program, Isis will be responsible for providing API to AstraZeneca in accordance with Section 4.6.1.

(b) **Other STAT3 Program and [***] Program Costs**.

(i) **Under the R&D Research and Development Plan**. AstraZeneca will be responsible for paying Isis any costs and expenses associated with Isis' regulatory support and safety reporting work for the [***] ([***]) and, in accordance with Section 4.6.1, the cost of the API and finished Product for the [***]. In addition, AstraZeneca will be responsible for paying as a lump sum any Additional Plan Costs resulting from AstraZeneca-Initiated Changes. Isis will permit AstraZeneca to review and approve the Additional Plan Costs before implementing any AstraZeneca-Initiated Changes. Isis and AstraZeneca will update the R&D Research and Development Plan with any such revised studies and Isis will invoice AstraZeneca for any such approved Additional Plan Costs within 30 days after such Additional Plan Costs are approved. AstraZeneca will pay the invoices submitted pursuant to this Section 4.5.1(b)(i) for such [***]-related work costs and approved Additional Plan Costs within 30 days after AstraZeneca's receipt of the applicable invoice.

(ii) **Generally**. Except as otherwise provided under this Section 4.5.1, AstraZeneca will be solely responsible for the costs and expenses related to the Development, Manufacture and Commercialization of STAT3 Products and [***] Products, including the AstraZeneca Conducted Activities.

4.5.2. Oncology Collaboration Program Costs and Expenses.

(a) Oncology Research and Development Plan Costs Paid by Isis. Until AstraZeneca exercises the Option for a particular Oncology Collaboration Program, except as otherwise provided under Section 3.3.4 or Section 4.5.2(b), Isis will be responsible for all costs and expenses associated with the Isis Conducted Activities designated under each Oncology Research and Development Plan and AstraZeneca will be responsible for all costs and expenses associated with the AstraZeneca Conducted Activities designated under each Oncology Research and Development Plan. With respect to each Oncology Collaboration Program, Isis will be responsible for providing API to AstraZeneca in accordance with Section 4.6.1.

(b) Oncology Research and Development Plan Costs Paid by AstraZeneca.

(i) **Before Option Exercise**. Before Option exercise, AstraZeneca will be responsible for all costs and expenses associated with the AstraZeneca Conducted Activities designated under each Oncology Research and Development Plan. In addition, AstraZeneca will be responsible for paying as a lump sum any Additional Plan Costs resulting from AstraZeneca-Initiated Changes. Isis will permit AstraZeneca to review and approve the Additional Plan Costs before implementing any AstraZeneca-Initiated Changes. Isis and AstraZeneca will update the applicable Oncology Research and Development Plan with any such revised studies and Isis will invoice AstraZeneca for any such approved Additional Plan Costs within 30 days after such Additional Plan Costs are approved. AstraZeneca will pay the invoices submitted pursuant to this Section 4.5.2(b)(i) for such approved Additional Plan Costs within 30 days after AstraZeneca's receipt of the applicable invoice.

(ii) **After Option Exercise**. After Option exercise, AstraZeneca will be solely responsible for the costs and expenses related to the Development, Manufacture and Commercialization of Products, including all AstraZeneca Conducted Activities.

4.6. Collaboration Manufacturing and Supply.

4.6.1. Supplies for Activities under the Collaboration Plans.

(a) **Isis Conducted Activities**. [***], Isis will supply API and finished Product sufficient to support the Isis Conducted Activities designated under a given Collaboration Plan, including but not limited to the API to support the IND Enabling Toxicology Studies for the [***] Program.

(b) **AstraZeneca Conducted Activities**. In addition, with respect to the AstraZeneca Conducted Activities, Isis will supply (the "***Initial Supply***"):

(i) ***STAT3 Program Supply***. API and finished Product sufficient to support the [***] that will be conducted by AstraZeneca under the STAT3 Research and Development Plan;

(ii) ***[***] Program Supply***. The quantity of API [***] (which will be set forth in the [***] Research and Development Plan) to support the [***] for the [***] Development Candidate; and

(iii) ***Oncology Programs***. The quantity of API [***] for each Oncology Development Candidate, and the quantity of API [***] (which will be set forth in the applicable Oncology Research and Development Plan) for each Oncology Development Candidate.

In each of the foregoing cases in this Section 4.6.1(b), AstraZeneca will pay Isis for such API and/or finished Product at [***], within 60 days after AstraZeneca's receipt of the applicable invoice. Other than the finished Product sufficient to support the [***] under the STAT3 Research and Development Plan, AstraZeneca is responsible for supplying finished Product for all AstraZeneca Conducted Activities. In addition, should AstraZeneca require additional API or research-grade Compound for the STAT3 Program or the [***] Program for pre-clinical studies in [***] not covered by the STAT3 or [***] Research and Development Plan or in connection with the Oncology Research and Development Plans, then, at AstraZeneca's reasonable request, Isis will use its reasonable endeavors to provide (A) such API to AstraZeneca at [***], or (B) such research-grade Compound for such [***] studies [***] of such Compound (and for any additional quantities of research-grade Compound, at [***].

It is intended that the API lot used for [***] under a given Collaboration Plan will be of sufficient size to also use in the [***] of the relevant Product.

(c) **Initial Supply Payment and Delivery Schedule**. The Parties will mutually agree on the respective delivery and payment schedule for the Initial Supply consistent with the applicable Collaboration Plan.

(d) **Manufacturing Services Agreement**. Each of the Parties agrees and acknowledges that a mutually agreed manufacturing services agreement ("***MSA***") is required to be put in place to govern the supply arrangements by Isis, which shall be negotiated in good faith between the Parties following the Effective Date. The Parties' objective is that the MSA shall be entered into within [***] after the Effective Date and shall include, amongst other appropriate and detailed provisions, the provisions set out in Schedule 4.6.1(d).

4.6.2. **After Isis Completes the Isis Conducted Activities**. Once Isis completes the Isis Conducted Activities designated under a given Collaboration Plan, in addition to the Initial Supply, Isis will sell to AstraZeneca, if AstraZeneca desires, any other inventory of cGMP API, finished Product and packaged clinical trial material in Isis' possession [***]. In addition, if requested by AstraZeneca, Isis will negotiate in good faith to provide:

(a) additional API supply for [***], and

(b) if AstraZeneca [***].

4.7. **Applicable Laws and Bioethics**. The Research to be conducted by each Party (including by its subcontractors) pursuant to this Agreement shall be carried out in good scientific manner, and in compliance with all Applicable Laws, as well as the AstraZeneca bioethics policy attached at SCHEDULE 4.7, to attempt to achieve efficiently and expeditiously the objectives of the applicable Collaboration Plan. In respect of any Isis Conducted Activities to be initiated after the Effective Date, Isis and AstraZeneca will mutually agree on [***] and, prior to award of the work, shall work together to secure compliance with AstraZeneca's bioethics policy. Where a [***], the Parties will discuss and agree whether such [***]. Insofar as the requirements of complying with such policy will result in additional [***] costs being charged to Isis for work [***] for Isis Conducted Activities, compared to [***], AstraZeneca agrees to be responsible for such additional costs [***]. The Parties will agree when such costs will be invoiced by Isis and AstraZeneca will pay such costs to Isis within 60 days after AstraZeneca's receipt of an invoice from Isis. The Parties' agreement under this Section 4.7 can be through the JSC.

ARTICLE 5.
EXCLUSIVITY COVENANTS

5.1. Exclusivity Covenants.

5.1.1. Isis' and AstraZeneca's Exclusivity Covenants. Except in the performance of its obligations under this Agreement and except as set forth in Section 5.1.2 or Section 5.1.3, on a Gene Target-by-Gene Target basis, Isis and AstraZeneca will not work independently or for or with any of its Affiliates or any Third Party (including the grant of any license to any Third Party) with respect to:

(a) ***STAT3 and [***]***. (A) The discovery, research or development of an ASO that is designed to bind to the RNA that encodes STAT3 or [***] in the Field until [***]; and (B) on a country-by-country basis, commercializing an ASO that is designed to bind to the RNA that encodes STAT3 or [***] in the Field until [***];

(b) ***Reserved Targets***. The discovery, research or development of an ASO that is designed to bind to the RNA that encodes any of the Reserved Targets, from the date each such oncology gene target becomes a Reserved Target under Section 3.3.5 until the date such Reserved Target ceases to be a Reserved Target by operation of Section 3.3.6;

(c) ***Oncology Targets During the Option Period***. The discovery, research or development of an ASO that is designed to bind to the RNA that encodes any Oncology Target, from the date each Oncology Target is agreed to by the Parties until the earlier of the date (y) AstraZeneca exercises the applicable Option for such Oncology Target, or (z) such Option expires unexercised or is terminated; and

(d) ***Oncology Targets After Option Exercise***. The discovery, research or development of an ASO that is designed to bind to the RNA that encodes an Oncology Target in the Field for which AstraZeneca has exercised its Option in accordance with this Agreement, (A) with respect to discovery, research or development of an ASO that is designed to bind to the RNA that encodes such Oncology Target, until [***], and (B) on a country by country basis with respect to commercialization of an ASO that is designed to bind to the RNA that encodes such Oncology Target in the Field, until [***].

5.1.2. Isis Follow-On Products. Notwithstanding the provisions of Section 5.1.1, on a Gene Target-by-Gene Target basis, if (A) AstraZeneca does not ask Isis to identify a follow-on product for a Gene Target by [***], or (B) Isis identifies a follow-on product for a Gene Target at AstraZeneca's request, but thereafter AstraZeneca does not use Commercially Reasonable Efforts to continue to develop and commercialize such follow-on compound, then Isis (for itself or with or for a Third Party) will be permitted to (i) discover, research and develop an ASO designed to bind to the RNA that encodes such Gene Target that is not the Product being developed by AstraZeneca (an "***Isis Follow-On Product***"), and (ii) after [***] for a Product, commercialize an Isis Follow-On Product.

5.1.3. Limitations and Exceptions to Each Party's [***] Rights.

(a) **Exception and Limitations**. The Parties acknowledge and agree that, in addition to playing a role in cancer, the gene target, [***], is also known to potentially play a role outside of oncology (e.g., [***]), and therefore targeting [***] with an [***] ASO is a possible approach for the treatment of non-oncology diseases. In exchange for AstraZeneca's agreement to not develop or commercialize an ASO targeting [***] for [***] and to not develop or commercialize an [***] for [***], Isis has agreed to [***] ASOs outside of [***] that [***].

Therefore, with respect to [***], the Parties memorialize the foregoing general principles by hereby agreeing to the following specific restrictions and limitations:

(i) **AstraZeneca's [***] Field**.

(1) ***[***]***. AstraZeneca does not have the right under Section 6.1.2 (nor does AstraZeneca have a license under Section 6.1.2 of this Agreement) to research, develop, manufacture, have manufactured, register, market and/or commercialize any ASO that is designed to bind to the RNA that encodes [***], for the diagnosis, prevention and/or treatment of [***].

(2) ***[***] and Other Indications***. AstraZeneca has the right under Section 6.1.2 (and has a license under Section 6.1.2 of this Agreement) to research, develop, manufacture, have manufactured, register, market and/or commercialize, on its own or with a Third Party (including granting an option or a license to a Third Party to do so), any ASO that is designed to bind to the RNA that encodes [***] for the diagnosis, prevention and/or treatment of:

a. ***[***]***. Any [***] disease in humans or animals for any [***] indication using any [***] ([***]); and

b. ***All Other Indications***. Any indications other than [***] and [***], using any [***] other than [***],

(such field described in this Section 5.1.3(a)(i), the "***AstraZeneca [***]-Field***").

(ii) **Isis' [***] Field**. Isis has the right (including to grant an option or a license to a Third Party) to research, develop, manufacture, have manufactured, register, market and commercialize, on its own or with a Third Party (including granting an option or a license to a Third Party to do so), any ASO that has all of the following attributes:

(1) is for the diagnosis, prevention and/or treatment of any disease in humans or animals other than for [***];

(2) [***];

(3) [***]; and

(4) [***] (each such [***] Compound, an "[***] ***Lead Compound***").

Each such [***] ASO Isis is permitted to exploit is an "***Isis [***]-Field ASO***," and the field described in this Section 5.1.3(a)(ii) is the "***Isis [***]-Field***."

(b) **Other Limitations and Exceptions to Isis' Exclusivity Covenants**. Notwithstanding anything to the contrary in this Agreement, Isis' practice of the following will not violate Section 5.1.1 or Section 5.1.2:

(i) Performance of the Isis Conducted Activities;

(ii) Any activities permitted under the Prior Agreements as such agreements are in effect on the Effective Date and have been disclosed to AstraZeneca (and not as such Prior Agreements may be amended after the Effective Date); and

(iii) The granting of, or performance of obligations under, Permitted Licenses.

(c) **Other Limitations and Exceptions to AstraZeneca's Exclusivity Covenants**. Notwithstanding anything to the contrary in this Agreement, AstraZeneca's performance of the AstraZeneca Conducted Activities will not violate Section 5.1.1 or Section 5.1.2.

Nothing in this ARTICLE 5 will require AstraZeneca to make any explicit statements on the [***] Product label in order to comply with AstraZeneca's obligations in Section 5.1.3(a)(i).

5.2. **Effect of Exclusivity on Indications**. The Compounds are designed to bind to the RNA that encodes the Gene Targets in the Field, which are known to play a role in cancer. Isis and AstraZeneca are subject to exclusivity obligations under Section 5.1.1 and Section 5.1.2; *however*, the Parties acknowledge and agree that each Party (on its own or with a Third Party) may continue to discover, research, develop, manufacture and commercialize products that are designed to bind to the RNA that encodes a gene that is *not* a Gene Target (except, with respect to [***], Isis may do so with Isis [***]-Field ASOs) for any indication, even if such products are designed to treat cancer.

ARTICLE 6.
LICENSE GRANTS; TECHNOLOGY TRANSFER AND SUPPORT

6.1. **License Grants to AstraZeneca**.

6.1.1. **STAT3 Development and Commercialization License**. Subject to the terms and conditions of this Agreement, Isis hereby grants to AstraZeneca a worldwide, exclusive (including with regard to Isis and its Affiliates), royalty-bearing, sublicensable (in accordance with Section 6.1.4 below) license under the Licensed Technology to research, Develop, Manufacture, have Manufactured (in accordance with Section 6.1.4 below), register, market and Commercialize STAT3 Products in the Field.

6.1.2. **[***] Development and Commercialization License**. Subject to the terms and conditions of this Agreement (including the provisions of Section 5.1.3(a)(i)), Isis hereby grants to AstraZeneca a worldwide, exclusive (including with regard to Isis and its Affiliates), royalty-bearing, sublicensable (in accordance with Section 6.1.4 below) license under the Licensed Technology to research, Develop, Manufacture, have Manufactured (in accordance with Section 6.1.4 below), register, market and Commercialize [***] Products in the Field.

6.1.3. **Oncology Target Development and Commercialization Licenses**. On an Oncology Target-by-Oncology Target basis, subject to the terms and conditions of this Agreement, effective upon AstraZeneca's exercise of the Option for such Oncology Target in accordance with Section 3.5, Isis grants to AstraZeneca a worldwide, exclusive (including with regard to Isis and its Affiliates), royalty-bearing, sublicensable (in accordance with Section 6.1.4 below) license under the Licensed Technology to research, Develop, Manufacture, have Manufactured (in accordance with Section 6.1.4 below), register, market and Commercialize Oncology Products in the Field.

6.1.4. Sublicense Rights.

(a) **Right to Grant Sublicenses**. Subject to the terms and conditions of this Agreement, AstraZeneca will have the right to grant sublicenses through multiple tiers of sublicenses under the licenses granted under Section 6.1.1, Section 6.1.2 and Section 6.1.3 above:

(i) under the Isis Core Technology Patents, Isis Product-Specific Patents and Isis Know-How to an Affiliate of AstraZeneca or a Third Party; and

(ii) under the Isis Manufacturing and Analytical Patents and Isis Manufacturing and Analytical Know-How solely to (y) an Affiliate of AstraZeneca or (z) a Third Party with a valid license granted by Isis under the Isis Manufacturing and Analytical Patents and Isis Manufacturing and Analytical Know-How to manufacture Products in a manufacturing facility owned or operated by such Third Party (each, a "***Licensed CMO***");

provided that each such sublicense is for the continued development, manufacture and/or commercialization of a Product, and is subject to, and consistent with, the terms and conditions of this Agreement. AstraZeneca shall use reasonable efforts to ensure that all Persons to which it grants sublicenses comply with such terms and conditions.

(b) **Enforcing Sublicense Agreements**. If, within [***] days after first learning of any breach of such sublicense terms, AstraZeneca fails to take any action to enforce the sublicense terms of a sublicense granted pursuant to this Section 6.1.4, which failure, in Isis' good faith determination, could cause [***], AstraZeneca hereby grants Isis the right to enforce such sublicense terms on AstraZeneca's behalf and will cooperate with Isis (which cooperation will be at AstraZeneca's sole expense and will include, AstraZeneca joining any action before a court or administrative body filed by Isis against such Sublicensee if and to the extent necessary for Isis to have legal standing before such court or administrative body) in connection with enforcing such terms. AstraZeneca will provide Isis with written notice of any sublicense granted pursuant to this Section 6.1.4 that grants a Third Party rights to commercialize or manufacture a Product, within 30 days after the execution thereof, and if requested by Isis, a true and complete copy of any such sublicense or any sublicense that is the subject of a breach of terms sublicensed under this Agreement within 10 days of Isis' request, subject to AstraZeneca being entitled to make appropriate redaction for commercially sensitive information provided it is not relevant to enforcement or is not reasonably necessary for Isis to determine AstraZeneca's compliance with the terms of this Agreement.

(c) **Requests to Grant Sublicenses to CMOs**. In addition, if AstraZeneca provides Isis with a written request that Isis grant a license under the Isis Manufacturing and Analytical Patents and Isis Manufacturing and Analytical Know-How to a CMO designated by AstraZeneca that is not a Licensed CMO, solely for such CMO to manufacture Products for AstraZeneca, its Affiliate or Sublicensee in a manufacturing facility owned or operated by such CMO, Isis will offer to grant such a license to such CMO on terms that are substantially similar to the terms Isis has previously agreed to with its Licensed CMOs.

(d) **Effect of Termination on Sublicenses**. If this Agreement terminates for any reason, any Sublicensee will, from the effective date of such termination, automatically become a direct licensee of Isis with respect to the rights sublicensed to the Sublicensee by AstraZeneca; *so long as* (i) such Sublicensee is not in breach of its sublicense agreement, (ii) such Sublicensee agrees in writing to comply with all of the terms of this Agreement to the extent applicable to the rights originally sublicensed to it by AstraZeneca, and (iii) such Sublicensee agrees to pay directly to Isis such Sublicensee's payments under this Agreement to the extent applicable to the rights sublicensed to it by AstraZeneca. AstraZeneca agrees that it will confirm clause (i) of the foregoing in writing at the request and for the benefit of Isis and if requested, the Sublicensee.

(e) **Master Services Agreements and Material Transfer Agreements**. This Section 6.1.4 is not intended to require AstraZeneca to amend the standard terms and conditions of a master services agreement with a Third Party in place as of the Effective Date to conduct preclinical and/or clinical research and development on AstraZeneca's behalf, or material transfer agreements with academic collaborators or non-profit institutions, entered into after the Effective Date by AstraZeneca in connection with the Licensed Technology. However, after the Effective Date such agreements shall be subject to the approval of Isis for so long as Isis had decision making authority on the JSC, such approval not to be unreasonably withheld or delayed.

6.1.5. **Consequence of Natural Expiration of this Agreement**. On a Product-by-Product basis, if with respect to a particular Product this Agreement expires (i.e., is not terminated early) in a particular country in accordance with Section 12.1 then, in addition to the terms set forth in Section 12.3.1(c), Section 12.3.1(e), Section 12.3.1(f) and Section 12.3.1(g), Isis will and hereby does grant to AstraZeneca a perpetual, nonexclusive, worldwide, royalty-free, fully paid-up, sublicensable license under the Licensed Know-How to Manufacture, Develop and Commercialize the Product that is the subject of such expiration in such country.

6.1.6. **No Implied Licenses**. All rights in and to Licensed Technology not expressly licensed to AstraZeneca under this Agreement are hereby retained by Isis or its Affiliates. All rights in and to AstraZeneca Technology not expressly licensed or assigned to Isis under this Agreement, are hereby retained by AstraZeneca or its Affiliates. Except as expressly provided in this Agreement, no Party will be deemed by estoppel or implication to have granted the other Party any license or other right with respect to any intellectual property.

6.1.7. **License Conditions; Limitations**. Subject to Section 8.9, the licenses granted under Section 6.1.1, Section 6.1.2 and Section 6.1.3 and the sublicense rights under Section 6.1.4 are subject to and limited by (i) any applicable Target Encumbrances, (ii) in respect of the licenses granted under Section 6.1.1 and Section 6.1.2, the Prior Agreements as such agreements are in effect on the Effective Date and have been disclosed to AstraZeneca (and not as such Prior Agreement may be amended after the Effective Date), (iii) the Isis In-License Agreements as such agreements are in effect on the Effective Date (and not as such Isis In-License Agreements may be amended after the Effective Date); and (iv) the granting of, or performance of obligations under, Permitted Licenses.

6.1.8. **Trademarks for Products**. To the extent that (i) Isis owns any trademark(s) specific to a Product licensed under Section 6.1.1, Section 6.1.2 or Section 6.1.3, and (ii) AstraZeneca reasonably believes such trademark(s) are necessary or useful for such Product, then upon AstraZeneca's request and at AstraZeneca's sole cost and expense, Isis will assign its rights and title to such trademark(s) to AstraZeneca sufficiently in advance of the First Commercial Sale of a Product. Other than any such trademarks, AstraZeneca is solely responsible for all trademarks, trade dress, logos, slogans, designs, copyrights and domain names used on or in connection with Products licensed under Section 6.1.1, Section 6.1.2 or Section 6.1.3.

6.1.9. **[***]**

6.2. **License Grant to Conduct the Isis and AstraZeneca Conducted Activities**.

6.2.1 As of the Effective Date, AstraZeneca hereby grants to Isis a worldwide, co-exclusive, royalty-free, fully paid up, license (with the right to sublicense to Third Parties solely to perform the Isis Conducted Activities) under the (i) Licensed Technology licensed to AstraZeneca under Section 6.1.1 and Section 6.1.2, and (ii) the AstraZeneca Technology, in each case for the sole purpose of Isis performing the Isis Conducted Activities under this Agreement.

6.2.2 On an Oncology Target-by-Oncology Target basis, as of the Effective Date and until the Option Deadline, Isis hereby grants to AstraZeneca a worldwide, non-exclusive, royalty-free, license (with the right to sublicense to Third Parties solely to perform the AstraZeneca Conducted Activities) under the Licensed Technology for the sole purpose of AstraZeneca performing the AstraZeneca Conducted Activities under this Agreement.

6.3. **Assignment of Isis Product-Specific Patents; Grant Back to Isis**.

6.3.1. On a Gene Target-by-Gene Target basis, with respect to any Gene Target for which AstraZeneca has an exclusive license under Section 6.1.1, Section 6.1.2 and Section 6.1.3, at AstraZeneca's request at any time after completion of the first Phase 2 Trial for the applicable Product, after discussion at the JPC, Isis will assign to AstraZeneca, Isis' ownership interest in:

(a) with respect to STAT3 Products or Oncology Products (as the case may be), all Isis Product-Specific Patents within the Licensed Patents that are owned by Isis (whether solely owned or jointly owned with one or more Third Parties); and

(b) with respect to [***] Products, all Assignable [***] Product-Specific Patents within the Licensed Patents that are owned by Isis (whether solely owned or jointly owned with one or more Third Parties).

6.3.2. AstraZeneca grants to Isis a worldwide, exclusive, sublicensable license under any Patent Rights assigned to AstraZeneca under Section 6.3.1 (i) for all purposes outside of the Field (except to license or Commercialize a compound from the STAT3, [***] or Oncology Product Specific Patents that specifically claim the STAT3 Product, [***] Product or Oncology Product being Developed and Commercialized by AstraZeneca), and (ii) to research, Develop, Manufacture, have Manufactured, register, market and Commercialize Isis Follow-On Products in accordance with Section 5.1.2, in each case to the extent permitted by this Agreement.

6.4. **Subcontracting**. Subject to the terms of this Section 6.4, each Party will have the right to engage Third-Party subcontractors to perform certain of its obligations under this Agreement. Any subcontractor to be engaged by a Party to perform a Party's obligations set forth in this Agreement will meet the qualifications typically required by such Party for the performance of work similar in scope and complexity to the subcontracted activity and will enter into such Party's standard nondisclosure agreement consistent with such Party's standard practices. Any Party engaging a subcontractor hereunder will remain responsible and obligated for such activities and will not grant rights to such subcontractor that interfere with the rights of the other Party under this Agreement.

6.5. **Technology Transfer**. After (i) the Effective Date, in the case of the Licensed Know-How licensed to AstraZeneca under Section 6.1.1 and Section 6.1.2, or (ii) on an Oncology Target-by-Oncology Target basis, the date the license under Section 6.1.3 is granted to AstraZeneca for such Oncology Target, Isis will deliver to AstraZeneca the following Licensed Know-How pursuant to a technology transfer plan to be mutually agreed by Isis and AstraZeneca:

6.5.1. **Licensed Know-How - Generally**. Copies of Licensed Know-How (other than the Isis Manufacturing and Analytical Know-How) in the Field in Isis' possession that has not previously been provided hereunder, for use solely in accordance with the licenses granted under Section 6.1.1, Section 6.1.2 or Section 6.1.3, as the case may be, to AstraZeneca together with all regulatory documentation (including drafts) related to each Product (except that the [***]). To assist with the transfer of such Licensed Know-How, Isis will make its personnel reasonably available to AstraZeneca during normal business hours for up to [***] ([***]) of Isis' time to transfer such Licensed Know-How under this Section 6.5.1. Thereafter, if requested by AstraZeneca, Isis will provide AstraZeneca with a reasonable level of assistance in connection with such transfer, which AstraZeneca will reimburse Isis for its time incurred in providing such assistance at the FTE rate, and any of Isis' reasonable travel expenses for travel requested by AstraZeneca, and any outside consultants' costs and consultants' reasonable travel expenses incurred by Isis agreed in advance by AstraZeneca.

6.5.2. **Isis Manufacturing and Analytical Know-How**. Solely for use by AstraZeneca, its Affiliates or a Third Party acting on AstraZeneca's behalf to Manufacture API in AstraZeneca's own or an Affiliate's manufacturing facility, copies of the Isis Manufacturing and Analytical Know-How relating to Products in Isis' possession that has not previously been provided hereunder, which is necessary for the exercise by AstraZeneca, its Affiliates or a Third Party of the Manufacturing rights granted under Section 6.1.1, Section 6.1.2 or Section 6.1.3, as the case may be. AstraZeneca will reimburse Isis for its time incurred in performing such technology transfer at the FTE rate, and any of Isis' reasonable travel expenses for travel requested by AstraZeneca, and any of its outside consultants' costs and consultants' reasonable travel expenses incurred by Isis agreed in advance by AstraZeneca.

ARTICLE 7.
DEVELOPMENT, MANUFACTURING AND COMMERCIALIZATION

7.1. **AstraZeneca Diligence**. Commencing on (i) the Effective Date, with respect to STAT3 Products and [***] Products licensed to AstraZeneca under Section 6.1.1 and Section 6.1.2, and (ii) on an Oncology Target-by-Oncology Target and Product-by-Product basis, the date Isis grants AstraZeneca the license under Section 6.1.3 related to such Oncology Target, except for the Isis Conducted Activities that do not involve Additional Plan Costs, AstraZeneca is solely responsible for all Development, Manufacturing and Commercialization activities, and for all costs and expenses associated therewith, with respect to the Development, Manufacture and Commercialization of Products.

7.1.1. **Integrated Development Plans**. AstraZeneca will prepare a Development and global integrated Product plan outlining key aspects of the Development of each Product licensed by AstraZeneca under Section 6.1.1, Section 6.1.2 and Section 6.1.3 through Approval as well as key aspects of worldwide regulatory strategy, market launch, and Commercialization (each plan, an "***Integrated Development Plan***" or "***IDP***"). On a Product-by-Product basis, for each Product licensed by AstraZeneca under Section 6.1.1, Section 6.1.2 or Section 6.1.3, as the case may be, AstraZeneca will prepare the IDP no later than [***] for such Product, and the IDP will contain information consistent with AstraZeneca's Development and Commercialization plans for its similar products at similar stages of development. Once AstraZeneca has prepared such plans, AstraZeneca will update the IDP consistent with AstraZeneca's standard practice and provide such updates to Isis Annually. AstraZeneca and Isis will meet on a yearly basis to discuss the draft of the IDP and AstraZeneca will consider, in good faith, any proposals and comments made by Isis for incorporation in the final IDP. Notwithstanding the foregoing, on a Gene Target-by-Gene Target basis, AstraZeneca's obligations to provide Isis with information or reports under this Section 7.1.1 will terminate if Isis independently or for or with an Affiliate or Third Party engages in any activity to discover, research or develop an ASO designed to bind to the RNA that encodes such Gene Target in the Field other than in the course of performing its obligations under, or to the extent permitted by, this Agreement.

7.1.2. **Investigator's Brochure**. Within 30 days after the Effective Date, Isis will provide to AstraZeneca the then current version of the Investigator's Brochure for ISIS-STAT3$_{Rx}$. AstraZeneca will keep Isis reasonably informed with respect to the status, activities and progress of Development of Products licensed by AstraZeneca hereunder by providing updated versions of the Investigator's Brochure to Isis Annually and when Development of the Products results in any substantive change to the safety or risk to the Products. On a Product-by-Product basis, AstraZeneca's obligations under this Section 7.1.2 will terminate if Isis independently or for or with an Affiliate or Third Party engages in any activity to discover, research or develop an ASO designed to bind to the RNA that encodes the Gene Target targeted by such Product in the Field other than in the course of performing its obligations under, or to the extent permitted by, this Agreement.

7.1.3. **Participation in Regulatory Meetings**. Each Party will provide the other Party with as much advance written notice as practicable of any meetings such Party has or plans to have with a Regulatory Authority regarding pre-approval or Approval matters for a Product (or, in the case of Isis as the invitee, that relate to Isis' antisense oligonucleotide platform), and will allow one representative of the invited Party to participate (as an observer) in any such meeting that is [***] (e.g., meetings regarding [***]) The costs associated with such observer attendance will be met by the invitee Party, except if Isis' presence has been specifically requested by AstraZeneca, in which case AstraZeneca will reimburse Isis for its time incurred in attending at the FTE Rate. To the extent that AstraZeneca has not fully used the [***] available to it pursuant to Section 6.5.1 or Section 7.1.5, then AstraZeneca shall be entitled to allocate such [***] to the activities to be performed by Isis pursuant to this Section 7.1.3.

7.1.4. **Regulatory Communications**. Each Party will provide the other Party with copies of documents and communications submitted to (including such drafts as the providing Party considers reasonably practicable but to include at least one pre finalization draft thereof) and received from Regulatory Authorities that materially impact the Development or Commercialization of Products for the other Party's review and comment, and the submitting Party will consider in good faith including any comments provided by the reviewing Party to such documents and communications.

7.1.5. **Assistance with Regulatory Filings**. On a Gene Target-by-Gene Target basis, following Lead Candidate designation for an applicable Gene Target, upon AstraZeneca's written request, Isis will assist AstraZeneca in preparing regulatory filings for the Products (including INDs and other regulatory filings for which AstraZeneca is the sponsor) and, except with respect to regulatory filing-related activities outlined in Section 7.1.3 and Section 7.1.4, such regulatory filings assistance will be [***]. Thereafter, upon AstraZeneca's written request, Isis will assist AstraZeneca in preparing regulatory filings for the Products at the FTE Rate, and any of Isis' reasonable travel expenses for travel requested by AstraZeneca, and any of its outside consultants' costs and consultants' reasonable travel expenses incurred by Isis agreed in advance by AstraZeneca. An estimate of such costs and expenses will be provided to AstraZeneca before initiation of agreed work.

7.1.6. **Class Generic Claims**. To the extent AstraZeneca intends to make any claims in a Product label or regulatory filing that are class generic to ASOs or Isis' generation 2.0 or 2.5 chemistry platform(s), AstraZeneca will provide such claims and regulatory filings to Isis in advance and will consider in good faith any proposals and comments made by Isis.

7.1.7. **Applicable Laws**. AstraZeneca will perform its activities pursuant to this Agreement in compliance with good laboratory and clinical practices and cGMP, in each case as applicable under the laws and regulations of the country and the state and local government wherein such activities are conducted.

7.2. Isis' Antisense Safety Database.

7.2.1. Isis maintains an internal database that includes information regarding the tolerability of its drug compounds, individually and as a class, including information discovered during pre-clinical and clinical development (the "***Isis Internal ASO Safety Database***"). In an effort to maximize understanding of the safety profile and pharmacokinetics of Isis compounds, AstraZeneca will cooperate in connection with populating the Isis Internal ASO Safety Database. To the extent collected by AstraZeneca and in the form in which AstraZeneca uses/stores such information for its own purposes, AstraZeneca will provide Isis with information concerning toxicology, pharmacokinetics, safety pharmacology study(ies), serious adverse events and other safety information related to Products licensed by AstraZeneca under this Agreement as soon as practicable following the date such information is available to AstraZeneca (but not later than 30 days after AstraZeneca's receipt of such information). In connection with any reported serious adverse event, AstraZeneca will provide Isis all serious adverse event reports, including initial, interim, follow-up, amended, and final reports. In addition, with respect to Products, AstraZeneca will provide Isis with copies of Annual safety updates filed with each IND and the safety sections of any final Clinical Study reports within 30 days following the date such information is filed or is available to AstraZeneca, as applicable. Furthermore, AstraZeneca will promptly provide Isis with any supporting data and answer any follow-up questions reasonably requested by Isis. All such information disclosed by AstraZeneca to Isis will be AstraZeneca Confidential Information; *provided*, *however*, that so long as Isis does not disclose the identity of a Product or AstraZeneca's identity, Isis may disclose any such AstraZeneca Confidential Information to (i) Isis' other partners pursuant to Section 7.2.2 below if such information is regarding class generic properties of ASOs, or (ii) any Third Party. AstraZeneca will deliver all such information to Isis for the Isis Internal ASO Safety Database to Isis Pharmaceuticals, Inc., 2855 Gazelle Court, Carlsbad, California 92010, Attention: Chief Medical Officer (or to such other address/contact designated in writing by Isis). AstraZeneca will also cause its Affiliates and Sublicensees to comply with this Section 7.2.1.

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

7.3 **Pharmacovigilance; ISIS-STAT3 Rx Safety Reporting**.

7.3.1 The Parties acknowledge that until [***] Isis will remain the holder of the original IND for ISIS-STAT3$_{Rx}$ (although this does not preclude AstraZeneca opening its own US IND for ISIS-STAT3$_{Rx}$ during that period) and that because AstraZeneca will conduct a Clinical Study in [***] in accordance with the STAT3 Research and Development Plan during such period, it is important that Isis and AstraZeneca coordinate their respective ISIS-STAT3$_{Rx}$ clinical trial and pre-clinical activities, including the collection and reporting of adverse events involving ISIS-STAT3$_{Rx}$. Within [***] days after the Effective Date, the Parties will develop and agree in writing on a Drug Safety Information Agreement that will include safety data delivery procedures governing the collection, investigation, reporting, and delivery of information from AstraZeneca to Isis concerning any adverse experiences, and any product quality and product complaints involving adverse experiences related to ISIS-STAT3$_{Rx}$, sufficient to enable Isis to comply with its legal and regulatory obligations and internal processes and consistent with the terms of this Agreement. Upon transfer of Isis' ISIS-STAT3$_{Rx}$ IND to AstraZeneca and assumption by AstraZeneca of regulatory responsibilities under the IND, AstraZeneca will assume responsibility for the global safety database related to ISIS-STAT3$_{Rx}$, and will be solely responsible for reporting to Regulatory Authorities in accordance with the Applicable Law for expeditable adverse events and for periodic safety reporting relating to the safety of ISIS-STAT3$_{Rx}$ and will furnish copies of such reports to Isis. The Drug Safety Information Agreement will be revised following the closure of Isis' IND.

7.3.2 Within [***] after the Effective Date with respect to the STAT3 Program, and prior to the [***] with respect to each of the other Collaboration Programs, the Parties shall enter into a mutually agreed pharmacovigilance agreement (the "***Pharmacovigilance Agreement***"). The Parties shall comply with the provisions of such agreement. If there is any inconsistency between this Agreement and the Pharmacovigilance Agreement as it relates to Product safety, the terms of the Pharmacovigilance Agreement will prevail to the extent of such inconsistency.

ARTICLE 8.
FINANCIAL PROVISIONS

8.1. **STAT3 and [***] License Fee; Oncology Target Option Fees**. Within 30 days following the Effective Date, AstraZeneca will pay Isis an up-front fee of $25,000,000, allocated as follows:

(i) $[***] in partial consideration for the licenses granted by Isis to AstraZeneca under Section 6.1.1 for STAT3 Products;

(ii) $[***] in partial consideration for the licenses granted by Isis to AstraZeneca under Section 6.1.2 for [***] Products; and

(iii) An initial payment of $[***] in partial consideration for the Options granted by Isis to AstraZeneca under Section 3.5 for each Oncology Target.

8.2. **Oncology Target License Fees**. On an Option-by-Option basis, following AstraZeneca's written notice to Isis stating that AstraZeneca is exercising such Option in accordance with this Agreement, AstraZeneca will pay Isis a license fee of $[***] within 30 days after AstraZeneca's receipt from Isis of an invoice for such license fee (for a total of $[***] if AstraZeneca exercises all three of its Options hereunder or, a total of $[***] if a fourth Oncology Collaboration Program is added under Section 2.2.4 (for a total of four Options) and AstraZeneca exercises all four of its Options hereunder).

8.3. **Remaining Payment for the Options to the Oncology Targets**. In partial consideration for the Options granted by Isis to AstraZeneca under Section 3.5 for each Oncology Target, within [***] days following the Effective Date, AstraZeneca shall notify Isis whether it wishes to continue with the Oncology Collaboration, and if it does will pay Isis $6,000,000 within 30 days after AstraZeneca's receipt from Isis of an invoice from Isis for such amount. For the avoidance of doubt, only one payment of $6,000,000 is payable under this Section 8.3. If AstraZeneca either (i) does not notify Isis in writing within [***] days following the Effective Date that it wishes to proceed with the Oncology Collaboration, or (ii) notifies Isis in writing that AstraZeneca is not proceeding, then all of the Options will expire and the remaining payment of $6,000,000 under this Section 8.3 shall not be payable.

8.4. **Milestone Payments for Achievement of Milestone Events by a STAT3 Product**. If there is a High Response Outcome in the Phase 1/2 Trial and the license granted by Isis to AstraZeneca under Section 6.1.1 is not terminated under Section 1.2.3(f)(i) above, then, in accordance with Section 8.7.5, AstraZeneca will pay to Isis the milestone payments as set forth in Column 1 of TABLE 1 below when a milestone event listed in TABLE 1 is first achieved by a STAT3 Product. If there is a Medium Response Outcome (or a Low Response Outcome) in the Phase 1/2 Trial and the license granted by Isis to AstraZeneca under Section 6.1.1 is not terminated under Section 1.2.3(f)(i) above, then, in accordance with Section 8.7.5 and subject to the terms of Section 1.2.3(h), AstraZeneca will pay to Isis the milestone payments as set forth in Column 2 of TABLE 1 below when a milestone event listed in TABLE 1 is first achieved by a STAT3 Product:

TABLE 1

STAT3 Product Milestone Event	**Column 1** **STAT3 Product Milestone Event Payment for High Response Outcome**	**Column 2** **STAT3 Product Milestone Event Payment for Medium Response Outcome or Low Response Outcome**
[***]	$[***]	$[***]
[***]	$[***]	$[***]
[***]	$[***]	$[***]
[***]	$[***]	$[***]
[***]	$[***]	$[***]
[***]	$[***]	$[***]
[***]	$[***]	$[***]
[***]	$[***]	$[***]
[***]	$[***]	$[***]
[***]	$[***]	$[***]
[***]	$[***]	$[***]
[***]	$[***]	$[***]

8.5. **Milestone Payments for Achievement of Milestone Events by an [***] Product**. In accordance with Section 8.7.5, AstraZeneca will pay to Isis the milestone payments as set forth in TABLE 2 below when a milestone event listed in TABLE 2 is first achieved by an [***] Product:

TABLE 2

[***] Product Milestone Event	**[***] Product Milestone Event Payment**
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]

8.6. **Milestone Payments for Achievement of Milestone Events by an Oncology Product**. On an Oncology Target-by-Oncology Target basis, in accordance with Section 8.7.5, AstraZeneca will pay to Isis the milestone payments as set forth in TABLE 3 below when a milestone event listed in TABLE 3 is first achieved by an Oncology Product targeting such Oncology Target:

TABLE 3	
Oncology Product Milestone Event	**Oncology Product Milestone Event Payment**
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]

8.7. **Limitations on Milestone Payments; Exceptions; Notice**.

8.7.1. Each milestone payment set forth in TABLE 1 and TABLE 2 above will be paid only once upon the first achievement of the milestone event regardless of how many Products achieve such milestone event.

8.7.2. Each milestone payment set forth in TABLE 3 above will be paid only once per each Oncology Target upon the first achievement of the milestone event regardless of how many Products for such Oncology Target achieve such milestone event.

8.7.3. If a particular milestone event is not achieved because Development or Commercial activities transpired such that achievement of such earlier milestone event was unnecessary or did not otherwise occur, then upon achievement of a later milestone event the milestone event payment applicable to such earlier milestone event will also be due. For example, if a Party proceeds directly to [***] without achieving the [***] then upon achieving the [***] milestone event, both the [***] and [***] milestone event payments are due. Similarly, if a Party proceeds directly to [***] without achieving the [***] then upon achieving the [***] milestone event, both the [***] and [***] milestone event payments are due.

8.7.4. In addition, if a particular milestone event is achieved contemporaneously or in connection with another milestone event, then upon achievement of one such milestone event the other milestone event will also be deemed achieved and the milestone payments for both milestone events are due. For example, if AstraZeneca achieves the [***] milestone event and the [***] ([***]) that was the subject of such milestone event [***], then both the [***] and the [***] milestone event payments are due. Similarly, if AstraZeneca achieves the [***] milestone event and the [***] ([***]) that was the subject of such milestone event [***], then both the [***] and the [***] milestone event payments are due.

8.7.5. Each time a milestone event is achieved under this ARTICLE 8, AstraZeneca will send Isis, or Isis will send AstraZeneca, as the case may be, a written notice thereof promptly (but no later than five Business Days) following the date of achievement of such milestone event. Thereafter, Isis will promptly invoice AstraZeneca for the achievement of any milestone event under this ARTICLE 8 and such milestone payment will be due within 30 days after AstraZeneca's receipt of such invoice.

8.8. Royalty Payments to Isis.

8.8.1. **AstraZeneca Full Royalty**. As partial consideration for the rights granted to AstraZeneca hereunder, subject to the provisions of this Section 8.8.1 and Section 8.8.2, AstraZeneca will pay to Isis royalties on Annual worldwide Net Sales of Products sold by AstraZeneca, its Affiliates or Sublicensees, on a country-by-country and Product-by-Product basis, in each case in the amounts as follows in TABLE 4 below (the "***AstraZeneca Full Royalty***"):

TABLE 4			
Royalty Tier	**Annual Worldwide Net Sales of STAT3 Products**	**High Response Outcome Royalty Rate**	**Medium Response Outcome/Low Response Outcome Royalty Rate**
1	For the portion of Annual Worldwide Net Sales < $[***]	[***]%	[***]%
2	For the portion of Annual Worldwide Net Sales ≥ $[***] but < $[***]	[***]%	[***]%
3	For the portion of Annual Worldwide Net Sales ≥ $[***] but < $[***]	[***]%	[***]%
4	For the portion of Annual Worldwide Net Sales ≥ $[***]	[***]%	[***]%

Royalty Tier	**Annual Worldwide Net Sales of [***] Products**	**Royalty Rate**
1	For the portion of Annual Worldwide Net Sales < $[***]	[***]%
2	For the portion of Annual Worldwide Net Sales ≥ $[***] but < $[***]	[***]%
3	For the portion of Annual Worldwide Net Sales ≥ $[***]	[***]%

Royalty Tier	**Annual Worldwide Net Sales of Oncology Products**	**Royalty Rate**
1	For the portion of Annual Worldwide Net Sales < $[***]	[***]%
2	For the portion of Annual Worldwide Net Sales ≥ $[***] but < $[***]	[***]%
3	For the portion of Annual Worldwide Net Sales ≥ $[***] but < $[***]	[***]%
4	For the portion of Annual Worldwide Net Sales ≥ $[***]	[***]%

Annual worldwide Net Sales will be calculated by taking the aggregate sum of Net Sales of Products for all countries worldwide.

(a) AstraZeneca will pay Isis royalties on Net Sales of Products arising from named patient and other similar programs under Applicable Laws, and AstraZeneca will provide reports and payments to Isis consistent with Section 8.10. No royalties are due on Net Sales of Products arising from compassionate use and other programs providing for the delivery of Product at no cost. The sales of Products arising from named patient, compassionate use, or other similar programs will not be considered a First Commercial Sale for purposes of calculating the Royalty Period.

(b) For purposes of clarification, any Isis Product-Specific Patents assigned to AstraZeneca as set forth in Section 6.3.1 will still be considered Isis Product-Specific Patents for determining the royalty term and applicable royalty rates under this ARTICLE 8.

8.8.2. **Application of Royalty Rates**. All royalties set forth under Section 8.8.1 are subject to the provisions of this Section 8.8.2, and are payable as follows:

(a) **Royalty Period**. AstraZeneca's obligation to pay Isis the AstraZeneca Full Royalty above with respect to a Product will continue on a country-by-country and Product-by-Product basis from the date of First Commercial Sale of such Product until the later of the date of expiration of (i) the last Valid Claim within the Licensed Patents Covering such Product in the country in which such Product is made, used or sold, (ii) the data exclusivity period conferred by the applicable Regulatory Authority in such country with respect to such Product (e.g., such as in the case of an orphan drug), and (iii) the [***] ([***]) anniversary of the First Commercial Sale of such Product in such country (such royalty period, the "***Royalty Period***").

(b) **Limitation on Aggregate Reduction for AstraZeneca Royalties**. In no event will the aggregate royalty offsets under Section 8.9.2(a)(i) and Section 8.9.4(b) reduce the royalties payable to Isis on Net Sales of a Product in any given period to an amount that is less than the greater of [***].

(c) **End of Royalty Obligation**. On a country-by-country and Product-by-Product basis, other than [***], AstraZeneca's obligation to make royalty payments hereunder in such country will end on the expiration of the Royalty Period in such country.

8.9. Third Party Payment Obligations.

8.9.1. Existing In-License Agreements.

(a) ***Isis' Existing In-License Agreements***. Certain of the Licensed Technology Controlled by Isis as of the Effective Date licensed to AstraZeneca under Section 6.1.1 and Section 6.1.2 or that may be licensed to AstraZeneca under Section 6.1.3, as the case may be, are in-licensed or were acquired by Isis under the agreements with Third Party licensors or sellers listed in APPENDIX 6 (such license or purchase agreements being the "***Isis In-License Agreements***"), and certain milestone or royalty payments and license maintenance fees may become payable by Isis to such Third Parties under the Isis In-License Agreements based on the Development or Commercialization of a Product by AstraZeneca, its Affiliate or Sublicensee under this Agreement. Any payment obligations arising under the Isis In-License Agreements:

(i) as they apply to STAT3 Products or [***] Products, will be paid by [***] as [***], and

(ii) as they apply to Isis Product Specific Patents licensed in connection with the applicable Oncology Product after Option exercise, will be paid by [***] as [***], and

(iii) in connection with the applicable Oncology Product as they apply to Isis Core Technology Patents and Isis Manufacturing and Analytical Know-How and Isis Manufacturing and Analytical Patents will be paid by [***] as [***].

(b) ***AstraZeneca's Existing In-License Agreements***. AstraZeneca will be solely responsible for any Third Party Obligations that become payable by AstraZeneca to Third Parties under any agreements or arrangements AstraZeneca has with such Third Parties as of the Effective Date, based on the Development or Commercialization of a Product by AstraZeneca, its Affiliate or Sublicensee under this Agreement. Any such payment obligations will be paid by AstraZeneca as AstraZeneca Supported Pass-Through Costs under this Agreement.

8.9.2. New In-Licensed Additional Product-Specific Patents.

(a) Additional STAT3/[***] Product-Specific Patents.

(i) AstraZeneca or Isis, as the case may be, will promptly provide the other Party written notice of any additional Third Party Patent Rights necessary to practice an Isis Product-Specific Patent to Commercialize a STAT3 Product or [***] Product ("***Additional STAT3/[***] Product-Specific Patents***") it believes it has identified and AstraZeneca will have the first right, but not the obligation, to negotiate with, and obtain a license from the Third Party Controlling such Additional STAT3/[***] Product-Specific Patents. If AstraZeneca obtains any such Additional STAT3/[***] Product-Specific Patents then, subject to Section 8.8.2(b), AstraZeneca may offset an amount equal to [***]% of any [***] paid by AstraZeneca to such Third Party with respect to such Product against any [***]. [***].

(ii) If, however, AstraZeneca elects not to obtain such a license to such Additional STAT3/[***] Product-Specific Patents, AstraZeneca will so notify Isis, and Isis may obtain such a license to such Additional STAT3/[***] Product-Specific Patents and will include such Additional STAT3/[***] Product-Specific Patents in the license granted to AstraZeneca under Section 6.1.1 or Section 6.1.2 (as applicable) if AstraZeneca agrees in writing to pay Isis as AstraZeneca Supported Pass-Through Costs any and all costs arising under such Third Party agreement as they apply to STAT3 Products or [***] Products.

(b) **Additional Oncology Collaboration Product-Specific Patents**.

(i) **Prior to Option Exercise**. If, after an Oncology Target is selected but prior to Option exercise for a particular Oncology Target, Isis obtains Third Party Patent Rights necessary to Commercialize an Oncology Product where such Patent Right would have satisfied the definition of an Isis Product-Specific Patent had Isis Controlled such Patent Rights on the Effective Date, then to the extent Controlled by Isis, Isis will include such Third Party Patent Rights in the license to be granted to AstraZeneca under Section 6.1.3 if AstraZeneca agrees in writing to pay Isis as AstraZeneca Supported Pass-Through Costs any and all costs arising under such Third Party agreement as they apply to such Oncology Products.

(ii) **After Option Exercise**.

(1) On an Oncology Target-by-Oncology Target basis, after Option exercise, AstraZeneca or Isis, as the case may be, will promptly provide the other Party written notice of any additional Third Party Patent Rights necessary to practice an Isis Product-Specific Patent to Commercialize an Oncology Product ("***Additional Oncology Product-Specific Patents***") it believes it has identified and AstraZeneca will have the first right, but not the obligation, to negotiate with, and obtain a license from the Third Party Controlling such Additional Oncology Product-Specific Patents. If AstraZeneca obtains any such Additional Oncology Product-Specific Patents then any and all Third Party Obligations arising under such Third Party agreement will be paid by AstraZeneca as AstraZeneca Supported Pass-Through Costs.

(2) If, however, AstraZeneca elects not to obtain such a license to such Additional Oncology Product-Specific Patents, AstraZeneca will so notify Isis, and Isis may obtain such a license to such Additional Oncology Product-Specific Patents and will include such Additional Oncology Product-Specific Patents in the license granted to AstraZeneca under Section 6.1.3 if AstraZeneca agrees in writing to pay Isis as AstraZeneca Supported Pass-Through Costs any and all costs arising under such Third Party agreement as they apply to such Oncology Products.

8.9.3. **Additional Core IP In-License Agreements**. Isis will negotiate with, and use Commercially Reasonable Efforts to obtain a license from, any Third Party controlling intellectual property that is necessary to practice an Isis Core Technology Patent to Commercialize a Product ("***Additional Core IP***"). For clarity, Additional Core IP does not include any Patent Rights claiming (or intellectual property related to) specific drug compositions, sequences, therapeutic methods, formulation or delivery technology, manufacturing or analytical methods, or other active ingredients. If Isis obtains such a Third Party license, Isis will include such Additional Core IP in the license granted to AstraZeneca under Section 6.1.1, Section 6.1.2 or Section 6.1.3 (as the case may be), and any financial obligations under such Third Party agreement will be paid solely by [***] as [***].

8.9.4. **Disputes Regarding Additional STAT3/[***] Product-Specific Patents and Additional Core IP**.

(a) If Isis does not agree that certain intellectual property identified by AstraZeneca pursuant to Section 8.9.2(a) is an Additional STAT3/[***] Product-Specific Patent, or if AstraZeneca does not agree that a license is not necessary to practice an Isis Core Technology Patent to Commercialize a Product as provided in Section 8.9.3, Isis or AstraZeneca, as applicable will send written notice to such effect to the other Party, and the Parties will engage a mutually agreed upon independent Third Party intellectual property lawyer with expertise in the patenting of ASOs, and appropriate professional credentials in the relevant jurisdiction, to determine the question of whether or not such Third Party intellectual property is an Additional STAT3/[***] Product-Specific Patent or whether a license is necessary to practice an Isis Core Technology Patent to Commercialize a Product. The determination of the Third Party expert engaged under the preceding sentence will be binding on the Parties solely for purposes of determining whether [***]. The costs of any Third Party expert engaged under this Section 8.9.4 will be paid by the Party against whose position the Third Party lawyer's determination is made.

(b) Notwithstanding the determination of the Third Party lawyer under Section 8.9.4(a), if a Third Party Controlling an Additional STAT3/[***] Product-Specific Patent is awarded a judgment from a court of competent jurisdiction arising from its claim against AstraZeneca asserting that [***], AstraZeneca will be permitted to [***].

8.10. Payments.

8.10.1. Commencement. Beginning with the Calendar Quarter in which the First Commercial Sale for a Product is made and for each Calendar Quarter thereafter, AstraZeneca will make royalty payments to Isis under this Agreement within [***] following the end of each such Calendar Quarter. Each royalty payment will be accompanied by a report, summarizing Net Sales for Products during the relevant Calendar Quarter and the calculation of royalties due thereon, including country, units, sales price and the exchange rate used. If no royalties are payable in respect of a given Calendar Quarter, AstraZeneca will submit a written royalty report to Isis so indicating together with an explanation as to why no such royalties are payable. In addition, beginning with the Calendar Quarter in which the First Commercial Sale for a Product is made and for each Calendar Quarter thereafter, within [***] following the end of each such Calendar Quarter, AstraZeneca will provide Isis a preliminary, non-binding Product sales estimate for such Calendar Quarter.

8.10.2. Mode of Payment. All payments under this Agreement will be (i) payable in full in U.S. dollars, regardless of the country(ies) in which sales are made, (ii) made by wire transfer of immediately available funds to an account designated by Isis in writing, and (iii) non-creditable (except as otherwise provided in Section 8.11), and non-refundable. Whenever for the purposes of calculating the royalties payable under this Agreement conversion from any foreign currency will be required, all amounts will first be calculated in the currency of sale and then converted into United States dollars by AstraZeneca in accordance with the rates of exchange for the relevant month for converting such other currency into US Dollars used by AstraZeneca's internal accounting systems, which are independently audited on an annual basis and which are in accordance with generally accepted accounting principles, fairly applied and as employed on a consistent basis throughout AstraZeneca's operations.

8.10.3. Records Retention. Commencing with the First Commercial Sale of a Product, AstraZeneca will keep complete and accurate records pertaining to the sale of Products for a period of [***] after the year in which such sales occurred, and in sufficient detail to permit Isis to confirm the accuracy of the Net Sales or royalties paid by AstraZeneca hereunder.

8.11. **Audits**. During the Agreement Term and for a period of [***] thereafter, at the request and expense of Isis, AstraZeneca will permit an independent certified public accountant of nationally recognized standing appointed by Isis and reasonably acceptable to AstraZeneca, at reasonable times and upon reasonable notice, but in no case more than [***], to examine such records as may be necessary for the purpose of verifying the calculation and reporting of Net Sales and the correctness of any royalty payment made under this Agreement for any period within the preceding [***]. As a condition to examining any records of AstraZeneca, such auditor will sign a nondisclosure agreement reasonably acceptable to AstraZeneca in form and substance. Any and all records of AstraZeneca examined by such independent certified public accountant will be deemed AstraZeneca's Confidential Information. Upon completion of the audit, the accounting firm will provide both AstraZeneca and Isis with a written report disclosing whether the royalty payments made by AstraZeneca are correct or incorrect and the specific details concerning any discrepancies ("***Audit Report***"). If, as a result of any inspection of the books and records of AstraZeneca, it is shown that AstraZeneca's payments under this Agreement were more or less than the royalty amount which should have been paid, then the relevant Party will make all payments required to be made by paying the other Party the difference between such amounts to eliminate any discrepancy revealed by said inspection within 45 days of receiving the Audit Report, with interest calculated in accordance with Section 8.13; *provided, however*, that any such payment by Isis to AstraZeneca will be [***]. Isis will pay for such audit, except that if AstraZeneca is found to have underpaid Isis by more than [***] of the amount that should have been paid for the audited period, AstraZeneca will reimburse Isis the reasonable fees and expenses charged by the accounting firm for the audit.

8.12. **Taxes**.

8.12.1. **Taxes On Income**. Each Party alone will be solely responsible for paying any and all Taxes (other than withholding taxes required by Applicable Law to be paid by AstraZeneca or Isis (as the case may be) levied on account of, or measured in whole or in part by reference to, the income of such Party.

8.12.2. **Indirect Taxes** All payments are exclusive of Indirect Taxes. If any Indirect Taxes are chargeable in respect of any payments, the paying Party shall pay such Indirect Taxes at the applicable rate in respect of such payments following receipt, where applicable, of an Indirect Taxes invoice in the appropriate form issued by the receiving Party in respect of those payments.

The Parties shall issue invoices for all amounts payable under this Agreement consistent with Indirect Tax requirements and irrespective of whether the sums may be netted for settlement purposes. If such amounts of Indirect Taxes are refunded by the applicable Governmental Authority or other fiscal authority subsequent to payment, the Party receiving such refund will transfer such amount to the paying Party within forty-five (45) days of receipt. The Parties agree to reasonably cooperate to provide any information required by the Party pursuing a refund of Indirect Taxes paid.

8.12.3. **Withholding Tax**. To the extent the paying Party is required to deduct and withhold taxes on any payment, the paying Party will pay the amounts of such taxes to the proper governmental authority for the account of the receiving Party and remit the net amount to the receiving Party in a timely manner. The paying Party will promptly furnish the receiving Party with proof of payment of such taxes. If documentation is necessary in order to secure an exemption from, or a reduction in, any withholding taxes, the Parties will provide such documentation to the extent they are entitled to do so. In accordance with the procedures set forth in Section 11.3 and Section 11.4, (i) the receiving Party will also indemnify the paying Party for any tax, interest or penalties imposed on the paying Party if the paying Party improperly reduces or eliminates withholding tax based upon representations made by the receiving Party, and (ii) Isis will indemnify AstraZeneca for any withholding tax incurred on Isis Supported Pass-Through Costs that arises because these costs are deemed to not be beneficially owned by Isis.

8.12.4. **Tax Cooperation**. At least 15 days prior to the date a given payment is due under this Agreement, the non-paying Party will provide the paying Party with any and all tax forms that may be reasonably necessary in order for the paying Party to lawfully not withhold tax or to withhold tax at a reduced rate with respect to such payment under an applicable bilateral income tax treaty. Following the paying Party's timely receipt of such tax forms from the non-paying Party, the paying Party will not withhold tax or will withhold tax at a reduced rate under an applicable bilateral income tax treaty, if appropriate under the Applicable Laws. The non-paying Party will provide any such tax forms to the paying Party upon request and in advance of the due date. Each Party will provide the other with reasonable assistance to enable the recovery, as permitted by Applicable Law, of withholding taxes resulting from payments made under this Agreement, such recovery to be for the benefit of the Party who would have been entitled to receive the money but for the application of withholding tax under this Section 8.12.

The provisions of this Section 8.12 are to be read in conjunction with the provisions of Section 14.3 below.

8.13. **Interest**. Any undisputed payments to be made hereunder that are not paid on or before the date such payments are due under this Agreement, and any payments that are pending resolution of any dispute (including under Section 1.2.4) unless the dispute is ruled in favour of the paying Party, will bear interest at a rate per annum equal to the lesser of (i) the rate announced by Bank of America (or its successor) as its prime rate in effect on the date that such payment would have been first due plus 1% or (ii) the maximum rate permissible under applicable law.

ARTICLE 9.
INTELLECTUAL PROPERTY

9.1. Ownership.

9.1.1. Isis Technology and AstraZeneca Technology. As between the Parties, Isis will own and retain all of its rights, title and interest in and to the Licensed Know-How and Licensed Patents and AstraZeneca will own and retain all of its rights, title and interest in and to the AstraZeneca Know-How and AstraZeneca Patents, subject to any assignments, rights or licenses expressly granted by one Party to the other Party under this Agreement. For clarity, except as otherwise expressly provided in this Agreement, the scope of licenses granted by AstraZeneca under this Agreement shall not include AstraZeneca Background Intellectual Property.

9.1.2. Agreement Technology. Each Party will promptly disclose to the other Party in writing, and will cause its Affiliates to so disclose, the discovery, development, or creation of any invention made solely or jointly by the Parties in connection with the performance of obligations under this Agreement. Except as otherwise expressly permitted under this Agreement, neither Party or their Affiliates or respective Sublicensees shall license or exploit the Jointly-Owned Collaboration Technology outside the scope of this Agreement without the consent of the other Party, such consent not to be unreasonably withheld.

9.1.3. Joint Patent Committee.

(a) The Parties will establish a "***Joint Patent Committee***" or "***JPC***." The JPC will serve as the primary contact and forum for discussion between the Parties with respect to intellectual property matters arising under this Agreement, and will cooperate with respect to the activities set forth in this ARTICLE 9. A strategy will be discussed with regard to (x) prosecution and maintenance, defense and enforcement of Isis Product-Specific Patents, AstraZeneca Product-Specific Patents and Jointly-Owned Collaboration Patents that would be and/or are licensed to AstraZeneca under Section 6.1.1, Section 6.1.2 or Section 6.1.3, (y) defense against allegations of infringement of Third Party Patent Rights, and (z) licenses to Third Party Patent Rights or Know-How, in each case to the extent such matter would be reasonably likely to have a material impact on this Agreement or the licenses granted hereunder. In addition, the JPC will ensure that all Patent Rights claiming (i) the specific composition of matter (the exact sequence and chemistry) of the [***] Development Candidate and the other [***] Lead Compounds and/or an Oncology Development Candidate, and/or (ii) methods of using such [***] Development Candidate and such [***] Lead Compounds and/or an Oncology Development Candidate as a prophylactic, therapeutic or diagnostic, will be separated into their own patent applications separate from other subject matter to ensure any such claims are licensed to AstraZeneca under Section 6.1.2 and assigned as Assignable [***] Product-Specific Patents and/or Isis Product Specific Patents under Section 6.3.1. Isis' obligation to participate in the JPC will terminate on the date Isis is no longer obligated to participate in the JSC. Thereafter, Isis will have the right and expects, but is not obligated, to participate in JPC meetings. In the case of existing Licensed Patents as of the Effective Date (e.g., STAT3) that are necessary or useful to exploit a STAT3 Compound/Product in the Field, the Parties are obligated to participate in JPC meetings to cooperate with respect to the activities set forth in this ARTICLE 9.

(b) In addition, the JPC will be responsible for the determination of inventorship. The determination of inventorship will be made in accordance with United States patent laws and therefore this will determine if the invention is solely or jointly owned by the relevant Party or Parties. The JPC will comprise an equal number of members from each Party, which may be one from each Party. The Joint Patent Committee will meet as often as agreed by them (and at least semi-Annually), to discuss matters arising out of the activities set forth in this ARTICLE 9. The JPC will determine by unanimous consent the JPC operating procedures at its first meeting, including the JPC's policies for replacement of JPC members, and the location of meetings, which will be codified in the written minutes of the first JPC meeting. To the extent reasonably requested by either Party, the Joint Patent Committee will solicit the involvement of more senior members of their respective legal departments (up to the most senior intellectual property attorney, where appropriate) with respect to critical issues, and may escalate issues to the Senior Representatives for input and resolution pursuant to Section 14.1.1. Each Party's representatives on the Joint Patent Committee will consider comments and suggestions made by the other in good faith. If either Party deems it reasonably advisable, the Parties will enter into a mutually agreeable common interest agreement covering the matters contemplated by this Agreement.

9.2. Prosecution and Maintenance of Patents.

9.2.1. Patent Filings. The Party responsible for Prosecution and Maintenance of any Patent Rights as set forth in Section 9.2.2, Section 9.2.3 or Section 9.2.4 will endeavor to obtain patent protection for the Product as it Prosecutes and Maintains its other patents Covering products in development, using counsel of its own choice but reasonably acceptable to the other Party, in such countries as the responsible Party sees fit.

9.2.2. Licensed Patents and AstraZeneca Patents.

(a) **Isis Core Technology Patents and Isis Manufacturing and Analytical Patents**. During the Agreement Term, Isis will control and be responsible for all aspects of the Isis Core Technology Patents, Isis Manufacturing and Analytical Patents and, subject to Section 9.2.4, Licensable [***] Product-Specific Patents.

(b) **Isis Product-Specific Patents and Jointly-Owned Collaboration Patents**. On a Gene Target-by-Gene Target basis, so long as the applicable license to AstraZeneca under Section 6.1.1, Section 6.1.2 or Section 6.1.3 (as applicable) is in effect, AstraZeneca will control and be responsible for all aspects of the Prosecution and Maintenance of:

(i) With respect to STAT3 Products and Oncology Products licensed to AstraZeneca, the Isis Product-Specific Patents and Jointly-Owned Collaboration Patents; and

(ii) With respect to [***] Products, the Assignable [***] Product-Specific Patents,

In each case to the same extent Isis had the right to control and was responsible for such Prosecution and Maintenance immediately prior to such license, subject to Section 9.2.3 and Section 9.2.4, and AstraZeneca will grant Isis the license set forth in Section 6.3.2.

(c) **AstraZeneca Patents**. AstraZeneca will control and be responsible for all aspects of the Prosecution and Maintenance of all AstraZeneca Patents, subject to Section 9.2.3 and Section 9.2.5.

9.2.3. **Jointly-Owned Collaboration Patents**. Isis will control and be responsible for all aspects of the Prosecution and Maintenance of Jointly-Owned Collaboration Patents that (i) do not Cover Products, and (ii) have not been licensed to AstraZeneca under Section 6.1.1, Section 6.1.2 or Section 6.1.3 (as applicable) that Cover Products. AstraZeneca will control and be responsible for all aspects of the Prosecution and Maintenance of Jointly-Owned Collaboration Patents licensed to AstraZeneca under Section 6.1.1, Section 6.1.2 or Section 6.1.3 (as applicable) that Cover Products.

9.2.4. **Prosecution of Licensable [***] Product-Specific Patents**.

(a) ***Prosecution Principles***. Because the license granted by Isis to AstraZeneca under Section 6.1.2 is limited in scope to the AstraZeneca [***]-Field, Isis may have an additional licensee under the Licensable [***] Product-Specific Patents to exploit Isis [***]-Field ASOs in the Isis [***]-Field (an "***Isis [***]-Field ASO Licensee***"). The purpose of this provision is to foster the full and complete development, maintenance, and protection of the Licensable [***] Product-Specific Patents and to protect the rights of all interested parties, by outlining (i) the procedures for filing, prosecuting, and maintaining the Licensable [***] Product-Specific Patents, (ii) Isis' commitment to fairly control filing, prosecution, and maintenance of the Licensable [***] Product-Specific Patents, and (iii) equitable cost-sharing allocations between AstraZeneca and the Isis [***]-Field ASO Licensee related thereto.

(b) ***Procedures for Prosecution of Licensable [***] Product-Specific Patents***. Isis will have the sole right and responsibility to obtain, prosecute, and maintain throughout the world (in such countries as are commercially appropriate) the Licensable [***] Product-Specific Patents using Commercially Reasonable Efforts with the objective of obtaining maximum claim coverage for all compounds and products (including [***] Compounds and [***] Products and their uses in the Field), with Patent Costs shared equally between the Isis [***]-Field ASO Licensee and AstraZeneca (collectively, the "***Participating Parties***"), or shared equally between AstraZeneca and Isis if no such Isis [***]-Field ASO Licensee exists. Isis, as controlling party (or its outside counsel), will provide the Participating Parties with an update of the filing, prosecution, and maintenance status for each of such Licensable [***] Product-Specific Patent on a periodic basis and will reasonably consult and cooperate with the Participating Parties with respect to the preparation, filing, prosecution, and maintenance of such Licensable [***] Product-Specific Patents, including providing the Participating Parties with drafts of proposed filings as soon as reasonably possible after such drafts are prepared and, in any case, in sufficient time to allow the Participating Parties to review and comment before such filings are due. Isis (or its outside counsel) will provide the Participating Parties with copies of any documents relating to the filing, prosecution, and maintenance of such Licensable [***] Product-Specific Patents promptly upon their being filed or received. For clarity, Isis may cease prosecuting or maintaining particular applications or patents in the Licensable [***] Product-Specific Patents in selected jurisdictions, if Isis determines that it is not commercially reasonable to continue such efforts; *provided, however*, that Isis will not discontinue such prosecution or maintenance with respect to a particular issued Licensable [***] Product-Specific Patent that Covers the [***] product, [***] Development Candidate or any other [***] Lead Compounds, or the use thereof and will not discontinue such prosecution or maintenance without first notifying AstraZeneca, and AstraZeneca will have the right, but not the obligation, to prosecute and maintain such Licensable [***] Product-Specific Patent in the applicable country at its own expense with counsel of its own choice by providing written notice to Isis within 30 days after AstraZeneca receives such discontinuance notice from Isis.

9.2.5. **Other Matters Pertaining to Prosecution and Maintenance of Patents**.

(a) Each Party will keep the other Party informed through the Joint Patent Committee as to material developments with respect to the Prosecution and Maintenance of the Product-Specific Patents or Jointly-Owned Collaboration Patents for which such Party has responsibility for Prosecution and Maintenance pursuant to Section 9.2.2, Section 9.2.3, Section 9.2.4 or this Section 9.2.5, including by providing copies of material data as it arises, any office actions or office action responses or other correspondence that such Party provides to or receives from any patent office, including notice of all interferences, reissues, re-examinations, oppositions or requests for patent term extensions, and all patent-related filings, and by providing the other Party the timely opportunity to have reasonable input into the strategic aspects of such Prosecution and Maintenance.

(b) If AstraZeneca elects (i) not to file and prosecute patent applications for the Jointly-Owned Collaboration Patents or Isis Product-Specific Patents that have been licensed or assigned to AstraZeneca under this Agreement or the AstraZeneca Product-Specific Patents ("***AstraZeneca-Prosecuted Patents***") in a particular country, (ii) not to continue the prosecution (including any interferences, oppositions, reissue proceedings, re-examinations, and patent term extensions, adjustments, and restorations) or maintenance of any AstraZeneca-Prosecuted Patent in a particular country, or (iii) not to file and prosecute patent applications for the AstraZeneca-Prosecuted Patent in a particular country following a written request from Isis to file and prosecute in such country, then AstraZeneca will so notify Isis promptly in writing of its intention (including a reasonably detailed rationale for doing so) in good time to enable Isis to meet any deadlines by which an action must be taken to establish or preserve any such Patent Right in such country; and Isis will have the right, but not the obligation, to file, prosecute, maintain, enforce, or otherwise pursue such AstraZeneca-Prosecuted Patent in the applicable country at its own expense with counsel of its own choice. In such case, AstraZeneca will cooperate with Isis to file for, or continue to Prosecute and Maintain or enforce, or otherwise pursue such AstraZeneca-Prosecuted Patent in such country in Isis' own name, but only to the extent that AstraZeneca is not required to take any position with respect to such abandoned AstraZeneca-Prosecuted Patent that would be reasonably likely to adversely affect the scope, validity or enforceability of any of the other Patent Rights being prosecuted and maintained by AstraZeneca under this Agreement. Notwithstanding anything to the contrary in this Agreement, if Isis assumes responsibility for the Prosecution and Maintenance of any such AstraZeneca-Prosecuted Patent under this Section 9.2.5(b), Isis will have no obligation to notify AstraZeneca if Isis intends to abandon such AstraZeneca-Prosecuted Patent.

(c) The Parties, through the Joint Patent Committee, will cooperate in good faith to determine if and when any divisional or continuation applications will be filed with respect to any Jointly-Owned Collaboration Patents or Product-Specific Patents, and where a divisional or continuation patent application filing would be practical and reasonable, then such a divisional or continuation filing will be made.

(d) If the Party responsible for Prosecution and Maintenance pursuant to Section 9.2.3 intends to abandon such Jointly-Owned Collaboration Patent without first filing a continuation or substitution, then such Party will notify the other Party of such intention at least 60 days before such Jointly-Owned Collaboration Patent will become abandoned, and such other Party will have the right, but not the obligation, to assume responsibility for the Prosecution and Maintenance thereof at its own expense (subject to Section 9.3.1) with counsel of its own choice, in which case the abandoning Party will, and will cause its Affiliates to, assign to the other Party (or, if such assignment is not possible, grant a fully-paid exclusive license in) all of their rights, title and interest in and to such Jointly-Owned Collaboration Patents. If a Party assumes responsibility for the Prosecution and Maintenance of any such Jointly-Owned Collaboration Patents under this Section 9.2.5(d), such Party will have no obligation to notify the other Party of any intention of such Party to abandon such Jointly-Owned Collaboration Patents.

(e) In addition, the Parties will consult, through the Joint Patent Committee, and take into consideration the comments of the other Party for all matters relating to interferences, reissues, re-examinations and oppositions with respect to those Patent Rights in which such other Party (i) has an ownership interest, (ii) has received a license thereunder in accordance with this Agreement, or (iii) may in the future, in accordance with this Agreement, obtain a license or sublicense thereunder.

9.3. Patent Costs.

9.3.1. Jointly-Owned Collaboration Patents. Unless the Parties agree otherwise, Isis and AstraZeneca will share equally the Patent Costs associated with the Prosecution and Maintenance of Jointly-Owned Collaboration Patents; *provided that,* either Party may decline to pay its share of costs for filing, prosecuting and maintaining any Jointly-Owned Collaboration Patents in a particular country or particular countries, in which case the declining Party will, and will cause its Affiliates to, assign to the other Party (or, if such assignment is not possible, grant a fully-paid exclusive license in) all of their rights, titles and interests in and to such Jointly-Owned Collaboration Patents.

9.3.2. Licensed Patents and AstraZeneca Patents. Except as set forth in Section 9.2.4 and Section 9.3.1, each Party will be responsible for all Patent Costs incurred by such Party prior to and after the Effective Date in all countries in the Prosecution and Maintenance of Patent Rights for which such Party is responsible under Section 9.2.

9.4. Defense of Claims Brought by Third Parties.

9.4.1. **Oncology Products – Prior to Option Exercise**. If a Third Party initiates a Proceeding claiming a Patent Right owned by or licensed to such Third Party is infringed by the Development, Manufacture or Commercialization of any Oncology Product being researched or developed under an Oncology Collaboration Program with respect to which AstraZeneca has not yet exercised its Option, Isis will have the first right, but not the obligation, to defend against any such Proceeding at its sole cost and expense. If Isis elects to defend against such Proceeding, then Isis will have the sole right to direct the defense and to elect whether to settle such claim; *provided, however*, Isis will not settle such Proceeding without the prior written consent of AstraZeneca (such consent not to be unreasonably withheld, conditioned or delayed). AstraZeneca will reasonably assist Isis in defending such Proceeding and cooperate in any such litigation at the request and expense of Isis. Isis will provide AstraZeneca with prompt written notice of the commencement of any such Proceeding that is of the type described in this Section 9.4, and Isis will keep AstraZeneca apprised of the progress of such Proceeding. If Isis elects not to defend against such a Proceeding, then Isis will so notify AstraZeneca in writing within 60 days after Isis first receives written notice of the initiation of such Proceeding, and AstraZeneca will have the right, but not the obligation, to defend against such Proceeding at its sole cost and expense and thereafter AstraZeneca will have the sole right to direct the defense thereof, including the right to settle such claim (but only with the prior written consent of Isis, which consent will not be unreasonably withheld, delayed or conditioned). In any event, the Party not defending such Proceeding will reasonably assist the other Party and cooperate in any such litigation at the request and expense of the Party defending such Proceeding. Each Party may at its own expense and with its own counsel join any defense initiated or directed by the other Party under this Section 9.4. Each Party will provide the other Party with prompt written notice of the commencement of any such Proceeding under this Section 9.4, and such Party will promptly furnish the other Party with a copy of each communication relating to the alleged infringement that is received by such Party.

9.4.2. **STAT3 Products, [***] Products and Oncology Products After Option Exercise**. If a Third Party initiates a Proceeding claiming a Patent Right owned by or licensed to such Third Party is infringed by the Development, Manufacture or Commercialization of any (i) STAT3 Product or [***] Product being developed or commercialized by AstraZeneca under a license granted under Section 6.1.1 or Section 6.1.2, or (ii) Oncology Product being developed or commercialized by AstraZeneca under a license granted under Section 6.1.3, then in any of those cases AstraZeneca will have the first right, but not the obligation, to defend against any such Proceeding at its sole cost and expense. If AstraZeneca elects to defend against such Proceeding, then AstraZeneca will have the sole right to direct the defense and to elect whether to settle such claim (but only with the prior written consent of Isis, not to be unreasonably withheld, conditioned or delayed). Isis will reasonably assist AstraZeneca in defending such Proceeding and cooperate in any such litigation at the request and expense of AstraZeneca. AstraZeneca will provide Isis with prompt written notice of the commencement of any such Proceeding that is of the type described in this Section 9.4, and AstraZeneca will keep Isis apprised of the progress of such Proceeding. If AstraZeneca elects not to defend against a Proceeding, then AstraZeneca will so notify Isis in writing within 60 days after AstraZeneca first receives written notice of the initiation of such Proceeding, and Isis will have the right, but not the obligation, to defend against such a Proceeding at its sole cost and expense and thereafter Isis will have the sole right to direct the defense thereof, including the right to settle such claim (but only with the prior written consent of AstraZeneca, which consent will not be unreasonably withheld, delayed or conditioned). Notwithstanding the foregoing, if [***]; *provided, however*, [***]. In any event, the Party not defending such Proceeding will reasonably assist the other Party and cooperate in any such litigation at the request and expense of the Party defending such Proceeding. Each Party may at its own expense and with its own counsel join any defense initiated or directed by the other Party under this Section 9.4. Each Party will provide the other Party with prompt written notice of the commencement of any such Proceeding under this Section 9.4, and such Party will promptly furnish the other Party with a copy of each communication relating to the alleged infringement that is received by such Party. Notwithstanding the foregoing, if a Proceeding described under this Section 9.4.2 involves one or more Licensable [***] Product-Specific Patents and there is an Isis [***]-Field ASO Licensee as contemplated under Section 9.2.4, then the defense against any such Proceeding will be conducted in the collective interest of, such Isis [***]-Field ASO Licensee and AstraZeneca, and this Section 9.4.2 will be read and construed in a manner that is consistent with the principles described in Section 9.2.4 except that AstraZeneca will retain sole control in respect of the defense strategy for the Assignable [***] Product-Specific Patents.

9.4.3. **Discontinued Product**. If a Third Party initiates a Proceeding claiming that any Patent Right or Know-How owned by or licensed to such Third Party is infringed by the Development, Manufacture or Commercialization of a Discontinued Product, Isis will have the first right, but not the obligation, to defend against and settle such Proceeding at its sole cost and expense. AstraZeneca will reasonably assist Isis in defending such Proceeding and cooperate in any such litigation at the request and expense of Isis. Each Party may at its own expense and with its own counsel join any defense directed by the other Party. Isis will provide AstraZeneca with prompt written notice of the commencement of any such Proceeding, or of any allegation of infringement of which Isis becomes aware and that is of the type described in this Section 9.4.3, and Isis will promptly furnish AstraZeneca with a copy of each communication relating to the alleged infringement received by Isis.

9.4.4. **Interplay Between Enforcement of IP and Defense of Third Party Claims**. Notwithstanding the provisions of Section 9.4.1 and Section 9.4.3, to the extent that a Party's defense against a Third Party claim of infringement under this Section 9.4 involves (i) the enforcement of the other Party's Know-How or Patent Rights, or (ii) the defense of an invalidity claim with respect to such other Party's Know-How or Patent Rights, then, in each case, the general concepts of Section 9.5 will apply to the enforcement of such other Party's Know-How or Patent Rights or the defense of such invalidity claim (i.e., each Party has the right to enforce its own intellectual property, except that the relevant Commercializing Party will have the initial right, to the extent provided in Section 9.5, to enforce such Know-How or Patent Rights or defend such invalidity claim, and the other Party will have a step-in right, to the extent provided in Section 9.5, to enforce such Know-How or Patent Rights or defend such invalidity claim).

9.5. **Enforcement of Patents Against Competitive Infringement**.

9.5.1. **Duty to Notify of Competitive Infringement**. If either Party learns of an infringement, unauthorized use, misappropriation or threatened infringement by a Third Party to which such Party does not owe any obligation of confidentiality with respect to any Product-Specific Patents by reason of the development, manufacture, use or commercialization of a product directed against the RNA that encodes a Gene Target in the Field ("***Competitive Infringement***"), such Party will promptly notify the other Party in writing and will provide such other Party with available evidence of such Competitive Infringement; *provided, however*, that for cases of Competitive Infringement under Section 9.5.6 below, such written notice will be given within 10 days.

9.5.2. **Control of Competitive Infringement Proceedings**. For any Competitive Infringement with respect to a Product (except for a Discontinued Product) licensed to AstraZeneca under Section 6.1.1, Section 6.1.2 or Section 6.1.3 (as applicable) that occurs after AstraZeneca is granted such license, so long as part of such Proceeding AstraZeneca also enforces any Patent Rights Controlled by AstraZeneca (including any Isis Product-Specific Patents assigned by Isis to AstraZeneca under this Agreement) being infringed that Cover such Product, then AstraZeneca will have the first right, but not the obligation, to institute, prosecute, and control a Proceeding with respect thereto by counsel of its own choice at its own expense, and Isis will have the right, at its own expense, to be represented in that action by counsel of its own choice, *however,* AstraZeneca will have the right to control such litigation. If AstraZeneca fails to initiate a Proceeding within a period of 90 days after receipt of written notice of such Competitive Infringement (subject to a 90 day extension to conclude negotiations, if AstraZeneca has commenced good faith negotiations with an alleged infringer for elimination of such Competitive Infringement within such 90 day period), Isis will have the right to initiate and control a Proceeding with respect to such Competitive Infringement by counsel of its own choice, and AstraZeneca will have the right to be represented in any such action by counsel of its own choice at its own expense. Notwithstanding the foregoing, if [***]; *provided, however*, [***]. Notwithstanding the foregoing, if a Competitive Infringement described under this Section 9.5 involves one or more Licensable [***] Product-Specific Patents and there is an Isis [***]-Field ASO Licensee as contemplated under Section 9.2.4, then the institution, prosecution, and control of a Proceeding with respect thereto will be conducted in the collective interest of, such Isis [***]-Field ASO Licensee and AstraZeneca, and this Section 9.5 will be read and construed in a manner that is consistent with the principles described in Section 9.2.4 except that AstraZeneca will retain sole control in respect of the defense strategy for the Assignable [***] Product-Specific Patents.

9.5.3. **Joinder**.

(a) If a Party initiates a Proceeding in accordance with this Section 9.5, the other Party agrees to be joined as a party plaintiff where necessary and to give the first Party reasonable assistance and authority to file and prosecute the Proceeding. Subject to Section 9.5.4, the costs and expenses of each Party incurred pursuant to this Section 9.5.3(a) will be borne by the Party initiating such Proceeding.

(b) If one Party initiates a Proceeding in accordance with this Section 9.5.3, the other Party may join such Proceeding as a party plaintiff where necessary for such other Party to seek lost profits with respect to such infringement.

9.5.4. **Share of Recoveries**. Any damages or other monetary awards recovered with respect to a Proceeding brought pursuant to this Section 9.5 will be shared as follows:

(a) the amount of such recovery will first be applied to the Parties' reasonable out-of-pocket costs incurred in connection with such Proceeding (which amounts will be allocated *pro rata* if insufficient to cover the totality of such expenses); then

(b) any remaining proceeds will be allocated as follows: (A) if Isis initiates the Proceeding pursuant to Section 9.4.1, Section 9.4.2 or Section 9.4.3, [***]; (B) if AstraZeneca initiates the Proceeding pursuant to Section 9.4.1, AstraZeneca will receive and retain [***]% the remaining proceeds and Isis will receive and retain [***]% of the remaining proceeds; and (C) if AstraZeneca initiates the Proceeding pursuant to Section 9.4.2, [***].

9.5.5. **Settlement**. Notwithstanding anything to the contrary in this ARTICLE 9, neither Party may enter a settlement, consent judgment or other voluntary final disposition of a suit under this ARTICLE 9 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.

9.5.6. **35 USC 271(e)(2) Infringement**. Notwithstanding anything to the contrary in this Section 9.5, solely with respect to Licensed Patents that have not been assigned to AstraZeneca under this Agreement for a Competitive Infringement under 35 USC 271(e)(2), the time period set forth in Section 9.5.2 during which a Party will have the initial right to bring a Proceeding will be shortened to a total of 25 days, so that, to the extent the other Party has the right, pursuant to such Section to initiate a Proceeding if the first Party does not initiate a Proceeding, such other Party will have such right if the first Party does not initiate a Proceeding within 25 days after such first Party's receipt of written notice of such Competitive Infringement.

9.6. **Other Infringement**.

9.6.1. **Jointly-Owned Collaboration Patents**. With respect to the infringement in the Field of a Jointly-Owned Collaboration Patent which is not a Competitive Infringement, the Parties will cooperate in good faith to bring suit together against such infringing party or the Parties may decide to permit one Party to solely bring suit. Any damages or other monetary awards recovered with respect to a Proceeding brought pursuant to this Section 9.6.1 will be shared as follows: (i) the amount of such recovery will first be applied to the Parties' reasonable out-of-pocket costs incurred in connection with such Proceeding (which amounts will be allocated *pro rata* if insufficient to cover the totality of such expenses); (ii) (A) if the Parties jointly initiate a Proceeding pursuant to this Section 9.6.1, [***]; and (B) if only one Party initiates the Proceeding pursuant to this Section 9.6.1, [***].

9.6.2. **Patents Solely Owned by Isis**. Isis will retain all rights to pursue an infringement of any Patent Right solely owned by Isis which is other than a Competitive Infringement and Isis will retain all recoveries with respect thereto.

9.6.3. **Patents Solely Owned by AstraZeneca**. AstraZeneca will retain all rights to pursue an infringement of any Patent Right solely owned by AstraZeneca which is other than a Competitive Infringement and AstraZeneca will retain all recoveries with respect thereto.

9.7. **Patent Listing**.

9.7.1. **AstraZeneca's Obligations**. AstraZeneca will promptly, accurately and completely list, with the applicable Regulatory Authorities during the Agreement Term, all applicable Patent Rights that Cover a Product licensed to AstraZeneca under Section 6.1.1, Section 6.1.2 or Section 6.1.3 (as applicable). Prior to such listings, the Parties will meet, through the Joint Patent Committee, to evaluate and identify all applicable Patent Rights, and AstraZeneca will have the right to review, where reasonable, original records relating to any invention for which Patent Rights are being considered by the Joint Patent Committee for any such listing. Notwithstanding the preceding sentence, AstraZeneca will retain final decision-making authority as to the listing of all applicable Patent Rights for a Product that are not Isis Core Technology Patents, Isis Manufacturing and Analytical Patents or Licensable [***] Product-Specific Patents, regardless of which Party owns such Patent Rights.

9.7.2. **Isis' Obligations**. Isis will promptly, accurately and completely list, with the applicable Regulatory Authorities during the Agreement Term, all applicable Patent Rights that Cover a Discontinued Product. Prior to such listings, the Parties will meet, through the Joint Patent Committee, to evaluate and identify all applicable Patent Rights, and Isis will have the right to review, where reasonable, original records relating to any invention for which Patent Rights are being considered by the Joint Patent Committee for any such listing. Notwithstanding the preceding sentence, Isis will retain final decision-making authority as to the listing of all applicable Patent Rights for such Discontinued Products, as applicable, regardless of which Party owns such Patent Rights.

9.8. **CREATE Act**. Notwithstanding anything to the contrary in this ARTICLE 9, neither Party will have the right to make an election under the CREATE Act when exercising its rights under this ARTICLE 9 without the prior written consent of the other Party, which will not be unreasonably withheld, conditioned or delayed. With respect to any such permitted election, 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 this Agreement is a "*joint research agreement*" as defined in the CREATE Act.

9.9. **Obligations to Third Parties**. Notwithstanding any of the foregoing, each Party's rights and obligations with respect to Licensed Technology under this ARTICLE 9 will be subject to the Third Party rights and obligations under any (i) Third Party agreements the restrictions and obligations of which AstraZeneca has agreed to under Section 8.9.2(a)(ii), Section 8.9.2(b)(i) or Section 8.9.2(b)(ii)(2), (ii) Prior Agreements, and (iii) Isis In-License Agreements; *provided*, *however*, that, to the extent that Isis has a non-transferable right to prosecute, maintain or enforce any Patent Rights licensed to AstraZeneca hereunder and, this Agreement purports to grant any such rights to AstraZeneca, Isis will act in such regard with respect to such Patent Rights at AstraZeneca's direction.

9.10. **Additional Rights and Exceptions**. Notwithstanding any provision of this ARTICLE 9, but subject to Section 9.2.4 and Section 9.4.4, Isis retains the sole right to Prosecute and Maintain Isis Core Technology Patents, Isis Manufacturing and Analytical Patents and Licensable [***] Product-Specific Patents during the Agreement Term and to control any enforcement of Isis Core Technology Patents and Isis Manufacturing and Analytical Patents, and will take the lead on such enforcement solely to the extent that the scope or validity of any Patent Rights Controlled by Isis and Covering the Isis Core Technology Patents or Isis Manufacturing and Analytical Patents is at risk.

9.11. **Patent Term Extension.** The Parties will cooperate with each other in gaining patent term extension wherever applicable to a Product, and AstraZeneca will determine which Isis Product-Specific Patents will be extended. For clarity, with respect to any Isis Product-Specific Patent for which AstraZeneca has an exclusive license under Section 6.1.1, Section 6.1.2 or Section 6.1.3 (as applicable), as between AstraZeneca and any Third Party granted a license by Isis outside the Field under any such Isis Product-Specific Patents, AstraZeneca will determine which Isis Product-Specific Patents will be extended.

9.12. **No Challenge**. As a material inducement for Isis entering into this Agreement, AstraZeneca covenants to Isis that during the Agreement Term, solely with respect to rights to the Licensed Patents that are included in a license granted or that may be granted to AstraZeneca under Section 6.1.1, Section 6.1.2 or Section 6.1.3 (as applicable), AstraZeneca, its Affiliates or Sublicensees will not, in the United States or any other country, (a) commence or otherwise voluntarily determine to participate in (other than as may be necessary or reasonably required to assert a cross-claim or a counter-claim or to respond to a court request or order or administrative law request or order) any action or proceeding, challenging or denying the enforceability or validity of any claim within an issued patent or patent application within such Licensed Patents, or (b) direct, support or actively assist any other Person (other than as may be necessary or reasonably required to assert a cross-claim or a counter-claim or to respond to a court request or order or administrative law request or order) in bringing or prosecuting any action or proceeding challenging or denying the validity of any claim within an issued patent or patent application within such Licensed Patents. For purposes of clarification and without limiting any other available remedies, subject to any applicable cure period provided herein for breaches of this Section 9.12 that are curable (i.e., which would allow AstraZeneca the opportunity to rescind any wrongfully brought actions by it, its Affiliates, or Sublicensees), if AstraZeneca takes any of the actions described in clause (a) or clause (b) of this Section 9.12, AstraZeneca will have materially breached this Agreement and Isis may terminate this Agreement under Section 12.2.2(b).

ARTICLE 10.
REPRESENTATIONS AND WARRANTIES

10.1. **Representations and Warranties of Both Parties**. Each Party hereby represents and warrants as of the Effective Date, and covenants, to the other Party that:

10.1.1. it has the power and authority and the legal right to enter into this Agreement and perform its obligations hereunder, and that it has taken all necessary action on its part required to authorize the execution and delivery of this Agreement and the performance of its obligations hereunder;

10.1.2. this Agreement has been duly executed and delivered on behalf of such Party and constitutes a legal, valid and binding obligation of such Party and is enforceable against it in accordance with its terms subject to the effects of bankruptcy, insolvency or other laws of general application affecting the enforcement of creditor rights and judicial principles affecting the availability of specific performance and general principles of equity, whether enforceability is considered a proceeding at law or equity;

10.1.3. all necessary consents, approvals and authorizations of all Regulatory Authorities and other parties required to be obtained by such Party in connection with the execution and delivery of this Agreement and the performance of its obligations hereunder have been obtained;

10.1.4. the execution and delivery of this Agreement and the performance of such Party's obligations hereunder (a) do not conflict with or violate any requirement of Applicable Law or any provision of the certificate of incorporation, bylaws or any similar instrument of such Party, as applicable, in any material way, and (b) do not conflict with, violate, or breach or constitute a default or require any consent not already obtained under, any contractual obligation or court or administrative order by which such Party is bound;

10.1.5. All employees, consultants, or (sub)contractors (except academic collaborators or Third Parties under the Permitted Licenses or Prior Agreements) of such Party or Affiliates performing development activities hereunder on behalf of such Party are, and such Party hereby covenants to the other Party that they will be, obligated to assign all right, title and interest in and to any inventions developed by them, whether or not patentable, to such Party or Affiliate, respectively, as the sole owner thereof;

10.1.6. Such Party will, and such Party hereby covenants to the other Party that it will, perform its activities pursuant to this Agreement in compliance with good laboratory and clinical practices and cGMP and Applicable Law, in each case as applicable under the laws and regulations of the country and the state and local government wherein such activities are conducted, and with respect to the care, handling and use in development activities hereunder of any non-human animals by or on behalf of such Party, will at all times comply (and will ensure compliance by any of its subcontractors) with all applicable national, federal, state and local laws, regulations and ordinances in performing its obligations under this Agreement; and

10.1.7. Such Party is not debarred under the United States Federal Food, Drug and Cosmetic Act or comparable Applicable Laws and it does not, and will not during the Agreement Term, employ or use the services of any person or entity who is debarred, in connection with the development, manufacture or commercialization of the Compounds or Products. If either Party becomes aware of the debarment or threatened debarment of any person or entity providing services to such Party, including the Party itself and its Affiliates or Sublicensees, which directly or indirectly relate to activities under this Agreement, the other Party will be immediately notified in writing.

10.2. **Representations, Warranties and Covenants of Isis**. Isis hereby represents and warrants to AstraZeneca, as of the Effective Date, that:

10.2.1. Isis is the owner of, or otherwise has the right to grant all rights and licenses it purports to grant to AstraZeneca with respect to the Licensed Technology under this Agreement for Compounds identified by Isis on or before the Effective Date or Oncology Collaboration Programs as they exist on the Effective Date;

10.2.2. To Isis' Knowledge, all Licensed Patents that are owned by Isis ("***Isis Owned Patents***") have been filed and maintained properly and correctly in all material respects.

10.2.3. Isis has not previously entered into any agreement, whether written or oral, with respect to, or otherwise assigned, transferred, licensed, conveyed or otherwise encumbered its right, title or interest in or to, the Licensed Technology (including by granting any covenant not to sue with respect thereto) in such a way as to make the representation set forth in Section 10.2.1 not true, and it will not enter into any such agreements or grant any such right, title or interest to any Person that is inconsistent with the rights and licenses granted to AstraZeneca under this Agreement;

10.2.4. To Isis' Knowledge, each of the Isis Owned Patents properly identifies each and every inventor of the claims thereof as determined in accordance with the laws of the jurisdiction in which such Patent Right is issued or such application is pending;

10.2.5. Isis has not received any written claim alleging that any of the Isis Owned Patents are invalid or unenforceable, including any Isis Owned Patents required in order for Isis to conduct its obligations under the Collaboration Plans as they exist on the Effective Date, in each case with respect to the Compounds and Products identified by Isis on or before the Effective Date;

10.2.6. Isis has not received any written claim alleging that any of Isis' activities relating to the Compounds and Products identified by Isis on or before the Effective Date infringe any intellectual property rights of a Third Party;

10.2.7. To Isis' Knowledge, (i) the licenses granted to Isis under the Isis In-License Agreements are in full force and effect, (ii) Isis has not received any written notice, and is not aware, of any breach by any party to the Isis In-License Agreements, and (iii) Isis' performance of its obligations under this Agreement (including the Collaboration Plans as they exist on the Effective Date) will not constitute a breach of Isis' obligations under the Isis In-License Agreements and the licenses granted to Isis thereunder;

10.2.8. To Isis' Knowledge, Isis does not require any additional licenses or other intellectual property rights in order for Isis to conduct its obligations under the Collaboration Plans as they exist on the Effective Date, in each case with respect to the Compounds identified by Isis on or before the Effective Date;

10.2.9. To Isis' Knowledge, in respect of the pending United States patent applications included in the Isis Owned Patents, Isis has submitted all material prior art of which it is aware in accordance with the requirements of the United States Patent and Trademark Office;

10.2.10. To Isis' Knowledge, neither Isis nor its Affiliates owns or Controls any Patent Rights or Know How covering formulation or delivery technology as of the Effective Date that would be necessary or useful in order for AstraZeneca to further Develop or Commercialize Compounds contemplated under the Collaboration Plans as they exist on the Effective Date;

10.2.11. APPENDIX 10 (Prior Agreements) is a complete and accurate list of all agreements between Isis and Third Parties as of the Effective Date with respect to the Gene Targets included in this Agreement as of the Effective Date, that create material Third Party Obligations that affect the rights granted by Isis to AstraZeneca under this Agreement. The Prior Agreements have not been materially amended or extended since first being placed in the Isis data room to which AstraZeneca was given access during the negotiation of this Agreement and subject to redactions represent a true and complete and accurate copy thereof, and any such redactions are of information not necessary to disclose to understand the implications of such Prior Agreements to this Agreement; and

10.2.12. Isis has conducted, and has required its contractors and consultants to conduct, any and all preclinical and clinical studies related to the Compounds and Products in compliance with good laboratory and clinical practices and cGMP and Applicable Law, in each case as applicable under the laws and regulations of the country and the state and local government wherein such activities were conducted.

10.2.13. Isis has made available to AstraZeneca all material Regulatory Documentation for ISIS-STAT3$_{Rx}$. Isis has prepared, maintained and retained such Regulatory Documentation required to be maintained or reported pursuant to and in accordance with Applicable Law and such Regulatory Documentation does not contain any materially false or misleading statements.

10.3. **Representations, Warranties and Covenants of AstraZeneca**. AstraZeneca hereby represents and warrants to Isis that as of the Effective Date, except as explicitly disclosed in writing by AstraZeneca to Isis there are no Patent Rights comprised in AstraZeneca Background IP related to STAT3 or [***] with respect to which AstraZeneca does not have the ability to grant a license or sublicense hereunder to Isis without violating the terms of any agreement with any Third Party.

10.4. **DISCLAIMER OF WARRANTY. EXCEPT FOR THE EXPRESS WARRANTIES SET FORTH IN THIS ARTICLE 10, ASTRAZENECA AND ISIS MAKE NO REPRESENTATIONS AND GRANT NO WARRANTIES, EXPRESS OR IMPLIED, EITHER IN FACT OR BY OPERATION OF LAW, BY STATUTE OR OTHERWISE, AND ASTRAZENECA AND ISIS EACH SPECIFICALLY DISCLAIM ANY WARRANTIES, WHETHER WRITTEN OR ORAL, OR EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OF QUALITY, MERCHANTABILITY OR FITNESS FOR A PARTICULAR USE OR PURPOSE OR ANY WARRANTY AS TO THE VALIDITY OF ANY PATENT RIGHTS OR THE NON-INFRINGEMENT OF ANY INTELLECTUAL PROPERTY RIGHTS OF THIRD PARTIES.**

ARTICLE 11.
INDEMNIFICATION; INSURANCE

11.1. **Indemnification by AstraZeneca**. AstraZeneca agrees to defend Isis, its Affiliates and their respective directors, officers, stockholders, employees and agents, and their respective successors, heirs and assigns (collectively, the "***Isis Indemnitees***"), and will indemnify and hold harmless the Isis Indemnitees, from and against any liabilities, losses, costs, damages, fees or expenses payable to a Third Party, and reasonable attorneys' fees and other legal expenses with respect thereto (collectively, "***Losses***") arising out of any claim, action, lawsuit or other proceeding by a Third Party (collectively, "***Third Party Claims***") brought against any Isis Indemnitee and resulting from or occurring as a result of: (a) any activities conducted by an AstraZeneca employee, consultant or (sub)contractor in the performance of the AstraZeneca Conducted Activities, (b) the Development or Commercialization of any Compound or Product by AstraZeneca or its Affiliates, Sublicensees or contractors, (c) any breach by AstraZeneca of any of its representations, warranties or covenants pursuant to this Agreement, or (d) the negligence or willful misconduct of AstraZeneca or any AstraZeneca Affiliate or Sublicensee in the performance of this Agreement; *except* in any such case to the extent such Losses result from: (i) the negligence or willful misconduct of any Isis Indemnitee, (ii) any breach by Isis of any of its representations, warranties, covenants or obligations pursuant to this Agreement, or (iii) any breach of Applicable Law by any Isis Indemnitee.

11.2. **Indemnification by Isis**. Isis agrees to defend AstraZeneca, its Affiliates and their respective directors, officers, stockholders, employees and agents, and their respective successors, heirs and assigns (collectively, the "***AstraZeneca Indemnitees***"), and will indemnify and hold harmless the AstraZeneca Indemnitees, from and against any Losses arising out of Third Party Claims brought against any AstraZeneca Indemnitee and resulting from or occurring as a result of: (a) any activities conducted by an Isis employee, consultant or (sub)contractor in the performance of the Isis Conducted Activities; (b) any breach by Isis of any of its representations, warranties or covenants pursuant to this Agreement, (c) the negligence or willful misconduct of any Isis Indemnitee or any (sub)contractor of Isis in the performance of this Agreement, or (d) the Development or Commercialization of any Discontinued Product by Isis or its Affiliates, Sublicensees or contractors; *except* in any such case to the extent such Losses result from: (i) the negligence or willful misconduct of any AstraZeneca Indemnitee, (ii) any breach by AstraZeneca of any of its representations, warranties, covenants or obligations pursuant to this Agreement, or (iii) any breach of Applicable Law by any AstraZeneca Indemnitee.

11.3. **Notice of Claim**. All indemnification claims provided for in Section 11.1 and Section 11.2 will be made solely by such Party to this Agreement (the "***Indemnified Party***"). The Indemnified Party will give the indemnifying Party prompt written notice (an "***Indemnification Claim Notice***") of any Losses or the discovery of any fact upon which the Indemnified Party intends to base a request for indemnification under Section 11.1 or Section 11.2, but in no event will the indemnifying Party be liable for any Losses to the extent such Losses result from any delay in providing such notice. Each Indemnification Claim Notice must contain a description of the claim and the nature and amount of such Loss (to the extent that the nature and amount of such Loss is known at such time). The Indemnified Party will furnish promptly to the indemnifying Party copies of all papers and official documents received in respect of any Losses and Third Party Claims.

11.4. **Defense, Settlement, Cooperation and Expenses**.

11.4.1. **Control of Defense**. At its option, the indemnifying Party may assume the defense of any Third Party Claim by giving written notice to the Indemnified Party within 30 days after the indemnifying Party's receipt of an Indemnification Claim Notice. The assumption of the defense of a Third Party Claim by the indemnifying Party will not be construed as an acknowledgment that the indemnifying Party is liable to indemnify the Indemnified Party in respect of the Third Party Claim, nor will it constitute a waiver by the indemnifying Party of any defenses it may assert against the Indemnified Party's claim for indemnification. Upon assuming the defense of a Third Party Claim, the indemnifying Party may appoint as lead counsel in the defense of the Third Party Claim any legal counsel selected by the indemnifying Party. In the event the indemnifying Party assumes the defense of a Third Party Claim, the Indemnified Party will as soon as is reasonably possible deliver to the indemnifying Party all original notices and documents (including court papers) received by the Indemnified Party in connection with the Third Party Claim. Should the indemnifying Party assume the defense of a Third Party Claim, except as provided in this Section 11.4.1, the Indemnified Party will be responsible for the legal costs or expenses subsequently incurred by such Indemnified Party in connection with the analysis, defense or settlement of the Third Party Claim.

11.4.2. **Right to Participate in Defense**. Without limiting Section 11.4.1, any Indemnified Party will be entitled to participate in, but not control, the defense of such Third Party Claim and to employ counsel of its choice for such purpose; *provided, however*, that such employment will be at the Indemnified Party's own cost and expense unless (a) the employment thereof has been specifically authorized by the indemnifying Party in writing, (b) the indemnifying Party has failed to assume the defense and employ counsel in accordance with Section 11.4.1 (in which case the Indemnified Party will control the defense), or (c) the interests of the Indemnified Party and the indemnifying Party with respect to such Third Party Claim are sufficiently adverse to prohibit the representation by the same counsel of both Parties under Applicable Law, ethical rules or equitable principles in which case the indemnifying Party will be responsible for any such costs and expenses of counsel for the Indemnified Party.

11.4.3. **Settlement**. With respect to any Third Party Claims relating solely to the payment of money damages in connection with a Third Party Claim and that will not admit liability or violation of Law on the part of the Indemnified Party or result in the Indemnified Party's becoming subject to injunctive or other relief or otherwise adversely affecting the business of the Indemnified Party in any manner (such as granting a license or admitting the invalidity of a Patent Right Controlled by an Indemnified Party), and as to which the indemnifying Party will have acknowledged in writing the obligation to indemnify the Indemnified Party hereunder, the indemnifying Party will have the sole right to consent to the entry of any judgment, enter into any settlement or otherwise dispose of such Loss, on such terms as the indemnifying Party, in its sole discretion, will deem appropriate. With respect to all other Losses in connection with Third Party Claims, where the indemnifying Party has assumed the defense of the Third Party Claim in accordance with Section 11.4.1, the indemnifying Party will have authority to consent to the entry of any judgment, enter into any settlement or otherwise dispose of such Loss provided it obtains the prior written consent of the Indemnified Party (which consent will not be unreasonably withheld). The indemnifying Party will not be liable for any settlement, consent to entry of judgment, or other disposition of a Loss by an Indemnified Party that is reached without the written consent of the indemnifying Party. Regardless of whether the indemnifying Party chooses to defend or prosecute any Third Party Claim, no Indemnified Party will admit any liability with respect to or settle, compromise or discharge, any Third Party Claim without the prior written consent of the indemnifying Party, such consent not to be unreasonably withheld.

11.4.4. **Cooperation**. Regardless of whether the indemnifying Party chooses to defend or prosecute any Third Party Claim, the Indemnified Party will, and will cause each other Indemnified Party to, cooperate in the defense or prosecution thereof and will furnish such records, information and testimony, provide such witnesses and attend such conferences, discovery proceedings, hearings, trials and appeals as may be reasonably requested in connection therewith. Such cooperation will include access during normal business hours afforded to indemnifying Party to, and reasonable retention by the Indemnified Party of, records and information that are reasonably relevant to such Third Party Claim, and making Indemnified Parties and other employees and agents available on a mutually convenient basis to provide additional information and explanation of any material provided hereunder, and the indemnifying Party will reimburse the Indemnified Party for all its reasonable out-of-pocket costs and expenses in connection therewith.

11.4.5. **Costs and Expenses**. Except as provided above in this Section 11.4, the costs and expenses, including attorneys' fees and expenses, incurred by the Indemnified Party in connection with any claim will be reimbursed on a Calendar Quarter basis by the indemnifying Party, without prejudice to the indemnifying Party's right to contest the Indemnified Party's right to indemnification and subject to refund in the event the indemnifying Party is ultimately held not to be obligated to indemnify the Indemnified Party.

11.5. **Insurance**.

11.5.1. **Isis' Insurance Obligations**. Isis will maintain, at its cost, reasonable insurance against liability and other risks associated with its activities contemplated by this Agreement, including but not limited to its indemnification obligations herein, in such amounts and on such terms as are customary for prudent practices for biotech companies of similar size and with similar resources in the pharmaceutical industry for the activities to be conducted by it under this Agreement taking into account the scope of development of products. Isis will furnish to AstraZeneca evidence of any insurance required under this Section 11.5.1, upon request.

11.5.2. **AstraZeneca's Insurance Obligations**. AstraZeneca hereby represents and warrants to Isis that it will maintain, at its cost, reasonable insurance against liability and other risks associated with its activities contemplated by this Agreement (including product liability), including but not limited to its indemnification obligations herein, in such amounts and on such terms as are customary for prudent practices for large companies in the pharmaceutical industry for the activities to be conducted by AstraZeneca under this Agreement. AstraZeneca will maintain such self insurance throughout the Agreement Term and for five years thereafter, and will furnish to Isis evidence of such insurance, upon request.

11.6. **LIMITATION OF CONSEQUENTIAL DAMAGES**. **EXCEPT FOR (a) CLAIMS OF A THIRD PARTY THAT ARE SUBJECT TO INDEMNIFICATION UNDER THIS ARTICLE 11 OR SECTION 12.3.2(i), (b) CLAIMS ARISING OUT OF A PARTY'S WILLFUL MISCONDUCT, (c) A PARTY'S BREACH OF ARTICLE 5, OR A BREACH OF SECTION 12.3.1(a) BY ASTRAZENECA OR ITS AFFILIATES OR (d) CLAIMS ARISING OUT OF A PARTY'S BREACH OF ITS CONFIDENTIALITY OBLIGATIONS UNDER THIS AGREEMENT, NEITHER PARTY NOR ANY OF ITS AFFILIATES WILL BE LIABLE TO THE OTHER PARTY TO THIS AGREEMENT OR ITS AFFILIATES FOR ANY INCIDENTAL, CONSEQUENTIAL, SPECIAL, PUNITIVE OR OTHER INDIRECT DAMAGES OR LOST OR IMPUTED PROFITS OR ROYALTIES, LOST DATA OR COST OF PROCUREMENT OF SUBSTITUTE GOODS OR SERVICES, WHETHER LIABILITY IS ASSERTED IN CONTRACT, TORT (INCLUDING NEGLIGENCE AND STRICT PRODUCT LIABILITY), INDEMNITY OR CONTRIBUTION, AND IRRESPECTIVE OF WHETHER THAT PARTY OR ANY REPRESENTATIVE OF THAT PARTY HAS BEEN ADVISED OF, OR OTHERWISE MIGHT HAVE ANTICIPATED THE POSSIBILITY OF, ANY SUCH LOSS OR DAMAGE.**

11.7. Anti-Bribery and Corruption Compliance.

11.7.1 Each Party agrees, on behalf of itself, its officers, directors and employees and on behalf of its Affiliates, agents, representatives, consultants and subcontractors hired for activities undertaken for or in connection with the performance of this Agreement (together with such Party, the "***Party Representatives***") that for the performance of its obligations hereunder:

Party Representatives shall not directly or indirectly pay, offer or promise to pay, or authorize the payment of any money, or give, offer or promise to give, or authorize the giving of anything else of value, to:

(1) any Government Official in order to influence official action;

(2) any Person (whether or not a Government Official) (i) to influence such Person to act in breach of a duty of good faith, impartiality or trust ("acting improperly"), (ii) to reward such Person for acting improperly, or (iii) where such Person would be acting improperly by receiving the money or other thing of value;

(3) any other Person while knowing or having reason to know that all or any portion of the money or other thing of value will be paid, offered, promised or given to, or will otherwise benefit, a Government Official in order to influence official action for or against either Party in connection with the matters that are the subject of this Agreement; or

(4) any Person to reward that Person for acting improperly or to induce that Person to act improperly.

11.7.2 Party Representatives shall not, directly or indirectly, solicit, receive or agree to accept any payment of money or anything else of value in violation of the Anti-Corruption Laws.

11.7.3 Each Party acknowledges that its undertakings given in Sections 11.7.1 and 11.7.2 are material to the other Party in entering into a relationship with such Party.

11.7.4 Each Party, on behalf of itself and its Party Representatives, represents and warrants to the other Party that for the term of this Agreement and six years thereafter, it shall and shall procure that its Party Representatives keep and maintain accurate books and reasonably detailed records in connection with the performance of its obligation under this Agreement including all records required to establish compliance with Sections 11.7.1 and 11.7.2 above.

11.7.5 Each Party shall promptly provide the other Party with written notice of the following events: (A) upon becoming aware of any breach or violation by it or its Party Representatives of any representation, warranty or undertaking set forth in Sections 11.7.1 and 11.7.2; and (B) upon receiving a formal notification that it is the target of a formal investigation by a Relevant Authority for a Material Anti-Corruption Law Violation or upon receipt of information from any of its Party Representatives connected with this Agreement that any of them is the target of a formal investigation by a Relevant Authority for a Material Anti-Corruption Law Violation.

11.7.6 For the term of this Agreement and six years thereafter, each Party shall for the purpose of auditing and monitoring the performance of its compliance with the Agreement and particularly this Section 11.7 permit the other Party, its Affiliates, any auditors of any of them and any Regulatory Authority to have access to any premises of such Party or its Party Representatives used in connection with this Agreement, together with a right to access personnel and records that relate to this Agreement ("***Audit***").

11.8 Each Party shall be responsible for any breach of any representation, warranty or undertaking in this Section 11.7 or of the Anti-Corruption Laws by any of its Party Representatives.

11.9 Each Party may disclose the terms of this Agreement or any action taken under this Section 11.7 to prevent a potential violation or continuing violation of applicable Anti-Corruption Laws, including the identity of the other Party and the payment terms, to any governmental authority if such Party determines, upon advice of counsel, that such disclosure is necessary.

ARTICLE 12.
TERM; TERMINATION

12.1. **Agreement Term; Expiration**. This Agreement is effective as of the Effective Date and, unless earlier terminated pursuant to the other provisions of this ARTICLE 12, will continue in full force and effect until this Agreement expires as follows:

12.1.1. on a country-by-country and Product-by-Product basis, on the date of expiration of all payment obligations by the Commercializing Party under this Agreement with respect to such Product (or such Discontinued Product) in such country; and

12.1.2. in its entirety upon the expiration of all payment obligations under this Agreement with respect to the last Product (or last Discontinued Product) in all countries pursuant to Section 12.1.1.

The period from the Effective Date until the date of expiration of this Agreement pursuant to this Section 12.1 is the "***Agreement Term***."

12.2. Termination of the Agreement.

12.2.1. AstraZeneca's Termination for Convenience or Change of Control.

(a) **Termination for Convenience**. At any time following payment by AstraZeneca of the upfront fee under Section 8.1, subject to Section 12.3.1 below, AstraZeneca will be entitled to terminate this Agreement in part with respect to STAT3 Products or [***] Products for convenience by providing 90 days written notice to Isis of such termination. In addition, at any time following payment by AstraZeneca of the upfront fee under Section 8.1 and the payment under Section 8.3, subject to Section 12.3.1 below, AstraZeneca will be entitled to terminate this Agreement in its entirety or in part on a Product-by-Product, Gene Target-by-Gene Target basis for convenience by providing 90 days written notice to Isis of such termination.

(b) **Change of Control Event**. Prior to the Option Deadline for an Oncology Target or until Isis has completed the Isis Conducted Activities with respect to the STAT3 Program or [***] Program under the R&D Research and Development Plan, AstraZeneca will have the right to terminate this Agreement in whole or in part with respect to one or more Oncology Targets for which AstraZeneca has not exercised its Option or with respect to a Licensed Target, immediately upon written notice to Isis provided at any time within 30 Business Days following notification by Isis to AstraZeneca of the closing of a Change of Control Event (and Isis shall be obliged to give notice on such closing, and in the event it fails to do so, AstraZeneca's right to terminate may be exercised within 90 Business Days of such closing coming to AstraZeneca's Knowledge), if such closing occurs during the Oncology Collaboration Term or before Isis has completed the Isis Conducted Activities with respect to the STAT3 Program or [***] Program under the R&D Research and Development Plan (as applicable). If at AstraZeneca's discretion, AstraZeneca decides not to terminate this Agreement with respect to a particular Gene Target pursuant to this Section 12.2.1(b) following the closing of a Change of Control Event during the Oncology Collaboration Term, then, subject to the below provisions in this Section 12.2.1, Isis' and AstraZeneca's obligations under ARTICLE 3 to perform the relevant Collaboration Program on such Gene Target will remain and Isis (or its successor) will use commercially reasonable efforts to perform the Oncology Collaboration Program on such Oncology Target in accordance with ARTICLE 3 while, to the extent reasonably practicable, maintaining confidentiality of AstraZeneca's Confidential Information from any entity acquiring Isis as a result of the Change of Control Event. As soon as reasonably possible after the public announcement of such a Change of Control Event, Isis (or its successor) and AstraZeneca will meet to discuss in good faith how Isis (or its successor) will continue to perform its obligations under this Agreement with respect to any Licensed Targets and Oncology Targets for which AstraZeneca has not exercised its Option so that AstraZeneca can consider whether to exercise its rights of termination under this Section 12.2.1(b). If AstraZeneca does not exercise its right of termination it shall have the right, by providing Isis with written notice within 30 Business Days following notification by Isis to AstraZeneca of the closing of a Change of Control Event, to require that Isis ceases performing any or certain activities and co-operate and take such measures as may be requested to ensure a prompt and smooth transition of such activities to AstraZeneca or its designee. AstraZeneca shall be entitled to deduct an amount equal to the [***]) from its next applicable milestone or license fee payment as applicable. Without prejudice to the foregoing, if requested by AstraZeneca such measures shall include a technology transfer pursuant to the provisions of Section 6.5 or Section 6.1.4(b), in either case without charge to AstraZeneca. Furthermore, if the surviving entity following such Change of Control Event is clinically developing or commercializing a product that is directly competing with a Product under this Agreement, then, solely with respect to the Product that is subjected to such competition, AstraZeneca will no longer be bound by the disclosure requirements of Section 4.3 hereof and may require that Isis cease to participate in the JSC.

12.2.2. Termination for Material Breach.

(a) **AstraZeneca's Right to Terminate**. If AstraZeneca has reason to believe that Isis is in material breach of this Agreement (other than with respect to a failure to use Commercially Reasonable Efforts under ARTICLE 1, ARTICLE 2 or ARTICLE 3, which is governed by Section 12.2.3 below), then AstraZeneca may deliver notice of such material breach to Isis. If the breach is curable, Isis will have 60 days to cure such breach. If Isis fails to cure such breach within the 60 day period, or if the breach is not subject to cure, AstraZeneca may terminate this Agreement in its entirety if such breach relates to this Agreement in its entirety, or in relevant part on a Product-by-Product, Gene Target-by-Gene Target basis if such breach does not relate to this Agreement in its entirety, by providing written notice to Isis.

(b) **Isis' Right to Terminate**. If Isis has reason to believe that AstraZeneca is in material breach of this Agreement (other than with respect to a failure to use Commercially Reasonable Efforts under ARTICLE 1, ARTICLE 2, ARTICLE 3 or Section 7.1, which is governed by Section 12.2.3 below), then Isis may deliver notice of such material breach to AstraZeneca. If the breach is curable, AstraZeneca will have 60 days to cure such breach (except to the extent such breach involves the failure to make a payment when due, which breach must be cured within 30 days following such notice). If AstraZeneca fails to cure such breach within the 60 day or 30 day period, as applicable, or if the breach is not subject to cure, Isis may terminate this Agreement in its entirety if such breach relates to this Agreement in its entirety, or in relevant part on a Product-by-Product, Gene Target-by-Gene Target basis if such breach does not relate to this Agreement in its entirety, by providing written notice to AstraZeneca.

12.2.3. Remedies for Failure to Use Commercially Reasonable Efforts.

(a) If Isis fails to use Commercially Reasonable Efforts as contemplated in ARTICLE 1, ARTICLE 2 or ARTICLE 3 (as determined in accordance with Section 14.1), AstraZeneca will notify Isis and, within 30 days thereafter, Isis and AstraZeneca will meet and confer to discuss and resolve the matter in good faith, and attempt to devise a mutually agreeable plan to address any outstanding issues related to Isis' use of Commercially Reasonable Efforts in ARTICLE 1, ARTICLE 2 or ARTICLE 3. Following such a meeting, if Isis fails to use Commercially Reasonable Efforts as contemplated in ARTICLE 1, ARTICLE 2 or ARTICLE 3, then subject to Section 12.2.4 below, AstraZeneca will have the right, at its sole discretion, to terminate this Agreement in whole or in part on a Product-by-Product, Gene Target-by-Gene Target basis.

(b) If AstraZeneca fails to use Commercially Reasonable Efforts as contemplated in ARTICLE 1, ARTICLE 2, ARTICLE 3 or Section 7.1 (as determined in accordance with Section 14.1), Isis will notify AstraZeneca and, within 30 days thereafter, Isis and AstraZeneca will meet and confer to discuss and resolve the matter in good faith, and attempt to devise a mutually agreeable plan to address any outstanding issues related to AstraZeneca's use of Commercially Reasonable Efforts in ARTICLE 1, ARTICLE 2, ARTICLE 3 or Section 7.1. Following such a meeting, if AstraZeneca fails to use Commercially Reasonable Efforts as contemplated in ARTICLE 1, ARTICLE 2, ARTICLE 3 or Section 7.1, then subject to Section 12.2.4 below, Isis will have the right, at its sole discretion, to terminate this Agreement in part on a Product-by-Product, Gene Target-by-Gene Target basis.

12.2.4. Disputes Regarding Material Breach. Notwithstanding the foregoing, if the Breaching Party in Section 12.2.2 or Section 12.2.3 disputes in good faith the existence, materiality, or failure to cure of any such breach which is not a payment breach, and provides notice to the Non-Breaching Party of such dispute within such 60 day period, the Non-Breaching Party will not have the right to terminate this Agreement in accordance with Section 12.2.2 or Section 12.2.3, unless and until it has been determined in accordance with Section 14.1 that this Agreement was materially breached by the Breaching Party and the Breaching Party fails to cure such breach within 30 days following such determination. It is understood and acknowledged that during the pendency of such dispute, all the terms and conditions of this Agreement will remain in effect and the Parties will continue to perform all of their respective obligations hereunder, including satisfying any payment obligations.

12.2.5. **Termination for Insolvency**.

(a) Either Party may terminate this Agreement if, at any time, the other Party files in any court or agency pursuant to any statute or regulation of any state or country a petition in bankruptcy or insolvency or for the appointment of a receiver or trustee of the Party or of substantially all of its assets; or if the other Party proposes a written agreement of composition or extension of substantially all of its debts; or if the other Party will be served with an involuntary petition against it, filed in any insolvency proceeding, and such petition will not be dismissed within 90 days after the filing thereof; or if the other Party will propose or be a party to any dissolution or liquidation; or if the other Party will make an assignment of substantially all of its assets for the benefit of creditors.

(b) All rights and licenses granted under or pursuant to any section of this Agreement are and will otherwise be deemed to be for purposes of Section 365(n) of Title 11, United States Code (the "***Bankruptcy Code***") or analogous provisions of Applicable Law outside the US licenses of rights to "intellectual property" as defined in Section 101(56) of the Bankruptcy Code or analogous provisions of Applicable Law outside the US. The Parties will retain and may fully exercise all of their respective rights and elections under the Bankruptcy Code or analogous provisions of Applicable Law outside the US. Upon the commencement of a bankruptcy proceeding of any Party, the non-bankrupt Party will further be entitled to a complete duplicate of, or complete access to, any such intellectual property, and all embodiments which, if not already in its possession, will be promptly delivered to the non-bankrupt Party upon written request.

12.3. **Consequences of Expiration or Termination of this Agreement**.

12.3.1. **Consequence of Termination of this Agreement**. If this Agreement is terminated by a Party in accordance with this ARTICLE 12 in its entirety or on a Product-by-Product, Gene Target-by-Gene Target basis (including under Section 1.2.3, Section 2.2.3 or Section 2.2.4(b)) at any time and for any reason, the following terms will apply to any such termination, but only to the extent of any such termination (i.e., in part or in its entirety):

(a) **Licenses**. The licenses granted by Isis to AstraZeneca under this Agreement will terminate and AstraZeneca, its Affiliates, Sublicensees and Distributors will cease selling Products; *provided, that* AstraZeneca, its Affiliates, Sublicensees and Distributors shall have the right to sell any remaining inventory of Product over a period of no greater than six months after the effective date of such termination, and AstraZeneca will pay Isis royalties in accordance with Section 8.8 on the Net Sales of such inventory of such Products, to the extent not already paid.

(b) **Option**. AstraZeneca's Option will terminate with respect to any terminated Oncology Target.

(c) **Exclusivity**. Neither Party will have any further obligations under Section 5.1 of this Agreement insofar as it relates to such termination.

(d) **Collaboration Plans**. Neither Party will have any further obligations with respect to the terminated Collaboration Plan(s).

(e) **Return of Information and Materials**. The Parties will return (or destroy, as directed by the other Party) all data, files, records and other materials containing or comprising the other Party's Confidential Information. Notwithstanding the foregoing, the Parties will be permitted to retain one copy of such data, files, records, and other materials for archival and legal compliance purposes.

(f) **Accrued Rights**. Termination of this Agreement for any reason will be without prejudice to any rights or financial compensation that will have accrued to the benefit of a Party prior to such termination. Such termination will not relieve a Party from obligations that are expressly indicated to survive the termination of this Agreement. For purposes of clarification, milestone payments under ARTICLE 8 accrue as of the date the applicable milestone event is achieved even if the payment is not due at that time.

(g) **Survival**. The following provisions of this Agreement will survive the expiration or earlier termination of this Agreement: Section 3.4 (Expiration of Oncology Collaboration Term) (but only with respect to the licenses and other rights granted by AstraZeneca to Isis therein), Section 3.5.2 (Options) (but only until any initiated but uncompleted IND-Enabling Toxicology Studies are completed), Section 6.1.4(d) (Effect of Termination on Sublicenses), Section 6.1.5 (Consequence of Natural Expiration of this Agreement), Section 6.3.2 (Grant-Back to Isis of Isis Product-Specific Patents), Section 8.10.3 (Record Retention), Section 8.11 (Audits), Section 8.12.3 (Withholding Tax) (but only with respect to any indemnification obligations therein), Section 9.1.1 (Isis Technology and AstraZeneca Technology), Section 9.1.2 (Agreement Technology), Section 12.2.5 (Termination for Insolvency), Section 12.3 (Consequences of Termination of this Agreement), ARTICLE 11 (Indemnification) (but excluding Section 11.7 through Section 11.9), ARTICLE 13 (Confidentiality), ARTICLE 14 (Miscellaneous) and APPENDIX 1 (Definitions) (to the extent definitions are embodied in the foregoing listed Articles and Sections).

12.3.2. **Isis: Special Consequences of Certain Terminations**. If (A) this Agreement is terminated under Section 1.2.3, Section 2.2.3 or Section 2.2.4(b) with respect to STAT3 or [***] (as applicable), (B) AstraZeneca terminates the Agreement under Section 12.2.1 or (C) Isis terminates this Agreement under Section 12.2.2(b), Section 12.2.3(b) or Section 12.2.5, then, in addition to the terms set forth in Section 12.3.1, the following additional terms will also apply:

(i) AstraZeneca will and hereby does grant to Isis:

(1) a sublicensable, worldwide, exclusive license or sublicense, as the case may be, under all AstraZeneca Technology (excluding AstraZeneca Background IP) Controlled by AstraZeneca as of the date of such reversion that Covers the Discontinued Product; and

(2) a sublicensable, worldwide, non-exclusive license or sublicense, as the case may be, under all AstraZeneca Background IP Controlled by AstraZeneca as of the date of such reversion that Covers the Discontinued Product;

in each case solely to Develop, make, have made, use, sell, offer for sale, have sold, import and otherwise Commercialize the Discontinued Product in the Field (such licenses will be sublicensable by Isis in accordance with Section 6.1.4, *mutatis mutandis*); and *provided that* Isis shall, in accordance with ARTICLE 11, indemnify and hold harmless AstraZeneca and its Affiliates and Sublicensees from any Losses with respect to the Development and Commercialization of such Discontinued Product under such licenses.

(ii) AstraZeneca will assign back to Isis any Patent Rights that relate to the Discontinued Product previously assigned by Isis to AstraZeneca under this Agreement;

(iii) AstraZeneca will transfer to Isis for use with respect to the Development and Commercialization of the Discontinued Product, any Know-How, data, results, regulatory information, filings, and files in the possession of AstraZeneca, or copies thereof, as of the date of such termination or reversion that relate solely to such Discontinued Product, and any other information or material specified in Section 6.5;

(iv) AstraZeneca will grant to Isis a non-exclusive, royalty-free, fully paid up license under any trademarks that are specific to a Discontinued Product solely for use with such Discontinued Product; *provided, however*, that in no event will AstraZeneca have any obligation to license to Isis any trademarks used by AstraZeneca both in connection with the Product and in connection with the sale of any other product or service, including any AstraZeneca- or AstraZeneca-formative marks;

(v) Isis will control and be responsible for all aspects of the Prosecution and Maintenance of all Jointly-Owned Collaboration Patents, and AstraZeneca will provide Isis with (and will instruct its counsel to provide Isis with) all of the information and records in AstraZeneca's and its counsel's possession related to the Prosecution and Maintenance of such Jointly-Owned Collaboration Patents only in respect of the Discontinued Product;

(vi) upon Isis' written request pursuant to a mutually agreed supply agreement, AstraZeneca will sell to Isis any bulk API and finished Product in AstraZeneca's possession related to the Compounds that are the subject of the termination at the time of such termination, at a price equal to AstraZeneca's cost at the time such material was produced;

(vii) If Isis or any of its Affiliates or Sublicensees Commercializes a Discontinued Product for which AstraZeneca has paid Isis the license fee under Section 8.1(i), Section 8.1(ii) or Section 8.2 (as applicable), then following the First Commercial Sale of such Discontinued Product by Isis or its Affiliates or Sublicensees, Isis will pay AstraZeneca a royalty of [***]% of Annual worldwide Net Sales of such Discontinued Product until [***]; and

(viii) If there are any licensed rights granted by AstraZeneca to Isis under Section 12.3.2(i)(2), the Parties shall negotiate in good faith regarding a reasonable royalty for such Discontinued Product (not to exceed [***]% of Annual worldwide Net Sales of such Discontinued Product) to be paid by Isis to AstraZeneca for Discontinued Products covered by such licensed rights, with such royalty payments beginning on the date [***] and ending on the earlier of [***].

12.3.3. AstraZeneca: Special Consequences of Certain Terminations.

(a) If AstraZeneca terminates this Agreement under Section 12.2.2(a), Section 12.2.3(a) or Section 12.2.5, all of the provisions of Section 12.3.1 shall apply, *except that* AstraZeneca, its Affiliates, Sublicensees and Distributors shall have the right to sell any remaining inventory of Product, and AstraZeneca will pay Isis royalties in accordance with Section 8.8 on the Net Sales of such inventory of such Products to the extent not already paid.

(b) If AstraZeneca has the right to terminate this Agreement under Section 12.2.2(a), Section 12.2.3(a) or Section 12.2.5, but elects to continue the Agreement, the following provisions which shall be effective upon AstraZeneca's notice of such election, shall apply:

(i) AstraZeneca may require that Isis ceases performing any activities and co-operate and take such measures as may be requested to ensure a prompt and smooth transition of such activities to AstraZeneca or its designee; and may require that Isis cease to participate in the JSC. Without prejudice to the foregoing, if requested by AstraZeneca such measures shall include a technology transfer pursuant to the provisions of Section 6.5 or Section 6.1.4(c), in either case without charge to AstraZeneca; and

(ii) any money damages that may be awarded to AstraZeneca arising from the circumstances which gave rise to the right to terminate, and any costs (the amount of such costs as mutually agreed in good faith by the Parties) incurred by AstraZeneca in connection with the transition of Isis' responsibilities under this Agreement to AstraZeneca or its designee may be setoff against any monies owed by AstraZeneca to Isis as provided in Section 14.2.2.

(c) The provisions of this Section 12.3.3 will not preclude any 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 any Party's right to obtain performance of any obligation.

ARTICLE 13.
CONFIDENTIALITY

13.1. **Confidentiality; Exceptions**. Except to the extent expressly authorized by this Agreement or otherwise agreed in writing, the Parties agree that, during the Agreement Term and for five years thereafter, the receiving Party (the "***Receiving Party***") and its Affiliates will keep confidential and will not publish or otherwise disclose or use for any purpose other than as provided for in this Agreement any Confidential Information disclosed by the other Party or its Affiliates (the "***Disclosing Party***").

13.2. **Prior Confidentiality Agreement**. The Mutual Confidential Disclosure Agreement executed by Isis and AstraZeneca on April 11, 2011 (including any and all amendments thereto) (the "***CDA***") will govern disclosures of Confidential Information (as defined in the CDA) between the Parties prior to the Effective Date. All Confidential Information exchanged between the Parties on or after the Effective Date under this Agreement will be subject to the terms of this ARTICLE 13.

13.3. **Authorized Disclosure**. Except as expressly provided otherwise in this Agreement, a Receiving Party or its Affiliates may use and disclose to Third Parties Confidential Information of the Disclosing Party as follows: (i) solely in connection with the performance of its obligations or exercise of rights granted or reserved in this Agreement under confidentiality provisions no less restrictive than those in this Agreement, *provided,* that Confidential Information may be disclosed by a Receiving Party to a governmental entity or agency without requiring such entity or agency to enter into a confidentiality agreement; (ii) to the extent reasonably necessary to file or prosecute patent, copyright and trademark applications (subject to Section 13.4 below), complying with applicable governmental regulations, obtaining Approvals, conducting Pre-Clinical Studies or Clinical Studies, marketing the Product, or as otherwise required by applicable law, regulation, rule or legal process (including the rules of the SEC and any stock exchange); *provided, however*, that if a Receiving Party or any of its Affiliates is required by law or regulation to make any such disclosure of a Disclosing Party's Confidential Information it will, except where impracticable for necessary disclosures, give reasonable advance notice to the Disclosing Party of such disclosure requirement and will use its reasonable efforts to secure confidential treatment of such Confidential Information required to be disclosed; (iii) in communication with actual or potential lenders, investors, merger partners, acquirers, consultants, or professional advisors on a need-to-know basis, in each case under confidentiality provisions no less restrictive than those of this Agreement; (iv) to the extent such disclosure is required to comply with existing expressly stated contractual obligations owed to such Party's or its Affiliates' licensor with respect to any intellectual property licensed to the other Party under this Agreement; (v) subject to the terms of any protective order the Disclosing Party is using to protect its own Confidential Information, to prosecute or defend litigation as permitted by this Agreement, or (vi) as mutually agreed to in writing by the Parties.

13.4. **Press Release; Publications; Disclosure of Agreement**.

13.4.1. **Public Announcements – Generally**. Upon execution of this Agreement, the Parties will issue a joint press release announcing the existence of this Agreement in a form and substance agreed to in writing by the Parties. Except to the extent required to comply with Applicable Law, regulation, rule or legal process or as otherwise permitted in accordance with this Section 13.4, each Party agrees not to issue any other press release or other public statement disclosing other information relating to this Agreement or the terms of this Agreement or the transactions contemplated hereby without the prior written consent of the other Party, which consent will not be unreasonably withheld or delayed.

13.4.2. **Use of Name**. Except as set forth in Section 13.4.8, neither Party will use the other Party's name in a press release or other publication without first obtaining the prior consent of the Party to be named.

13.4.3. **Notice of Significant Events**. Each Party will immediately notify (and provide as much advance notice as possible, but at a minimum three Business Days advance notice to) the other of any significant event related to a Product (including any data or regulatory advice or approval) so that the Parties may analyze the need to or desirability of publicly disclosing or reporting such event. Notwithstanding Section 13.4.1 above, any press release or other similar public communication by either Party related to a Product's efficacy or safety data and/or results, will be submitted to the other Party for review and approval at least three Business Days in advance of such proposed public disclosure, which approval will not be unreasonably withheld or delayed.

13.4.4. **Disclosure of Information Related to Products**. The Party that has primary control of a Product (i.e., Isis, with respect to Products for which AstraZeneca has not exercised its Option; and AstraZeneca, with respect to STAT3 Products, [***] Products and Products for which AstraZeneca has exercised its Option) has the sole right, consistent with its practice with its other products, to issue press releases or other similar public communications to disclose the progress and results regarding such Product to the public in order to satisfy its disclosure obligations under Applicable Law or to remain consistent with its normal public disclosure practices (but for clarity, in connection with the Oncology Collaboration, such disclosure would not involve disclosing a Reserved Target or an Oncology Lead Candidate until such target had become a Development Candidate) ; *provided, that* any proposed press release or other similar public communication by such controlling Party disclosing regulatory discussions, the efficacy or safety data or results related to the Product or such controlling Party's sales projections, (i) such controlling Party will submit such proposed communication to the non-controlling Party for review at least two Business Days in advance of such proposed public disclosure, (ii) the non-controlling Party will have the right to review and recommend changes to such communication, and (iii) the controlling Party will in good faith consider any changes that are timely recommended by the non-controlling Party. In addition, if at any time during such two Business Day review period, the other Party informs such Party that its proposed public disclosure discloses inventions made by either Party in the course of the research or development under this Agreement that have not yet been protected through the filing of a patent application, or the public disclosure could be expected to have a material adverse effect on any Patent Rights or Know-How solely owned or Controlled by such other Party, then such Party will either (x) delay such proposed publication for a period of time reasonably necessary to permit the timely preparation and first filing of patent application(s) on the information involved, or (y) to the extent permitted by Applicable Law, remove the identified information prior to disclosure. While the Parties acknowledge that it may be interpreted that there is overlap between this Section 13.4.4 and Section 13.4.5, for clarity, the Parties intend for this Section 13.4.4 to address public disclosures that are not primarily of a scientific or scholarly nature (which are meant to be disclosed in accordance with Section 13.4.5 below) but rather this Section 13.4.4 is designed to address more urgent disclosures required under Applicable Law or to provide investors with material information regarding Products or this Agreement in a timely manner so that they may make informed investment decisions in Isis' or AstraZeneca's stock.

13.4.5. **Scientific or Clinical Presentations**. Regarding any proposed scientific publications or public presentations related to summaries of results from any Clinical Studies generated by Isis or AstraZeneca for a Product, the Parties acknowledge that scientific lead time is a key element of the value of a Product under this Agreement and further agree to use Commercially Reasonable Efforts to control public scientific disclosures of the results of the research or development activities under this Agreement to prevent any potential adverse effect of any premature public disclosure of such results, for example, without limitation, intellectual property protection, competitive intelligence, prejudicing the optimal presentation at major meetings. For clarity, in connection with the Oncology Collaboration, such disclosure would not involve disclosing a Reserved Target or an Oncology Lead Candidate until such target had become a Development Candidate unless agreed otherwise by the Parties. The Parties will establish a procedure for publication review and each Party will first submit to the other Party through the Joint Patent Committee an early draft of all such publications or presentations, whether they are to be presented orally or in written form, at least 30 days prior to submission for publication including to facilitate the publication of any summaries of Clinical Studies data and results as required on the clinical trial registry of each respective Party. Each Party will review such proposed publication in order to avoid the unauthorized disclosure of a Party's Confidential Information and to preserve the patentability of inventions arising from the Collaboration Plans. If, during such 30 day period, the other Party informs such Party that its proposed publication contains Confidential Information of the other Party, then such Party will delete such Confidential Information from its proposed publication. In addition, if at any time during such 30 day period, the other Party informs such Party that its proposed publication discloses inventions made by either Party in the course of the research or development under this Agreement that have not yet been protected through the filing of a patent application, or the public disclosure of such proposed publication could be expected to have a material adverse effect on any Patent Rights or Know-How solely owned or Controlled by such other Party, then such Party will either (i) delay such proposed publication for up to 60 days from the date the other Party informed such Party of its objection to the proposed publication, to permit the timely preparation and first filing of patent application(s) on the information involved or (ii) remove the identified disclosures prior to publication.

13.4.6. **SEC Filings**. Each Party will give the other Party a reasonable opportunity to review all material filings with the SEC describing the terms of this Agreement prior to submission of such filings, and will give due consideration to any reasonable comments by the non-filing Party relating to such filing.

13.4.7. **Subsequent Disclosure**. Notwithstanding the foregoing, to the extent information regarding this Agreement or the Product has already been publicly disclosed, either Party (or its Affiliates) may subsequently disclose the same information to the public without the consent of the other Party.

13.4.8. **Acknowledgment**. Each Party will acknowledge in any press release, public presentation or publication regarding the collaboration or the Product, the other Party's role in discovering and developing the Product or Discontinued Product, as applicable, that the Product is under license from Isis and otherwise acknowledge the contributions from the other Party, and each Party's stock ticker symbol (e.g., Nasdaq: ISIS; NYE: AZN). Isis may include the Product (and identify AstraZeneca as its partner for the Product) in Isis' drug pipeline.

ARTICLE 14.
MISCELLANEOUS

14.1. **Dispute Resolution**.

14.1.1. **Resolution by Senior Representatives**. The Parties will seek to settle amicably any and all disputes, controversies or claims arising out of or in connection with this Agreement. For clarity, any decision within the JSC's decision-making authority will be finally decided by the JSC. Any dispute between the Parties which is outside the JSC's decision-making authority will be promptly presented to the Senior Vice President, Research of AstraZeneca and the Chief Operating Officer of Isis (the "***Senior Representatives***"), or their respective designees, for resolution. Such Senior Representatives, or their respective designees, will meet in-person or by teleconference as soon as reasonably possible thereafter, and use their good faith efforts to mutually agree upon the resolution of the dispute, controversy or claim. Any dispute within the JSC's decision-making authority will not be subject to arbitration.

14.1.2. **Request for Arbitration**. If after negotiating in good faith pursuant to Section 14.1.1, the Parties fail after good faith discussions undertaken within reasonable promptness, to reach an amicable agreement within 90 days, then either Party may upon written notice to the other submit to binding arbitration pursuant to Section 14.1.3 below. No statements made by either Party during such discussions will be used by the other Party or admissible in arbitration or any other subsequent proceeding for resolving the dispute.

14.1.3. Arbitration.

(a) Subject to Section 14.2, any dispute, claim or controversy arising from or related in any way to this Agreement or the interpretation, application, breach, termination or validity thereof, including any claim of inducement of this Agreement by fraud or otherwise, not resolved under the provisions of Section 14.1.1 will be resolved by final and binding arbitration conducted in accordance with the terms of this Section 14.1.3. The arbitration will be held in New York, New York, USA according to Rules of Arbitration of the International Chamber of Commerce ("***ICC***"). The arbitration will be conducted by a panel of three arbitrators with significant experience in the pharmaceutical industry, unless otherwise agreed by the Parties, appointed in accordance with applicable ICC rules. Any arbitration herewith will be conducted in the English language to the maximum extent possible. The arbitrators will render a written decision no later than six months following the selection of the arbitrators, including a basis for any damages awarded and a statement of how the damages were calculated. Any award will be promptly paid in U.S. dollars free of any tax, deduction or offset. Each Party agrees to abide by the award rendered in any arbitration conducted pursuant to this Section 14.1.3. With respect to money damages, nothing contained herein will be construed to permit the arbitrator or any court or any other forum to award punitive or exemplary damages, except in the case of breach of ARTICLE 13. By entering into this agreement to arbitrate, the Parties expressly waive any claim for punitive or exemplary damages, except in the case of breach of ARTICLE 13. Each Party will pay its legal fees and costs related to the arbitration (including witness and expert fees). Judgment on the award so rendered will be final and may be entered in any court having jurisdiction thereof.

(b) EACH PARTY HERETO WAIVES ITS RIGHT TO TRIAL OF ANY ISSUE BY JURY. EACH PARTY HERETO WAIVES ANY CLAIM FOR ATTORNEYS' FEES AND COSTS AND PREJUDGMENT INTEREST FROM THE OTHER.

14.1.4. Court Actions. Nothing contained in this Agreement will deny either Party the right to seek injunctive or other equitable relief from a court of competent jurisdiction in the context of a *bona fide* emergency or prospective irreparable harm, and such an action may be filed and maintained notwithstanding any ongoing dispute resolution discussions or arbitration proceeding. In addition, either Party may bring an action in any court of competent jurisdiction to resolve disputes pertaining to the validity, construction, scope, enforceability, infringement or other violations of patents or other proprietary or intellectual property rights, and no such claim will be subject to arbitration pursuant to Section 14.1.3.

14.2. Governing Law; Jurisdiction; Equitable Relief, Losses.

14.2.1. This Agreement will be governed by and construed and enforced in accordance with the laws of the State of New York, USA, without reference to any rules of conflicts of laws. For clarification, any dispute relating to the scope, validity, enforceability or infringement of any Patents will be governed by and construed and enforced in accordance with the patent laws of the applicable jurisdiction.

14.2.2. Each Party acknowledges and agrees that the restrictions set forth in Section 5.1 of this Agreement are reasonable and necessary to protect the legitimate interests of the other Party and that the other Party would not have entered into this Agreement in the absence of such restrictions, and that any breach or threatened breach of any of these provisions will probably result in irreparable injury to the other Party for which there will be no adequate remedy at law. In the event of a breach or threatened breach of any such provision, each Party will be authorized and entitled to obtain from any court of competent jurisdiction equitable relief, whether preliminary or permanent, specific performance and an equitable accounting of all earnings, profits and other benefits arising from such breach, which rights will be cumulative and in addition to any other rights or remedies to which such Party may be entitled in law or equity. Each Party agrees to waive any requirement that the other Party (a) post a bond or other security as a condition for obtaining any such relief, and (b) show irreparable harm, balancing of harms, consideration of the public interest or inadequacy of monetary damages as a remedy. Nothing in this Section 14.2.2 is intended, or should be construed, to limit a Party's rights to equitable relief or any other remedy for a breach of any other provision of this Agreement. Except for (i) the offsets and credits explicitly set forth in Section 8.9.2(a), Section 8.9.4(b) and Section 8.11, (ii) any amount awarded to be paid by one Party to the other by the panel of arbitrators in a final and binding arbitration proceeding adjudicated under Section 14.1.3, and (iii) any offset of undisputed but unpaid amounts under this Agreement, neither Party will have the right to setoff any amount it is owed or believes it is owed against payments due or payable to the other Party under this Agreement.

14.2.3. Neither Party will be entitled to recover any Losses relating to any matter arising under one provision of this Agreement to the extent that such Party has already recovered Losses with respect to such matter pursuant to other provisions of this Agreement (including recoveries under Section 11.1 or Section 11.2, and the offsets under Section 8.9.4(b)).

14.3. **Assignment and Successors**. Neither this Agreement nor any obligation of a Party hereunder may be assigned by either Party without the consent of the other, which will not be unreasonably withheld, delayed or conditioned, except that each Party may assign this Agreement and the rights, obligations and interests of such Party, in whole or in part, without the other Party's consent, to any of its Affiliates, to any purchaser of all or substantially all of its assets to which this Agreement relates or to any successor corporation resulting from any merger, consolidation, share exchange or other similar transaction; *provided*, if a Party transfers or assigns this Agreement to [***] described in this Agreement, then such transferring Party (or such Affiliate) ("***Transferring Party***"), will [***] due that the Transferring Party is obligated to pay to the non-transferring Party ("***Non-Transferring Party***") under ARTICLE 8 for the [***] such that the Non-Transferring Party receives [***]. In addition, Isis may assign or transfer its rights to receive payments under this Agreement (but no liabilities), without AstraZeneca's consent, to an Affiliate or to a Third Party in connection with a payment factoring transaction; *provided, however*, that Isis will provide AstraZeneca advance notice of any such proposed payment factoring transaction giving AstraZeneca a reasonable opportunity to provides comments (which Isis will consider in good faith); [***]. Any purported assignment or transfer made in contravention of this Section 14.3 will be null and void.

To the extent the Non-Transferring Party utilizes a [***] in any year, the Non-Transferring Party will [***] the Transferring Party [***]. To assist the Transferring Party in determining when a [***] pursuant to the foregoing sentence, beginning with the first Annual tax return for the year in which the Transferring Party [***] payment under this Section 14.3, and each year thereafter (including, for clarity, all years in which the Non-Transferring Party [***] or [***]), the Non-Transferring Party will provide the Transferring Party with the Non-Transferring Party s' Annual tax returns (federal and state) and, in years in which the Non-Transferring Party utilizes the [***], supporting documentation for such [***].

14.4. **Force Majeure**. No Party will be held responsible to the other Party nor be deemed to be in default under, or in breach of any provision of, this Agreement for failure or delay in performing any obligation of this Agreement when such failure or delay is due to force majeure, and without the fault or negligence of the Party so failing or delaying. For purposes of this Agreement, force majeure means a cause beyond the reasonable control of a Party, which may include acts of God; acts, regulations, or laws of any government; war; terrorism; civil commotion; fire, flood, earthquake, tornado, tsunami, explosion or storm; pandemic; epidemic and failure of public utilities or common carriers. In such event the Party so failing or delaying 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 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 a maximum of 90 days, after which time the Parties will negotiate in good faith any modifications of the terms of this Agreement that may be necessary to arrive at an equitable solution, unless the Party giving such notice has set out a reasonable timeframe and plan to resolve the effects of such force majeure and executes such plan within such timeframe. To the extent possible, each Party will use reasonable efforts to minimize the duration of any force majeure.

14.5. **Notices**. Any notice or request required or permitted to be given under or in connection with this Agreement will be deemed to have been sufficiently given if in writing and personally delivered or sent by certified mail (return receipt requested), facsimile transmission (receipt verified), or overnight express courier service (signature required), prepaid, to the Party for which such notice is intended, at the address set forth for such Party below:

If to Isis, addressed to:	Isis Pharmaceuticals, Inc. 2855 Gazelle Court Carlsbad, CA 92010 Attention: Chief Operating Officer Fax: 760-918-3592
with a copy to:	Isis Pharmaceuticals, Inc. 2855 Gazelle Court Carlsbad, CA 92010 Attention: General Counsel Fax: 760-268-4922
If to AstraZeneca, addressed to:	AstraZeneca AB SE-431 83 Molndal Sweden Attention: Legal Department Fax: +46 31 7763871
with a copy to:	AstraZeneca UK Limited Strategic Planning and Business Development Alderley House Alderley Park Macclesfield Chehsire SK10 4TF Fax: +44 1625 518805

or to such other address for such Party as it will have specified by like notice to the other Party; *provided that* notices of a change of address will be effective only upon receipt thereof. If delivered personally or by facsimile transmission, the date of delivery will be deemed to be the date on which such notice or request was given. If sent by overnight express courier service, the date of delivery will be deemed to be the next Business Day after such notice or request was deposited with such service. If sent by certified mail, the date of delivery will be deemed to be the third Business Day after such notice or request was deposited with the U.S. Postal Service. It is understood and agreed that this Section is not intended to govern the day to day business communications necessary between the parties in performing their duties, in due course, under the terms of this Agreement.

14.6. **Export Clause**. Each Party acknowledges that the laws and regulations of the United States restrict the export and re-export of commodities and technical data of United States origin. Each Party agrees that it will not export or re-export restricted commodities or the technical data of the other Party in any form without the appropriate United States and foreign government licenses.

14.7. **Waiver**. Neither Party may waive or release any of its rights or interests in this Agreement except in writing. The failure of either Party to assert a right hereunder or to insist upon compliance with any term or condition of this Agreement will not constitute a waiver of that right or excuse a similar subsequent failure to perform any such term or condition. No waiver by either Party of any condition or term in any one or more instances will be construed as a continuing waiver or subsequent waiver of such condition or term or of another condition or term.

14.8. **Severability**. If any provision of this Agreement is held to be illegal, invalid or unenforceable by a court of competent jurisdiction, such adjudication will not affect or impair, in whole or in part, the validity, enforceability, or legality of any remaining portions of this Agreement. All remaining portions will remain in full force and effect as if the original Agreement had been executed without the invalidated, unenforceable or illegal part.

14.9. **Entire Agreement; Modifications**. This Agreement (including the attached Appendices and Schedules) sets forth and constitutes the entire agreement and understanding between the Parties with respect to the subject matter hereof, and all prior agreements, understanding, promises and representations, whether written or oral, with respect thereto are superseded hereby. Each Party confirms that it is not relying on any representations or warranties of the other Party except as specifically set forth herein. No amendment, modification, release or discharge will be binding upon the Parties unless in writing and duly executed by authorized representatives of both Parties.

14.10. **Relationship of the Parties**. It is expressly agreed that the Parties will be independent contractors of one another and that the relationship between the Parties will not constitute a partnership, joint venture or agency.

14.11. **Interpretation**. Except as otherwise explicitly specified to the contrary, (a) references to a section, exhibit or schedule means a section of, or schedule or exhibit to this Agreement, unless another agreement is specified, (b) the word "including" (in its various forms) means "including without limitation," (c) the words "will" and "shall" have the same meaning, (d) references to a particular statute or regulation include all rules and regulations thereunder and any predecessor or successor statute, rules or regulation, in each case as amended or otherwise modified from time to time, (e) references to a particular Person include such Person's successors and assigns to the extent not prohibited by this Agreement, (f) unless otherwise specified, "$" is in reference to United States dollars, and (g) the headings contained in this Agreement, in any exhibit or schedule to this Agreement and in the table of contents to this Agreement are for convenience only and will not in any way affect the construction of or be taken into consideration in interpreting this Agreement.

14.12. **Books and Records**. Any books and records to be maintained under this Agreement by a Party or its Affiliates or Sublicensees will be maintained in accordance with generally accepted accounting principles, or in the case of non-United States sales, other applicable accounting standards, consistently applied.

14.13. **Further Actions**. Each Party will execute, acknowledge and deliver such further instruments, and do all such other acts, as may be necessary or appropriate in order to carry out the expressly stated purposes and the clear intent of this Agreement.

14.14. **Construction of Agreement**. The terms and provisions of this Agreement represent the results of negotiations between the Parties and their representatives, each of which has been represented by counsel of its own choosing, and neither of which has acted under duress or compulsion, whether legal, economic or otherwise. Accordingly, the terms and provisions of this Agreement will be interpreted and construed in accordance with their usual and customary meanings, and each of the Parties hereto hereby waives the application in connection with the interpretation and construction of this Agreement of any rule of law to the effect that ambiguous or conflicting terms or provisions contained in this Agreement will be interpreted or construed against the Party whose attorney prepared the executed draft or any earlier draft of this Agreement.

14.15. **Supremacy**. In the event of any express conflict or inconsistency between this Agreement and any Schedule or Appendix hereto, the terms of this Agreement will apply. The Parties understand and agree that the Schedules and Appendices hereto are not intended to be the final and complete embodiment of any terms or provisions of this Agreement, and are to be updated from time to time during the Agreement Term, as appropriate and in accordance with the provisions of this Agreement.

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

14.17. **Compliance with Laws**. Each Party will, and will ensure that its Affiliates and Sublicensees will, comply with all relevant laws and regulations in exercising its rights and fulfilling its obligations under this Agreement.

[SIGNATURE PAGE FOLLOWS]

* - * - * - *

IN WITNESS WHEREOF, the Parties have caused this Agreement to be executed by their representatives thereunto duly authorized as of the Effective Date.

ASTRAZENECA AB

By: */s/ Jan-Olof Jacke*
Name: Jan-Olof Jacke
Title: CFO AstraZeneca AB

IN WITNESS WHEREOF, the Parties have caused this Agreement to be executed by their representatives thereunto duly authorized as of the Effective Date.

ISIS PHARMACEUTICALS, INC.

By: */s/ B. Lynne Parshall*
Name: B. Lynne Parshall
Title: Chief Operating Officer

List of Appendices and Schedules

APPENDIX 1 – Definitions

APPENDIX 2 –STAT3 Research and Development Plan and [***] Research and Development Plan

APPENDIX 3 – Oncology Research and Development Plans

APPENDIX 4 – Isis' Lead Candidate Checklist

APPENDIX 5 – Examples Illustrating Separate Indications

APPENDIX 6 – Isis In-License Agreements

APPENDIX 7 – Isis Core Technology Patents

APPENDIX 8 – Isis Manufacturing and Analytical Patents

APPENDIX 9 – Isis Product-Specific Patents

APPENDIX 10 – Prior Agreements

APPENDIX 11 – IND Support Package

SCHEDULE 3.3.6 – Flow chart of Reserved Target and Oncology Target selection

SCHEDULE 4.1.1 – JSC Governance

SCHEDULE 4.1.3(C) – AstraZeneca's Performance Metrics

SCHEDULE 4.2 – Alliance Management Activities

SCHEDULE 4.6.1 – Isis' Fully Absorbed Cost of Goods Methodology

SCHEDULE 4.6.1(D) – Manufacturing Services Agreement Principles

SCHEDULE 4.7 – Bioethics Policy

APPENDIX 1

DEFINITIONS

For purposes of this Agreement, the following capitalized terms will have the following meanings:

"$" means the lawful currency of the United States.

"***Acceptance of Filing***" means, with respect to an NDA, MAA or JNDA filed for a Product, (a) in the United States, the receipt of written notice from the FDA in accordance with 21 C.F.R. §314.101(a)(2) that such NDA is officially "*filed*," (b) in the European Union, receipt by AstraZeneca, its Affiliate or Sublicensee of written notice of acceptance by the EMA of such MAA for filing under the centralized European procedure in accordance with any feedback received from European Regulatory Authorities; *provided that* if the centralized filing procedure is not used, then Acceptance of Filing will be determined upon the acceptance of such MAA by the applicable Regulatory Authority in a Major Country in the EU, and (c) in Japan, receipt by AstraZeneca, its Affiliate or Sublicensee of written notice of acceptance of filing of such JNDA from the Koseisho (i.e., the Japanese Ministry of Health and Welfare, or any successor agency thereto).

"***Additional Core IP***" has the meaning set forth in Section 8.9.3.

"***Additional Plan Costs***" means [***].

"***Affiliate***" of an entity means any corporation, firm, partnership or other entity which directly or indirectly through one or more intermediaries controls, is controlled by or is under common control with a Party to this Agreement. An entity will be deemed to control another entity if it (i) owns, directly or indirectly, at least 50% of the outstanding voting securities or capital stock (or such lesser percentage which is the maximum allowed to be owned by a foreign corporation in a particular jurisdiction) of such other entity, or has other comparable ownership interest with respect to any entity other than a corporation; or (ii) has the power, whether pursuant to contract, ownership of securities or otherwise, to direct the management and policies of the entity.

"***Agreement***" has the meaning set forth in the Preamble of this Agreement.

"***Agreement Term***" has the meaning set forth in Section 12.1.

*"**Alliance Manager"*** has the meaning set forth in Section 4.2.

"***Annual***" or "***Annually***" means the period covering a Calendar Year or occurring once per Calendar Year, as the context requires.

"Anti-Corruption Laws" means the U.S. Foreign Corrupt Practices Act, as amended, the UK Bribery Act 2010, as amended, and any other applicable anti-corruption laws and laws for the prevention of fraud, racketeering, money laundering or terrorism.

"***API***" means the bulk active pharmaceutical ingredient manufactured in accordance with cGMP for a Product.

"***Applicable Law***" or "***Law***" means all applicable laws, statutes, rules, regulations and other pronouncements having the effect of law of any federal, national, multinational, state, provincial, county, city or other political subdivision, agency or other body, domestic or foreign, including any applicable rules, regulations, guidelines, or other requirements of the Regulatory Authorities that may be in effect from time to time.

"***Approval***" means (i) with respect to a Product in the EU, the earlier to occur of (A) approval from the applicable Regulatory Authority in at least one member state in the EU sufficient for the manufacture, distribution, use, marketing and sale of such Product, including pricing approval, in such jurisdiction in accordance with Applicable Laws, or (B) the first commercial sale of a Product in the EU; and (ii) with respect to a Product in any regulatory jurisdiction other than the EU, approval sufficient for the manufacture, distribution, use, marketing and sale of such Product in such jurisdiction in accordance with Applicable Laws.

"[***]" means [***].

"[***] ***Research and Development Plan***" means the research and development plan for the [***] Program (initially as attached hereto as Appendix 2) as amended from time to time in accordance with this Agreement.

"[***] ***Compound***" means any ASO that is designed to bind to the RNA that encodes [***], where such ASO is (i) discovered or Controlled by Isis prior to the Effective Date, or (ii) discovered by Isis in the performance of the [***] Research and Development Plan.

"[***] ***Development Candidate***" means the [***] Compound selected by AstraZeneca as a Development Candidate.

"[***] ***Development Candidate Decision Deadline***" has the meaning set forth in Section 2.2.3.

"[***] ***Lead Candidate***" means the Lead Candidate designated by Isis as a potential [***] Development Candidate.

"[***] ***Lead Compound***" has the meaning set forth in Section 5.1.3. The [***] Lead Compound sequences will be set forth in the minutes of the JSC.

"[***] ***Product***" means a finished product containing an [***] Compound as an active pharmaceutical ingredient (including any salt, hydrate, solvate, or prodrug thereof).

"[***] ***Program***" means the research and development program for [***] Products under this Agreement.

"***ASO***" means a single-stranded oligonucleotide compound, or analog, variant, mimic, or mimetic thereof, having a sequence that is at least six bases long and that modulates expression or splicing of a gene target via the binding, partially or wholly, of such compound to the RNA of such gene target.

"***Assignable*** [***] ***Product-Specific Patents***" means Patent Rights Controlled by Isis or any of its Affiliates on or after the Effective Date *claiming*: (i) the specific composition of matter (the exact sequence and chemistry) of the [***] Development Candidate and the other [***] Lead Compounds (or any [***] Product incorporating such [***] Development Candidate or other [***] Lead Compounds), and/or (ii) methods of using such [***] Development Candidate and such other [***] Lead Compounds (or any [***] Product incorporating such [***] Development Candidate or other [***] Lead Compounds) as a prophylactic, therapeutic or diagnostic.

"***AstraZeneca***" has the meaning set forth in the Preamble of this Agreement.

"***AstraZeneca*** [***]***-Field***" has the meaning set forth in Section 5.1.3(a)(i).

"***AstraZeneca Background Intellectual Property***" means any Know-How and Patent Rights that: (i) were Controlled by AstraZeneca prior to the Effective Date; and/or (ii) are Controlled by AstraZeneca on or after the Effective Date that were not created or acquired in connection with performance of any Collaboration Plan and/or in connection with the exploitation of a Compound or Product, which Patents and Know-How is necessary to Develop, register, Manufacture or Commercialize a Product in the Field.

"***AstraZeneca Conducted Activities***" means, under a Collaboration Plan, any and all research, pre-clinical and/or clinical activities that are not Isis Conducted Activities.

"***AstraZeneca Full Royalty***" has the meaning set forth in Section 8.8.1.

"***AstraZeneca Indemnitees***" has the meaning set forth in Section 11.2.

"***AstraZeneca-Initiated Changes***" means any changes (including number of subjects, duration of dosing, additional studies, additional endpoints, additional analysis, etc.) to a Collaboration Plan that are requested by AstraZeneca (including any changes requested or required by a Regulatory Authority).

"***AstraZeneca Know-How***" means any Know-How owned, used, developed by, or licensed to AstraZeneca or its Affiliates, in connection with AstraZeneca's performance of its obligations under this Agreement, in each case to the extent Controlled by AstraZeneca or its Affiliates at any time during the Agreement Term that is necessary to Develop, register, Manufacture or Commercialize a Product in the Field and such Know-How does not constitute AstraZeneca Background IP.

"***AstraZeneca Patents***" means any Patent Rights owned, used, developed by, or licensed to AstraZeneca or its Affiliates that are invented by AstraZeneca or its Affiliates or licensors in connection with AstraZeneca's performance of its obligations under this Agreement, in each case to the extent Controlled by AstraZeneca or its Affiliates at any time during the Agreement Term that is necessary or useful to Develop, register, Manufacture or Commercialize a Product in the Field and such patents do not constitute AstraZeneca Background IP.

"***AstraZeneca Product-Specific Patents***" means all Product-Specific Patents owned, used, created, developed by, or licensed to AstraZeneca or its Affiliates (i) as of the Effective Date, or (ii) arising at any time during the Agreement Term, in each case to the extent (x) Controlled by AstraZeneca or its Affiliates in connection with performance of obligations under this Agreement, and (y) such Product-Specific Patents do not constitute AstraZeneca Background IP.

"***AstraZeneca-Prosecuted Patents***" has the meaning set forth in Section 9.2.5(b).

"***AstraZeneca Supported Pass-Through Costs***" means [***].

"***AstraZeneca Technology***" means AstraZeneca's interest in Jointly-Owned Collaboration Technology, AstraZeneca Product-Specific Patents, AstraZeneca Know-How, AstraZeneca Patents, including AstraZeneca Background Intellectual Property, and any trademarks described in Section 6.1.8, owned, used, developed by, or licensed to AstraZeneca or its Affiliates that are necessary or useful to Develop, register, Manufacture or Commercialize a Product.

"***Audit***" has the meaning set forth in Section 11.7.6.

"***Audit Report***" has the meaning set forth in Section 8.11.

"***Bankruptcy Code***" has the meaning set forth in Section 12.2.5(b).

"***BMT Patient***" has the meaning set forth in Section 1.2.3(b).

"***Breaching Party***" means the Party that is believed by the Non-Breaching Party to be in material breach of this Agreement.

"***Business Day***" means any day other than a Saturday or Sunday on which banking institutions in New York, US and London, England are open for business.

"***Calendar Quarter***" means a period of three consecutive calendar months ending on the last day of March, June, September, or December, respectively, and will also include the period beginning on the Effective Date and ending on the last day of the Calendar Quarter in which the Effective Date falls.

"***Calendar Year***" means a year beginning on January 1 (or, with respect to 2012, the Effective Date) and ending on December 31.

"***CDA***" has the meaning set forth in Section 13.2.

"***cGMP***" means current Good Manufacturing Practices as specified in the United States Code of Federal Regulations, ICH Guideline Q7A, or equivalent laws, rules, or regulations of an applicable Regulatory Authority at the time of manufacture.

"***Change of Control Event***" means any (a) direct or indirect acquisition of all or substantially all of the assets of Isis, (b) direct or indirect acquisition by a Person, or group of Persons acting in concert, of [***]% or more of the voting equity interests of Isis, (c) tender offer or exchange offer that results in any Person, or group of Persons acting in concert, beneficially owning [***]% or more of the voting equity interests of Isis, or (d) merger, consolidation, other business combination or similar transaction involving Isis, pursuant to which any Person owns all or substantially all of the consolidated assets, net revenues or net income of Isis, taken as a whole, or which results in the holders of the voting equity interests of Isis immediately prior to such merger, consolidation, business combination or similar transaction ceasing to hold [***]% or more of the combined voting power of the surviving, purchasing or continuing entity immediately after such merger, consolidation, other business combination or similar transaction, in all cases where such transaction is to be entered into with any Person other than AstraZeneca or its Affiliates.

"***CMO***" means a Third Party primarily engaged in providing contract manufacturing or services and is not engaged in drug discovery, development or commercialization of pharmaceutical products.

"***Claims***" has the meaning set forth in Section 11.1.

"***Clinical Study***" or "***Clinical Studies***" means a Phase 1 Trial, Phase 2 Trial, a Registration-Directed Trial, or such other study in humans that is conducted in accordance with good clinical practices and is designed to generate data in support or maintenance of an NDA, MAA, JNDA or other similar marketing application.

"***Collaboration Plan***" means (i) the STAT3 Research and Development Plan, (ii) the [***] Research and Development Plan, or (iii) any Oncology Research and Development Plan.

"***Commercialize***," "***Commercialization***" or "***Commercializing***" means any and all activities directed to marketing, promoting, detailing, distributing, importing, having imported, exporting, having exported, selling or offering to sell a Product following receipt of Approval for the Product in the applicable country, including conducting pre-and post-Approval activities, including studies reasonably required to increase the market potential of the Product and studies to provide improved formulation and Product delivery, and launching and promoting the Product in each country.

"***Commercializing Party***" means (a) AstraZeneca, with respect to a Product that is being Developed and Commercialized by or on behalf of AstraZeneca, its Affiliates or Sublicensees hereunder, and (b) Isis, with respect to a Discontinued Product that is being Developed and Commercialized by or on behalf of Isis, its Affiliates or Sublicensees hereunder.

"***Commercially Reasonable Efforts***" means that level of efforts and resources, at the relevant point in time, commonly used in the pharmaceutical industry for a product of similar commercial potential at a similar stage in its lifecycle, taking into consideration relative safety and efficacy, product profile, the competitiveness of the marketplace, market potential, the relative profitability of the product (including pricing and reimbursement status) and other relevant factors, including technical, legal, scientific and/or medical factors. Without limiting any of the foregoing, (A) Commercially Reasonable Efforts as it applies to AstraZeneca's Development or Commercialization of a Product hereunder includes the use of Commercially Reasonable Efforts to perform the (i) AstraZeneca Conducted Activities under each Collaboration Plan in accordance with the timelines set forth therein, and (ii) activities set forth in each Integrated Product Plan; and (B) Commercially Reasonable Efforts as it applies to Isis' Development of a Product hereunder includes use of Commercially Reasonable Efforts to perform the Isis Conducted Activities under each Collaboration Plan in accordance with the timelines set forth therein.

"***Competitive Infringement***" has the meaning set forth in Section 9.5.1.

"***Completion of the IND-Enabling Toxicology Studies***" means [***].

"***Compound***" means (i) an [***] Compound, (ii) a STAT3 Compound, or (iii) an Oncology Compound.

"***Confidential Information***" means any confidential or proprietary information or materials, patentable or otherwise, in any form (written, oral, photographic, electronic, magnetic, or otherwise) which is disclosed by the Disclosing Party or otherwise received or accessed by the Receiving Party in the course of performing its obligations or exercising its rights under this Agreement, including trade secrets, Know-How, inventions or discoveries, proprietary information, formulae, processes, techniques and information relating to the past, present and future marketing, financial, and research and development activities of any product or potential product or useful technology of the Disclosing Party or its Affiliates and the pricing thereof. "*Confidential Information*" does not include information that:

(a) was in the lawful knowledge and possession of the Receiving Party or its Affiliates prior to the time it was disclosed to, or learned by, the Receiving Party or its Affiliates, or was otherwise developed independently by the Receiving Party or its Affiliates, as evidenced by written records kept in the ordinary course of business, or other documentary proof of actual use by the Receiving Party or its Affiliates;

(a) was generally available to the public or otherwise part of the public domain at the time of its disclosure to the Receiving Party or its Affiliates;

(b) became generally available to the public or otherwise part of the public domain after its disclosure and other than through any act or omission of the Receiving Party or its Affiliates in breach of this Agreement; or

(c) was disclosed to the Receiving Party or its Affiliates, other than under an obligation of confidentiality, by a Third Party who had no obligation to the Disclosing Party or its Affiliates not to disclose such information to others.

"***Control***" or "***Controlled***" means possession of the ability to grant a license or sublicense hereunder without violating the terms of any agreement with any Third Party; *provided, however*, that if a Party has a right to grant a license or sublicense, with respect to an item of intellectual property to the other Party only upon payment of compensation (including milestones or royalties) to a Third Party ("***Third Party Compensation***") (other than Isis Supported Pass-Through Costs in the case of Isis, and other than AstraZeneca Supported Pass-Through Costs in the case of AstraZeneca), then the first Party will be deemed to have "*Control*" of the relevant item of intellectual property only if the other Party agrees to bear the cost of such Third Party Compensation. Notwithstanding anything to the contrary under this Agreement, with respect to any Third Party that becomes an Affiliate of a Party after the Effective Date (including a Third Party acquirer), no intellectual property of such Third Party will be included in the licenses granted hereunder by virtue of such Third Party becoming an Affiliate of such Party.

"***Cover***," "***Covered***" or "***Covering***" means, with respect to a patent, that, but for rights granted to a Person under such patent, the act of making, using or selling by such Person would infringe a Valid Claim included in such patent, or in the case of a patent that is a patent application, would infringe a Valid Claim in such patent application if it were to issue as a patent.

"***CREATE Act***" means the Cooperative Research and Technology Enhancement Act of 2004, 35 U.S.C. § 103(c)(2)-(c)(3).

"***CSID Criteria***" means the candidate selection identification criteria used by AstraZeneca to seek internal approval to advance a Development Candidate.

"***Develop***," "***Developing***" or "***Development***" means with respect to a Product, any and all discovery, characterization, or preclinical (including IND-Enabling Toxicology Studies), clinical, or regulatory activity with respect to the Product to seek Approval (including the submission of all necessary filings with applicable Regulatory Authorities to support such preclinical and clinical activities and Approval), including human clinical trials conducted after Approval of a Product to seek Approval for additional indications for such Product.

"***Development Candidate***" means, in the case of the [***] Program or an Oncology Collaboration Program, a Compound that AstraZeneca has determined meets AstraZeneca's CSID Criteria and which it selects as ready to start IND-Enabling Toxicology Studies as provided herein.

"***Disclosing Party***" has the meaning set forth in Section 13.1.

"***Discontinued Product***" means a Product that is the subject of a termination under this Agreement.

"***Discontinued Target***" has the meaning set forth in Section 3.3.7(a).

[***]

"***DLBCL Patient***" means a patient that has diffuse large B-cell lymphoma.

"***Draft Report***" means a report containing the pharmacology, toxicology, and pharmacokinetic data generated from an IND-Enabling Toxicology Study.

"***Drug Safety Information Agreement***" means an agreement between the Parties which outlines the requirements and responsibilities for drug safety reporting and monitoring for ISIS-STAT3$_{Rx}$, as described in Section 7.3.1.

"***Durable Response***" has the meaning set forth in Section 1.2.3(b).

"***Effective Date***" has the meaning set forth in the Preamble of this Agreement.

"***EMA***" means the European Medicines Agency and any successor entity thereto.

"***European Union***" or "***EU***" means each and every country or territory that is officially part of the European Union from time to time.

"***FDA***" means the United States Food and Drug Administration and any successor entity thereto.

"***Field***" means (i) with respect to the practice of the Isis Core Technology Patents and the Isis Manufacturing and Analytical Patents, (A) the prophylactic or therapeutic use or form of administration in humans or animals of a STAT3 Product or Oncology Product for any indication, and (B) the prophylactic or therapeutic use or form of administration in humans or animals of an [***] Product in the AstraZeneca [***]-Field, and (ii) with respect to the practice of the Isis Product-Specific Patents, (Y) the prophylactic, therapeutic or diagnostic use or form of administration in humans or animals of a STAT3 Product or Oncology Product for any indication, and (Z) the prophylactic, therapeutic or diagnostic use or form of administration in humans or animals of an [***] Product in the AstraZeneca [***]-Field.

"***First Commercial Sale***" means the first sale of a Product by AstraZeneca, its Affiliate or its Sublicensee to a Third Party in a particular country after Approval of such Product has been obtained in such country.

"***FTE***" means the efforts of one or more employees of Isis equivalent to the efforts of one full-time Isis employee for one year, or in the case of less than a full-time dedicated person, a full-time equivalent person-year based upon a total of one thousand seven hundred and ten (1710) hours per year of work on the development program.

"***FTE Rate***" means [***].

"***Fully Absorbed Cost of Goods***" means the costs incurred by Isis as determined using the methodology set forth in SCHEDULE 4.6.1 fairly applied and as employed on a consistent basis throughout Isis' operations.

"***Gene Target***" means (i) a Licensed Target, or (ii) an Oncology Target. The term "***Gene Targets***" means collectively Licensed Targets and Oncology Targets.

"***Government Official***" means any Person employed by or acting on behalf of a government, government-controlled entity or public international organization; any political party, party official or candidate; any Person who holds or performs the duties of an appointment, office or position created by custom or convention; and any Person who hold himself out to be the authorized intermediary of any of the foregoing.

"[***]" means a patient enrolled in a Clinical Study of ISIS-STAT3$_{Rx}$ that [***].

"[***]" means a Clinical Study in [***].

"***High Response Outcome***" has the meaning set forth in Section 1.2.3(a).

"***ICC***" has the meaning set forth in Section 14.1.3(a).

"***IND***" means an Investigational New Drug Application (as defined in the Food, Drug and Cosmetic Act, as amended) filed with the FDA or its foreign counterparts.

"***IND-Enabling Toxicology Studies***" means the pharmacokinetic and toxicology studies required to meet the requirements for filing an IND, including API manufacturing to support such activities.

"***IND Support Package***" means the package of written materials that will support AstraZeneca's IND filings, which package will include Draft Reports generated from the studies listed on Appendix 11.

"***Indemnified Party***" has the meaning set forth in Section 11.3.

"***Indemnification Claim Notice***" has the meaning set forth in Section 11.3.

"***Indication***" means [***].

"***Indirect Taxes***" means value added taxes, sales taxes, consumption taxes and other similar taxes required by law to be disclosed on the invoice.

"***Initial Supply***" has the meaning set forth in Section 4.6.1(b).

"***Initiation***" or "***Initiate***" means, with respect to any Clinical Study, dosing of the first human subject in such Clinical Study.

"***Integrated Development Plan***" or "***IDP***" has the meaning set forth in Section 7.1.1.

"***Isis***" has the meaning set forth in the Preamble of this Agreement.

"***Isis [***]-Field***" has the meaning set forth in Section 5.1.3(a)(ii).

"***Isis [***]-Field ASO***" has the meaning set forth in Section 5.1.3(a)(ii).

"***Isis [***]-Field ASO Licensee***" has the meaning set forth in Section 9.2.4(a).

"***Isis Conducted Activities***" means the research, pre-clinical and/or clinical activities for which Isis is designated as responsible under any Collaboration Plan.

"***Isis Core Technology Patents***" means all Patent Rights owned, used, developed by, or licensed to Isis or its Affiliates, in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term, claiming subject matter generally applicable to ASOs, other than Isis Product-Specific Patents or Isis Manufacturing and Analytical Patents. A list of Isis Core Technology Patents as of the Effective Date is set forth on Appendix 7 attached hereto.

"***Isis In-License Agreements***" has the meaning set forth in Section 8.9.1(a).

"***Isis Indemnitees***" has the meaning set forth in Section 11.1.

"***Isis Internal ASO Safety Database***" has the meaning set forth in Section 7.2.

"***Isis Know-How***" means any Know-How, including Isis' interest in any Jointly-Owned Collaboration Know-How, owned, used, developed by, or licensed to Isis or its Affiliates, in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term that is necessary or useful to Develop, register, Manufacture or Commercialize a Product in the Field. Isis Know-How does not include the Isis Manufacturing and Analytical Know-How.

"***Isis Manufacturing and Analytical Know-How***" means Know-How, including Isis' interest in any Jointly-Owned Collaboration Know-How, that relates to the synthesis or analysis of a Product regardless of sequence or chemical modification, owned, used, developed by, or licensed to Isis or its Affiliates, in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term. Isis Manufacturing and Analytical Know-How does not include the Isis Know-How.

"***Isis Manufacturing and Analytical Patents***" means Patent Rights, including Isis' interest in any Jointly-Owned Collaboration Patents, that claim methods and materials used in the synthesis or analysis of a Product regardless of sequence or chemical modification, owned, used, developed by, or licensed to Isis or its Affiliates, in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term. A list of Isis Manufacturing and Analytical Patents as of the Effective Date is set forth on Appendix 8 attached hereto. Isis Manufacturing and Analytical Patents do not include the Isis Product-Specific Patents or the Isis Core Technology Patents.

"***Isis Owned Patents***" has the meaning set forth in Section 10.2.2.

"***Isis Product-Specific Patents***" means all Product-Specific Patents, in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term. A list of Isis Product-Specific Patents as of the Effective Date is set forth on Appendix 9 attached hereto.

"***Isis Supported Pass-Through Costs***" means [***].

"***Japan NDA***" or "***JNDA***" means the Japanese equivalent of an NDA filed with the Koseisho (i.e., the Japanese Ministry of Health and Welfare, or any successor agency thereto).

"***Joint Patent Committee***" or "***JPC***" has the meaning set forth in Section 9.1.3(a).

"***Jointly-Owned Collaboration Know-How***" means Know-How discovered, developed, invented or created jointly in the performance of a Collaboration Plan by or on behalf of both Parties or their respective Affiliates or Third Parties acting on their behalf that is necessary or useful to Develop, register, Manufacture or Commercialize a Product in the Field.

"***Jointly-Owned Collaboration Patents***" means any Patent Rights that claim or cover Jointly-Owned Collaboration Know-How.

"***Jointly-Owned Collaboration Technology***" means Jointly-Owned Collaboration Know-How and Jointly-Owned Collaboration Patents.

[***]

"***Know-How***" means inventions, technical information, know-how and materials, including technology, data, compositions, formulas, biological materials, assays, reagents, constructs, compounds, discoveries, procedures, processes, practices, protocols, methods, techniques, results of experimentation or testing, knowledge, trade secrets, skill and experience, in each case whether or not patentable or copyrightable.

"***Knowledge***" means a Party's and its Affiliates' good faith, actual understanding of the facts and information as of the Effective Date; *provided that*, with respect to information regarding the status of Patent Rights or other intellectual property rights, "*Knowledge*" means such Party's or its Affiliate's good faith, actual understanding of the facts and information as of the Effective Date after performing a diligent investigation with respect to such facts and information as is customary in the conduct of its business with respect to such Patent Rights or other intellectual property rights (and not, for clarity, a diligent investigation solely in connection with this Agreement).

"***Lead Candidate"*** means, in the case of the [***] Program or an Oncology Collaboration Program, a Compound that is reasonably determined by Isis' RMC in accordance with Isis' standard procedures for designating development candidates as ready to start IND-Enabling Toxicology Studies. The checklist Isis uses as of the Effective Date when reviewing potential development candidates for approval is attached hereto as APPENDIX 4.

"***Lead Candidate Data Package***" means, with respect to a Lead Candidate, the data package Isis presented to its Research Management Committee to approve a Compound as the Lead Candidate; *provided* such package contains the same level of detail as the data packages Isis currently presents to its Research Management Committee to approve Isis' own internal development candidates and is consistent with relevant Collaboration Plan agreed by the JSC for the [***] or the Oncology Target, as applicable.

"***Licensable [***] Product-Specific Patents***" means Patent Rights Controlled by Isis or any of its Affiliates on or after the Effective Date claiming both:

(i) a sequence-based composition of matter that generically encompasses the [***] Development Candidate or an [***] Lead Compound (or any [***] Product incorporating such [***] Development Candidate or any [***] Lead Compounds), or methods of using the [***] Development Candidate or an [***] Lead Compound (or any [***] Product incorporating such [***] Development Candidate or any [***] Lead Compounds), as a prophylactic, therapeutic or diagnostic but, in each case, does not claim the specific [***] Development Candidate or an [***] Lead Compound (or any [***] Product incorporating such [***] Development Candidate or any [***] Lead Compounds) (the exact sequence and chemistry); *and*

(ii) an Isis [***]-Field ASO, or method for [***] of Isis [***] Field ASOs for the treatment of a [***] disease.

"***Licensed CMO***" has the meaning set forth in Section 6.1.4(a)(ii).

"***Licensed Know-How***" means Isis Manufacturing and Analytical Know-How, and Isis Know-How. For clarity, Licensed Know-How does not include any Know-How covering formulation technology or delivery devices.

"***Licensed Patents***" means the Isis Product-Specific Patents, Isis Core Technology Patents, Isis Manufacturing and Analytical Patents and Isis' interest in Jointly-Owned Collaboration Patents. For clarity, Licensed Patents do not include any Patent Rights claiming formulation technology or delivery devices unless such Patent Rights are included in the Jointly-Owned Collaboration Patents.

"***Licensed Target***" means (i) STAT3, or (ii) [***]. The term "***Licensed Targets***" means collectively STAT3 and [***].

"***Licensed Technology***" means any and all Licensed Patents, Licensed Know-How, and any trademarks described in Section 6.1.8, to the extent necessary or useful to Develop, register, Manufacture or Commercialize a Product in the Field.

"***Losses***" has the meaning set forth in Section 11.1.

"***Low Response Outcome***" has the meaning set forth in Section 1.2.3(b).

"***MAA***" means a marketing authorization application filed with the EMA after completion of Clinical Studies to obtain Approval for a Product under the centralized European filing procedure or, if the centralized EMA filing procedure is not used, filed using the applicable procedures in any European Union country.

"***MAA Approval***" means the Approval of an MAA by the EMA for a Product in any country in the EU.

"***Manufacture***" or "***Manufactured***" or "***Manufacturing***" means any activity involved in or relating to the manufacturing, quality control testing (including in-process, release and stability testing), releasing or packaging, importing and keeping, for pre-clinical and clinical purposes, of API or a Product in finished form.

"Material Anti-Corruption Law Violation" means a violation of an Anti-Corruption Law relating to the subject matter of this Agreement which would if it were publicly known, in the reasonable view of AstraZeneca, have a material adverse effect on Isis or on the reputation of AstraZeneca because of its relationship with Isis.

"***Medium Response Outcome***" has the meaning set forth in Section 1.2.3(b).

"***Minimum Third Party Payments***" means ***].

[***]

"***MSA***" has the meaning set forth in Section 4.6.1(d).

"***NDA***" means a New Drug Application filed with the FDA after completion of Clinical Studies to obtain Approval for a Product in the United States.

"***Net Sales***" means the gross invoiced amount on sales of Products by or on behalf of AstraZeneca, its Affiliates, and Sublicensees to Third Parties (which will include Distributors) after deduction of the following amounts, to the extent taken:

(a) normal and customary trade, quantity or prompt settlement discounts (including chargebacks and allowances) actually allowed;

(b) amounts repaid or credited by reason of rejection, returns or recalls of goods, rebates or *bona fide* price reductions determined by AstraZeneca or its Affiliates in good faith;

(c) rebates and similar payments made with respect to sales paid for by any governmental or regulatory authority such as, by way of illustration and not in limitation of the Parties' rights hereunder, Federal or state Medicaid, Medicare or similar state program in the United States or equivalent governmental program in any other country;

(d) any invoiced amounts which are not collected by AstraZeneca or its Affiliates, including bad debts;

(e) excise taxes, Indirect Taxes, customs duties, customs levies and import fees imposed on the sale, importation, use or distribution of the Products; and

(f) any other similar and customary deductions that are consistent with generally accepted accounting principles, or in the case of non-United States sales, other applicable accounting standards; and

after deduction of (i) an allowance for transportation costs, distribution expenses, special packaging and related insurance charges equal to [***] ([***]) of the amount arrived at after application of the provisions of items (a) through (f) above; and (ii) the actual cost paid by AstraZeneca, its Affiliates or Sublicensees for Devices.

Net Sales will be calculated using AstraZeneca's internal audited systems used to report such sales as adjusted for any of the items above not taken into account in such systems. Deductions pursuant to subsection (d) above will be taken in the Calendar Quarter in which such sales are no longer recorded as a receivable. As used above, the term *"Device"* means any device approved by a Regulatory Authority for use with a Product that is necessary to administer the Product to a patient (i.e. without such device the Product cannot be delivered by any other means or methods).

If a Product is sold as part of a Combination Product (as defined below), the Net Sales from such Product, for the purposes of determining royalty payments, will be determined by multiplying the Net Sales (as determined without reference to this paragraph) of the Combination Product by the fraction A/(A+B), where A is the standard sales price of the ready-for-sale form of the Product, containing the same amount of Compound as the sole active ingredient as the Combination Product in question, in the given country when sold separately in finished form; and B is the standard sales price of the ready-for-sale form of the product containing the same amount of the other therapeutically active ingredient(s) that is contained in the Combination Product in question, in the given country, each during the applicable royalty period or, if sales of all compounds did not occur in such period, then in the most recent royalty reporting period. In the event, however, that if, in a specific country either or both of the Compound and the other therapeutically active ingredient in such Combination Product are not sold separately in such country, a market price for such Product and such other active ingredient shall be negotiated by the Parties in good faith for the purposes of performing the calculation above to determine royalty payments on the Net Sales from such Combination Product. As used above, the term ***"Combination Product"*** means a Product that includes at least one additional therapeutically active ingredient (whether coformulated or copackaged) and is not a Compound.

"***Non-Breaching Party***" means the Party that believes the Breaching Party is in material breach of this Agreement.

"***Non-Transferring Party***" has the meaning set forth in Section 14.3.

"***Oncology Compound***" means any ASO that is designed to bind to the RNA that encodes an Oncology Target, where such ASO is discovered by Isis prior to the Effective Date or in the performance of an Oncology Research and Development Plan.

"***Oncology Collaboration***" means the conduct of the Oncology Collaboration Programs in accordance with this Agreement.

"***Oncology Collaboration Program***" means a discovery research program focused on discovering Oncology Compounds to select an Oncology Development Candidate in accordance with the applicable Oncology Research and Development Plan.

"***Oncology Collaboration Term***" has the meaning set forth in Section 3.2.2.

"***Oncology Development Candidate***" means a Development Candidate selected by AstraZeneca arising out of the work conducted under an Oncology Research and Development Plan.

"***Oncology Development Candidate Decision Deadline***" has the meaning set forth in Section 3.3.3.

"***Oncology Lead Candidate***" means Lead Candidate designated by Isis as a potential Oncology Development Candidate

"***Oncology Product***" means a finished product containing an Oncology Compound as an active pharmaceutical ingredient (including any salt, hydrate, solvate, or prodrug thereof).

"***Oncology Research and Development Plan***" means any research and/or development plan attached hereto as Appendix 3 for an Oncology Collaboration Program focused on a particular Oncology Target as amended from time to time in accordance with this Agreement.

"***Oncology Target***" means (i) any of the three Reserved Targets that are selected under Section 3.3.6 to be the subject of an Oncology Collaboration Program, (ii) any Substitute Target, or (iii) any oncology target added to this Agreement under Section 2.2.4.

"***Option***" has the meaning set forth in Section 3.5.

"***Option Deadline***" has the meaning set forth in Section 3.5.

"***Outcome Notice***" has the meaning set forth in Section 1.2.3(e).

"***Participating Parties***" has the meaning set forth in Section 9.2.4(b).

"***Party***" or "***Parties***" means AstraZeneca and Isis individually or collectively.

"***Party Representatives***" has the meaning set forth in Section 11.7.1.

"***Patent Costs***" means the reasonable fees and expenses paid to outside legal counsel, and filing, maintenance and other reasonable out-of-pocket expenses paid to Third Parties, incurred in connection with the Prosecution and Maintenance of Patent Rights.

"***Patent Rights***" means (a) patents, patent applications and similar government-issued rights protecting inventions in any country or jurisdiction however denominated, (b) all priority applications, divisionals, continuations, substitutions, continuations-in-part of and similar applications claiming priority to any of the foregoing, and (c) all patents and similar government-issued rights protecting inventions issuing on any of the foregoing applications, together with all registrations, reissues, renewals, re-examinations, confirmations, supplementary protection certificates, and extensions of any of (a), (b) or (c).

"***Permitted Licenses***" means (1) licenses granted by Isis before or after the Effective Date to any Third Party under the Isis Core Technology Patents, the Isis Manufacturing and Analytical Patents, or the Isis Manufacturing and Analytical Know-How (but not under the Isis Product-Specific Patents) to (a) use oligonucleotides (or supply oligonucleotides to end users) solely to conduct pre-clinical research, or (b) enable such Third Party to manufacture or formulate oligonucleotides, where (i) such Third Party is primarily engaged in providing contract manufacturing or services and is not primarily engaged in drug discovery, development or commercialization of therapeutics; and (ii) Isis does not assist such Third Party to identify, discover or make a Compound or Product; and (2) material transfer agreements with academic collaborators or non-profit institutions in connection with the Isis Conducted Activities approved by AstraZeneca, such approval not to be unreasonably withheld or delayed.

"***Person***" means any corporation, limited or general partnership, limited liability company, joint venture, trust, unincorporated association, governmental body, authority, bureau or agency, any other entity or body, or an individual.

"***Pharmacovigilance Agreement***" has the meaning set forth in Section 7.3.2.

"***Phase 1 Trial***" means the initial clinical testing of a Product in humans (first-in-humans study) with the intention of gaining a preliminary assessment of the safety of such Product. "*Phase 1 Trial*" includes any clinical study designated under a Collaboration Plan as a "*Phase 1 Trial*" or "*Phase 1 Study*."

"***Phase 1/2 Trial***" means Isis' ongoing Clinical Study described in the STAT3 Research and Development Plan, including the expansion cohort for such trial.

"***Phase 1/2 Trial Data Package***" means, with respect to the Phase 1/2 Trial, the listing and tables of safety and efficacy data, radiographic scans of tumor assessments, radiologist reports and summary of biomarker or other assay data that was mutually agreed by Isis and AstraZeneca.

"***Phase 2 Trial***" means any Clinical Study in a single tumor type or enriched for a tumor type that is intended to show safety and efficacy (which efficacy may be shown by a biomarker or other assay) in the target population, at the intended clinical dose or doses or range of doses, on a sufficient number of subjects and for a sufficient period of time to confirm the optimal manner of use of the Product prior to initiation of the Phase 3 Trials, and which itself provides sufficient evidence of safety and efficacy to be included as a supportive study to the Phase 3 Trial in filings with Regulatory Authorities. "*Phase 2 Trial*" includes any clinical study designated under a Collaboration Plan as a "*Phase 2 Trial,*" "*Phase 2a Trial*," *Phase 2b Trial*," "*Phase 2 Study*," *Phase 2a Study*" or "*Phase 2b Study*."

"***Phase 3 Trial***" or "***Registration-Directed Trial***" means a pivotal Clinical Study (whether or not denominated as a "Phase 3" Clinical Study under applicable regulations) in human patients that is of the size and design intended to establish that a Product is safe and effective for its intended use; to define warnings, precautions and adverse reactions that are associated with the Product in the dosage range to be prescribed; and is intended to support Approval of such Product. "*Phase 3 Trial*" or "*Registration-Directed Trial*" includes any clinical study designated under a Collaboration Plan as a "*Phase 3 Trial,*" "*Phase 3 Study*" or "*Registration Trial*."

"***Pre-Clinical Studies***" means *in vitro* and *in vivo* studies of one or more Compounds, not in humans, including those studies conducted in whole animals and other test systems, designed to determine the toxicity, bioavailability, and pharmacokinetics of the Product and whether the Product has a desired effect.

"***Prior Agreements***" means the agreements listed on Appendix 10 attached hereto.

"***Proceeding***" means an action, suit or proceeding.

"***Product***" means, as applicable (i) a STAT3 Product, (ii) an [***] Product, or (iii) an Oncology Product.

"***Product-Specific Patents***" means:

(A) with respect to [***] Products: (i) Assignable [***] Product-Specific Patents; and (ii) Licensable [***] Product-Specific Patents, or

(B) with respect to STAT3 Products and Oncology Products: Patent Rights Controlled by a Party or any of its Affiliates on or after the Effective Date claiming: (i) the specific composition of matter of a STAT3 Product or Oncology Product, or (ii) methods of using such a Product as a prophylactic, therapeutic or diagnostic.

"***Proposed Substitute Target***" has the meaning set forth in Section 3.3.7(a).

"***Prosecution and Maintenance***" or "***Prosecute and Maintain***" means, with regard to a Patent Right, the preparing, filing, prosecuting and maintenance of such Patent Right, as well as handling re-examinations, reissues, and requests for patent term extensions with respect to such Patent Right, together with the conduct of interferences, the defense of oppositions and other similar proceedings with respect to the particular Patent Right. For clarification, "*Prosecution and Maintenance*" or "*Prosecute and Maintain*" will not include any other enforcement actions taken with respect to a Patent Right.

"***R&D Research and Development Plan***" means collectively the (i) STAT3 Research and Development Plan, and (ii) [***] Research and Development Plan.

"***Receiving Party***" has the meaning set forth in Section 13.1.

"***Regulatory Authority***" means any governmental authority, including the FDA, EMA or Koseisho (i.e., the Japanese Ministry of Health and Welfare, or any successor agency thereto), that has responsibility for granting any licenses or approvals or granting pricing or reimbursement approvals necessary for the marketing and sale of a Product in any country.

"Regulatory Documentation" means any regulatory submissions, notifications, registrations, approvals and/or other filings and correspondence made to or with a Regulatory Authority in any country or jurisdiction, and any other records required by Applicable Law to be maintained that may be necessary or useful to develop, manufacture, market, sell or otherwise commercialize a Product in the Field.

"***Relevant Authority***" means any court or government body, whether national, supra-national, federal, state, local, foreign or provincial, including any political subdivision thereof, including any department, commission, board, bureau, agency, or other regulatory or administrative governmental authority or instrumentality, and further including any quasi-governmental Person or entity exercising the functions of any of these.

"***Research***" means conducting the research activities with Compounds as set forth in a Collaboration Plan, including pre-clinical research and lead optimization, *but specifically excluding* Development and Commercialization. When used as a verb, "*Researching*" means to engage in Research.

"***Reserved Target***" means any gene target reserved for potential selection as an Oncology Target in accordance with Section 3.3.5.

"***RMC***" means Isis' Research Management Committee, or any successor committee.

"***Royalty Period***" has the meaning set forth in Section 8.8.2(a).

"***Safety Concern***" has the meaning set forth in Section 1.2.3(d).

"***Senior Representatives***" has meaning set forth in Section 14.1.1.

"***Service Provider***" means the Third Party(ies) conducting the original and revised studies under a Collaboration Plan.

"***STAT3***" means the gene, signal transduction and activation of transcription 3 (GenBank accession # NM_139276.2; Gene ID: 6774) (also known as acute-phase response factor (APRF)), or any alternative splice variants, mutants, polymorphisms and fragments thereof.

"***STAT3/[***] Collaboration***" means the conduct of the STAT3 Program and the [***] Program in accordance with this Agreement.

"***STAT3 Compound***" means any ASO that is designed to bind to the RNA that encodes STAT3, where such ASO is discovered or Controlled by Isis prior to the Effective Date or in the performance of the STAT3 Research and Development Plan, including the Compound known as ISIS-STAT3$_{Rx}$ (also referred to by compound number ISIS 481464).

"***STAT3 Product***" means any finished product containing a STAT3 Compound as an active pharmaceutical ingredient (including any salt, hydrate, solvate, or prodrug thereof).

"***STAT3 Program***" means the research and/or development program for STAT3 Products under this Agreement.

"***STAT3 Research and Development Plan***" means the research and/or development plan for the STAT3 Program (initially as attached hereto as Appendix 2) as amended from time to time in accordance with this Agreement.

"***Sublicensee***" means a Third Party to whom a Party or its Affiliates or Sublicensees has granted a sublicense or license under any Licensed Technology or AstraZeneca Technology, as the case may be, licensed to such Party in accordance with the terms of this Agreement.

"***Substitute Notice***" has the meaning set forth in Section 3.3.7(a).

"***Substitute Target***" has the meaning set forth in Section 3.3.7(b).

"***Target Encumbrances***" has the meaning set forth in Section 3.3.5.

"***Target Knock-Down***" has the meaning set forth in Section 1.2.3(c).

"***Target Sanction***" means the stage at which an Oncology Target has demonstrated sufficient therapeutic potential in pre-clinical disease models and has received the recommendation of the JSC to expend resources to identify an Oncology Development Candidate, all in accordance with the JSC's standard processes.

"***Third Party***" means a Person or entity other than the Parties or their respective Affiliates.

"***Third Party Claims***" has the meaning set forth in Section 11.1.

"***Third Party Obligations***" means any financial and non-financial encumbrances, obligations, restrictions, or limitations imposed by an agreement between a Party and a Third Party that relate to a Product or a Gene Target, including field or territory restrictions, covenants, milestone payments, diligence obligations, sublicense revenue, royalties, or other payments.

"***Transferring Party***" has the meaning set forth in Section 14.3.

"***United States***" or "***U.S.***" means the fifty states of the United States of America and all of its territories and possessions and the District of Columbia.

"***Valid Claim***" means a claim (i) of any issued, unexpired United States or foreign Patent Right, which will not, in the country of issuance, have been donated to the public, disclaimed, nor held invalid or unenforceable by a court of competent jurisdiction in an unappealed or unappealable decision, or (ii) of any United States or foreign patent application within a Patent Right, which will not, in the country in question, have been cancelled, withdrawn, abandoned nor been pending for more than seven years, not including in calculating such seven-year period of time in which such application is in interference or opposition or similar proceedings or time in which a decision of an examiner is being appealed. Notwithstanding the foregoing, on a country-by-country basis, a patent application pending for more than seven years will not be considered to have any Valid Claim for purposes of this Agreement unless and until a patent meeting the criteria set forth in clause (i) above with respect to such application issues.

APPENDIX 2

STAT3 Research and Development Plan and [***] Research and Development Plan

[***]

APPENDIX 3

Oncology Research and Development Plan

[***]

APPENDIX 4

Isis' Lead Candidate Checklist

[***]

APPENDIX 5

Examples (not an exhaustive list) Illustrating Separate Indications

[***]

APPENDIX 6

Isis In-License Agreements

(Relevant to the R&D Research and Development Plan as of the Effective Date)

[***]

APPENDIX 7

Isis Core Technology Patents

[***]

APPENDIX 8

Isis Manufacturing and Analytical Patents

[***]

APPENDIX 9

Isis Product-Specific Patents

[***]

APPENDIX 10

Prior Agreements

[***]

APPENDIX 11

IND Support Package

[***]

SCHEDULE 3.3.6

[***]

SCHEDULE 4.1.1

JSC GOVERNANCE

(a) The JSC will determine the JSC operating procedures, including frequency of meetings (at least quarterly), location of meetings, and responsibilities for agendas and minutes. The JSC will codify these operating procedures in the written minutes of the first meeting.

(d) The JSC may hold meetings in person or by audio or video conference as determined by the JSC; but at least two meetings per year will be in person (one held at Isis' facilities, and the other held at AstraZeneca's facilities outside of the U.S.). Alliance Managers will attend JSC meetings as participating non-members. In addition, upon prior approval of the other Party, each Party may invite its employees or consultants to attend JSC meetings, including any subject matter expert(s) with valuable knowledge of the relevant Gene Target.

(e) The co-chairs will be responsible for ensuring that activities occur as set forth in this Agreement, including ensuring that JSC meetings occur, JSC recommendations are properly reflected in the minutes, and any dispute is given prompt attention and resolved in accordance with Section 4.1.3, Section 9.1.3 and Section 14.1, as applicable.

(f) The JSC members from the same Party will collectively have one vote. The JSC will strive to make recommendations with approval of both Isis members and AstraZeneca members, and record such recommendations in the minutes of the applicable JSC meeting.

(G) The JSC may form subcommittees and working groups as it determines in order to carry out its activities under this Agreement, all of which will dissolve when the JSC dissolves.

SCHEDULE 4.1.3(C)

AstraZeneca's Performance Metrics

[***]

SCHEDULE 4.2

Alliance Management Activities

Each Alliance Manager is responsible for:

(a) Promoting the overall health of the relationship between the Parties;

(h) Developing a mutually agreed alliance launch plan covering any activities and systems that the Parties need to implement within the first 100 days after the Effective Date to support the Collaboration Plans;

(i) Organizing each JSC meeting, including agendas, drafting minutes, and publishing final minutes;

(j) Supporting the co-chairs of the JSC with organization of meetings, information exchange, meeting minutes, and facilitating dispute resolution as necessary;

(k) Preparing status and progress reports on the above as determined necessary by the JSC;

(l) Ensuring compliance in maintaining the Isis Internal ASO Safety Database as outlined in Section 7.2; and

(m) Ensuring proper approval of publications prior to submission as required in Section 13.4.

(n) Review Material Transfer Agreements.

SCHEDULE 4.6.1

Isis' Fully Absorbed Cost of Goods Methodology

[***]

SCHEDULE 4.6.1(d)

Manufacturing Services Agreement Principles

[***]

Schedule 4.7

AstraZeneca Bioethics Policy

[***]

EXECUTION COPY

Certain identified information in this exhibit, marked by [***], has been excluded because it is both (i) not material, and (ii) the type that the registrant treats as private or confidential.

AMENDMENT #1 TO COLLABORATION, LICENSE AND DEVELOPMENT AGREEMENT

This **AMENDMENT #1 TO COLLABORATION, LICENSE AND DEVELOPMENT AGREEMENT** (this "***Amendment***") is entered into as of the date of last signature hereof (the ***"Amendment Date"***) by and between **ISIS PHARMACEUTICALS, INC.**, a Delaware corporation, having its principal place of business at 2855 Gazelle Court, Carlsbad, CA 92010 ("***Isis***"), and **ASTRAZENECA AB**, a company incorporated in Sweden under no. 556011-7482 ("***AstraZeneca***"). Isis and AstraZeneca are each referred to herein by name or as a "***Party***" or, collectively, as "***Parties***."

RECITALS

WHEREAS, Isis and AstraZeneca are parties to the Collaboration, License and Development Agreement dated December 7, 2012 (the "***Agreement***");

WHEREAS, Isis and AstraZeneca desire to amend the Agreement to add an additional research program focused on the gene target [***] (GenBank accession # [***]) or any alternative splice variants, mutants, polymorphisms and fragments thereof (the ***"Amendment-Additional Collaboration Target"***); and

NOW, THEREFORE, in consideration of the premises and mutual covenants herein contained, and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, and solely with respect to the newly created program focused on the Amendment-Additional Collaboration Target, the Parties, intending to be legally bound, do hereby agree as follows:

1. **Amendment-Additional Collaboration Target Program**. In addition to the three Oncology Collaboration Programs under the Agreement, the Parties will conduct a research and development program on the Amendment-Additional Collaboration Target (the ***"Amendment-Additional Collaboration Target Program"***) in accordance with this Amendment and the plan for the research and development of the Amendment-Additional Collaboration Target (the ***"Amendment-Additional Collaboration Target Research and Development Plan"***). The initial Amendment-Additional Collaboration Target Research and Development Plan is attached hereto as ATTACHMENT 1 and sets forth the activities to be conducted by each Party to reach Target Sanction for the Amendment-Additional Collaboration Target. Once the Amendment-Additional Collaboration Target has reached Target Sanction, within [***] days the Parties will mutually agree to updates to the Amendment-Additional Collaboration Target Research and Development Plan to include the specific activities and studies under the Amendment-Additional Collaboration Target Research and Development Plan each Party will perform to identify a Development Candidate for the Amendment-Additional Collaboration Target. This Amendment is without prejudice to AstraZeneca's rights under Section 2.2.4(b) of the Agreement to add an additional Oncology Target to the Oncology Collaboration as set out therein.

2. **Amendment-Additional Collaboration Target Rights and Obligations.** For purposes of the Agreement (except as explicitly set forth in this Amendment):

a. the Amendment-Additional Collaboration Target will be considered a Gene Target under the Agreement and will be treated the same as an Oncology Target under the Agreement, including but not limited to Article 5 of the Agreement except that in Article 5.2 of the Agreement as it applies to the Amendment-Additional Collaboration Target the references to cancer shall be read as references to [***].

b. the Amendment-Additional Collaboration Target Research and Development Plan will be treated the same as an Oncology Research and Development Plan;

c. ASOs that are designed to bind to the RNA that encodes the Amendment-Additional Collaboration Target, where such ASO is discovered by Isis prior to the Amendment Date or in the performance of the Amendment-Additional Collaboration Target Research and Development Plan (***"Amendment-Additional Collaboration Target Compounds"***) will be treated the same as Oncology Compounds; the discovery research program focused on discovering Amendment-Additional Collaboration Target Compounds to select an Amendment-Additional Collaboration Target Development Candidate in accordance with the Amendment-Additional Collaboration Target Research and Development Plan will be treated the same as an Oncology Collaboration Program;

d. An Amendment-Additional Collaboration Target Compound that is determined by Isis' RMC in accordance with Isis' standard procedures for designating development candidates as ready to start IND-Enabling Toxicology Studies, will be treated the same as a Lead Candidate;

e. A Development Candidate selected by AstraZeneca arising out of the work conducted under the Amendment-Additional Collaboration Target Research and Development Plan (an ***"Amendment-Additional Collaboration Development Candidate"***) will be treated the same as an Oncology Development Candidate;

f. A finished product containing an Amendment-Additional Collaboration Target Compound as an active pharmaceutical ingredient (including any salt, hydrate, solvate or prodrug thereof) (a ***"Amendment-Additional Collaboration Target Product"***) will be treated the same as an Oncology Product;

And as such, except as explicitly set forth in this Amendment, each Party will have the same rights and obligations with respect to Amendment-Additional Collaboration Target Compounds and Amendment-Additional Collaboration Target Products as each has under the Agreement with respect to Oncology Compounds and Oncology Products, including but not limited to:

a. the Option under Section 3.5 of the Agreement to obtain the license set forth in Section 6.1.3 of the Agreement;

b. and the applicable financial provisions under Article 8 of the Agreement as specified in Section 7 of this Amendment.

And the terms of the Agreement as they apply to the Amendment-Additional Collaboration Target, except where the context otherwise requires, shall be construed such that the Effective Date is replaced with the Amendment Date, including but not limited to Section 6.1.4 (e), 6.1.7, 6.2 of the Agreement and relevant definitions, including but not limited to "AstraZeneca Background IP"; and with respect to Section 3.2.2 of the Agreement where the Oncology Collaboration Term as it applies to the Amendment-Additional Collaboration Target will begin on the Amendment Date and will end on [***] (for the purposes of this Amendment herein referred to as the **"*Amendment-Additional Collaboration Term*"**).

3. **No Substitution Rights.** The rights of substitution in Section 3.3.7 of the Agreement shall continue to apply to the Oncology Targets as set out therein but AstraZeneca will have no rights of substitution under the Agreement or this Amendment with respect to the Amendment-Additional Collaboration Target Program.

4. **Performing the Amendment-Additional Collaboration Target Research and Development Plan; Costs.**

a. Isis will use Commercially Reasonable Efforts to conduct the activities to be conducted by Isis designated under the Amendment-Additional Collaboration Target Research and Development Plan. Such activities will be treated the same as Isis Conducted Activities under the Agreement and the costs for such activities will be handled the same as the costs under Section 4.5.2 of the Agreement.

b. AstraZeneca will use Commercially Reasonable Efforts to conduct all other activities as described in the Amendment-Additional Collaboration Target Research and Development Plan. Such activities will be treated the same as AstraZeneca Conducted Activities under the Agreement and the costs for such activities will be handled the same as the costs under Section 4.5.2 of the Agreement.

5. **Manufacturing and Supply.**

The provisions of Section 4.6.1 (a) of the Agreement shall apply to Isis Conducted Activities designated under the Amendment-Additional Collaboration Target Research and Development Plan.

The provisions of Section 4.6.1 (b)(iii) (including the last two paragraphs of Section 4.6.1(b)) of the Agreement shall apply to AstraZeneca Conducted Activities under the Amendment-Additional Collaboration Target Research and Development Plan, as more specifically set out herein:

a. ***Research Compound Supply***. Isis will provide up to [***] of bulk unformulated research-grade Compound for Amendment-Additional Collaboration Target Compounds for up to [***] for each of [***] ([***] total) [***]. In addition, should AstraZeneca require additional research-grade Compound for the Amendment-Additional Collaboration Target Program for pre-clinical studies, then, at AstraZeneca's reasonable request, Isis will use its reasonable endeavors to provide such research-grade Compound for such pre-clinical studies at [***].

b. ***Development API Supply***. Isis will supply (at AstraZeneca's expense at [***] within 60 days after AstraZeneca's receipt of the applicable invoice) bulk unformulated API for the Amendment-Additional Collaboration Development Candidate sufficient to support the IND Enabling Toxicology Studies for the Amendment-Additional Collaboration Target Development Candidate, and the quantity of API determined by the JSC when the protocol is available for the first Clinical Study, consistent with Isis' obligations to supply the Oncology Programs under Section 4.6.1(b)(iii) of the Agreement.

c. ***Formulation***. AstraZeneca will be responsible for conducting and paying for all formulation work to conduct the Amendment-Additional Collaboration Target Program. If requested by AstraZeneca, during the Amendment-Additional Collaboration Term Isis will provide reasonable assistance to AstraZeneca for such work as set out in the Amendment-Additional Collaboration Target Research and Development Plan. Isis will provide such assistance on an hourly basis [***] up to a reasonable maximum number of hours set by the Amendment-Additional Collaboration Target Working Group for each year of the Amendment-Additional Collaboration Term, and thereafter at Isis' then current FTE Rate. AstraZeneca will resupply any finished Product necessary to support any Isis Conducted Activities, AstraZeneca Conducted Activities, IND toxicology studies and the Phase 1 Study for the Amendment-Additional Collaboration Target Program.

d. ***Manufacturing Services Agreement.*** The Parties have entered into a Manufacturing Services Agreement with effective date of 7 March 2013 as provided by Section 4.6.1 (b) of the Agreement and the Parties agree that they will use the MSA to facilitate the supply arrangements herein.

6. **Amendment-Additional Collaboration Target Working Group**.

a. ***Formation of the Amendment-Additional Collaboration Target Working Group***. Within [***] ([***]) days after the Amendment Date, with respect to the Amendment-Additional Collaboration Target Program, the Parties will establish an Amendment-Additional Collaboration Target Working Group (***"Amendment-Additional Collaboration Target Working Group"***) that will be separate and independent from the JSC, and will be responsible for the coordination and management of activities under the Amendment-Additional Collaboration Target Research and Development Plan. The Amendment-Additional Collaboration Target Working Group will consist of an equal number of representatives of each Party. The Amendment-Additional Collaboration Target Working Group will report into the JSC and will make decisions and resolve disputes in the same manner as the JSC.

b. ***Term of Amendment-Additional Collaboration Target Working Group***. The Amendment-Additional Collaboration Target Working Group (and any of its sub-teams and working groups) under this Amendment will cease to exist upon the earlier of Isis ceasing to participate in the JSC in respect of the Amendment-Additional Collaboration Target Program or the JSC ceasing to be responsible for making decisions in respect thereof, in each case as provided in Section 4.1.4 of the Agreement.

c. ***Meeting Coordination***. The Amendment-Additional Collaboration Target Working Group will meet at least once per quarter in person or via video conference or teleconference and more frequently whenever necessary and will meet in person at least twice a year. Isis and AstraZeneca will use commercially reasonable efforts to schedule meetings of the JSC and Amendment-Additional Collaboration Target Working Group to take place at the same location and on the same dates to maximize the use of each Party's time, increase information sharing efficiencies and reduce the cost of additional travel, lodging and related expenses.

7. **FTE hours.** Sections 6.5.1 and 7.1.5 of the Agreement will apply to the Amendment-Additional Collaboration Target in the same manner as applied to each Oncology Product, except the reference in those Sections to [***]. Instead, under each of Sections 6.5.1 and 7.1.5 of the Agreement up to [***] of Isis' time shall be available [***] to AstraZeneca (being [***] in total) specifically in respect of the Amendment-Additional Collaboration Target.

8. **Additional Financial Provisions.** The financial provisions set forth in Article 8 of the Agreement applicable to Oncology Products (including but not limited to Section 8.6 and Section 8.8) will apply to the Amendment-Additional Collaboration Target Products in the same manner as applied to each Oncology Product except that:

a. Section 8.1(iii) of the Agreement shall not apply with respect to the Amendment-Additional Collaboration Target Program, and instead Section 8.1 of the Agreement shall be amended to add that AstraZeneca shall pay Isis an additional up-front fee of $[***] in partial consideration for the Option granted by Isis to AstraZeneca under Section 3.5 for the Amendment-Additional Collaboration Target within 30 days after the Amendment Date;

b. In partial consideration for the Option granted by Isis to AstraZeneca under Section 3.5 of the Agreement in respect of the Amendment-Additional Collaboration Target, AstraZeneca will pay Isis $[***] when the Amendment-Additional Collaboration Target Program achieves Target Sanction, such payment to be due within 30 days following receipt of an invoice from Isis following such achievement; and

c. Section 8.2 of the Agreement shall be amended such that up to a total of $[***] may become due and payable thereunder for a total of five Options (if AstraZeneca exercises all of its Options under the Agreement and under this Amendment and if a fourth Oncology Collaboration Program is added under Section 2.2.4 of the Agreement).

9. **Termination.** If the Amendment-Additional Collaboration Target Program has not achieved Target Sanction by [***], then either Party may terminate this Amendment by providing the other party a written notice thereof by [***] with the consequences thereof as set forth in Section 3.4 of the Agreement. The Amendment-Additional Collaboration Target Program (and therefore this Amendment) will terminate at the end of the Amendment-Additional Collaboration Term if, despite the Parties' Commercially Reasonable Efforts, by the expiration of the Amendment-Additional Collaboration term, Isis has not designated an Amendment-Additional Collaboration Target Lead Candidate, with the consequences thereof as set forth in Section 3.4 of the Agreement. The licenses under the Cross-Licensed Collaboration Formulation IP granted by each Party under Section 11.c of this Amendment will survive termination of this Amendment or the Agreement.

10. **Representations and Warranties**.

a. Each Party hereby makes, as of the Amendment Date and solely with respect to the Amendment-Additional Collaboration Target Program, the same representations and warranties set forth in Section 10.1 of the Agreement.

b. Isis hereby makes to AstraZeneca, as of the Amendment Date and solely with respect to the Amendment-Additional Collaboration Target Program, the same representations and warranties set forth in Section 10.2 of the Agreement.

11. **Intellectual Property Rights**.

a. Isis Patents. Solely with respect to the Amendment-Additional Collaboration Target Program, the Patent Rights listed on ATTACHMENT 2 to this Amendment (i) are part of the Isis Core Technology Patents and (ii) will not be considered formulation technology excluded under the definitions of Licensed Know-How or Licensed Patents, *except* that the Patent Rights listed on ATTACHMENT 2 to this Amendment (A) will be considered formulation technology for purposes of Section 8.9.3, 8.9.4 of the Agreement and the definition of Additional Core IP under the Agreement, and (B) [***]. The Patent Rights listed on ATTACHMENT 3 to this Amendment are part of the Isis Product-Specific Patents, solely with respect to the Amendment-Additional Collaboration Target Program.

b. [***] Agreements. It is agreed by AstraZeneca and Isis that the Amendment-Additional Collaboration Target Compounds will be treated as [***] under AstraZeneca's agreements with [***] (the [***]), as such term is defined therein. As such, if clause (iv) of Section 3.4 of the Agreement or clause (i)(1) of Section 12.3.2 of the Agreement become applicable with respect to the Amendment-Additional Collaboration Target Program, then, subject to [***] right to use such results for research purposes as reserved to it in the [***], any results related to Amendment-Additional Collaboration Target Compounds owned by AstraZeneca under the [***] would be licensed to Isis under clause (iv) of Section 3.4 of the Agreement or clause (i)(1) of Section 12.3.2 of the Agreement, as the case may be. AstraZeneca will not provide [***] with any Amendment-Additional Collaboration Target Compounds unless and until [***] agrees in writing that such Compounds will be treated as [***] under the [***], and AstraZeneca will provide Isis such written agreement if requested by Isis. AstraZeneca will not amend (or waive any rights under) the [***] in any way that diminishes Isis' rights under this Section 11b without Isis' prior written consent.

c. Cross-Licenses to Collaboration Formulation IP. For purposes of this Amendment, ***"Cross-Licensed Collaboration Formulation IP"*** means (A) Patent Rights claiming formulation technology that is discovered, developed, invented, created or reduced to practice by or on behalf of a Party during the Agreement Term (i) in the performance of the Amendment-Additional Collaboration Target Plan, (ii) using the Amendment-Additional Collaboration Target Compounds, or (iii) using the inventions described in the Patent Rights listed on ATTACHMENT 2 to this Amendment, and (B) any Know-How related thereto, in each case to the extent Controlled by a Party at any time during the Agreement Term. Claims within a Patent Right claiming a specific combination of an Amendment-Additional Collaboration Target Compound and formulation technology will be Product-Specific Patents and will not be Cross-Licensed Collaboration Formulation IP. For purposes of the definition of Cross-Licensed Collaboration Formulation IP, [***].

i Isis hereby grants to AstraZeneca a perpetual, worldwide, non-exclusive, fully-paid, royalty-free, sublicensable license under the Cross-Licensed Collaboration Formulation IP to research, develop, manufacture, have manufactured, register, market and commercialize products.

ii AstraZeneca hereby grants to Isis a perpetual, worldwide, non-exclusive, sublicensable license under the Cross-Licensed Collaboration Formulation IP to research, develop, manufacture, have manufactured, register, market and commercialize products. *Notwithstanding the foregoing*, until the earlier of the [***] anniversary of the Amendment Date and the date Section 3.4 or Section 12.3.2 of the Agreement becomes applicable with respect to the Amendment-Additional Collaboration Target Program, Isis agrees that it will not (A) practice its license from AstraZeneca under any Patent Right within the Cross-Licensed Collaboration Formulation IP that is solely owned by AstraZeneca to develop, manufacture, have manufactured, register, market or commercialize products that [***] (such product, a ***"Restricted Product"***); *provided* that the restriction set forth in this clause (A) will not preclude Isis from conducting research on any ASOs prior to designation of such ASOs as a development candidate; or (B) [***] a Restricted Product as [***] where such Restricted Product is Covered by a Patent Right within the Cross-Licensed Collaboration Formulation IP that is solely owned by AstraZeneca.

12. **No Impact on Other Collaboration Programs**. Except as otherwise expressly amended by this Amendment, the Agreement remains in full force and effect in accordance with its terms. For the avoidance of doubt, this Amendment is solely intended to modify certain terms of the Agreement regarding the Amendment-Additional Collaboration Target Program, and does not amend the Agreement in any way with respect to the [***] Program, [***] Program or any of the Oncology Collaboration Programs.

13. **Entire Agreement and Governing Law**. Section 14.9 of the Agreement shall be construed as including this Amendment. This Amendment shall be construed and interpreted as per the Agreement, including but not limited to governing law and jurisdiction, and defined terms set out in the Agreement shall have the same meaning in this Amendment unless otherwise provided by this Amendment.

*** - * - * - ***

[Signature page follows]

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

ISIS PHARMACEUTICALS, INC.

By: */s/ B. Lynne Parshall*

Name: B. Lynne Parshall

Title:

Date:

ASTRAZENECA AB

By: */s/ Jan-Olof Jacke*

Name: Jan-Olaf Jacke

Title: CFO, AstraZeneca AB

Date: 2013-08-13

ATTACHMENT 1

Amendment-Additional Collaboration Target Research and Development Plan

[***]

ATTACHMENT 2

Amendment-Additional Collaboration Target Isis Core Technology Patents

[***]

ATTACHMENT 3

Amendment-Additional Collaboration Target Isis Product Specific Patents

[***]

Execution Copy

Certain identified information in this exhibit, marked by [***], has been excluded because it is both (i) not material, and (ii) the type that the registrant treats as private or confidential.

AMENDMENT NO.2

This Amendment No.2 ("the "Amendment") to the Collaboration, License and Development Agreement dated December 7th, 2012 (the "Agreement"), is made by and between

(1) ASTRAZENECA AB, a company incorporated in Sweden under no. 556011-7482 with its registered office at 151 85 Södertälje, Sweden and with offices at SE-43 183 Mölndal, Sweden ("AstraZeneca")
(2) ISIS PHARMACEUTICALS, INC., a Delaware corporation, having its principal place of business at 2855 Gazelle Court, Carlsbad, CA 92010 ("Isis")

and is made effective as of the 15th day of October, 2014 (the "Amendment Effective Date")

Recitals

WHEREAS, the Parties desire to further amend, modify and restate certain terms and conditions of the Agreement.

Agreement

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

1. Definitions

Any capitalized term not separately defined in this Amendment shall have the meaning ascribed to it in the Agreement.

2. Modifications

Article 8.4, Table 1, shall be deleted and replaced by the following:

TABLE 1		
STAT3 Product Milestone Event	**Column 1 STAT3 Product Milestone Event Payment for High Response Outcome**	**Column 2 STAT3 Product Milestone Event Payment for Medium Response Outcome or Low Response Outcome**
[***]	$[***]	$[***]
[***]	$[***]	$[***]
[***]	$[***]	$[***]
[***]	$[***]	$[***]
[***]	$[***]	$[***]
[***]	$[***]	$[***]
[***]	$[***]	$[***]
[***]	$[***]	$[***]
[***]	$[***]	$[***]
[***]	$[***]	$[***]
[***]	$[***]	$[***]
[***]	$[***]	$[***]

3. Amendment Effective Date

This Amendment shall become effective on the Amendment Effective Date.

4. Entire Agreement

This Amendment, together with the Agreement, constitutes the entire agreement between the Parties with respect to the subject matter of the Agreeement. The Agreeemnt together with this Amendment and any prior Amendments thereto supersedes all prior agreements, whether written or oral, with respect to the subject matter of the Agreeemnet, as amended. Each Party confirms that it is not relying on any representations, warranties or covenants of the other Party except as specifically set out in the Agreement as amended. Nothing in this Agreement is intended to limit or exclude any liability or fraud. All Schedules referred to in this Amendment are intended to be and are hereby specifically incorporated into and made a part of the Agreement. The Parties hereby agree that subject to the modifciations specifically stated in this Amendment, all other terms and conditions of the Agreement shall remain in full force and effect.

Execution

THIS AGREEMENT IS EXECUTED by the authorized representatives of the parties as of the date first written above.

ASTRAZENECA AB

Signature : */s/ M. Schindler*

Name : M. Schindler

Title : 16 10 14

ISIS Pharmaceuticals, INC

Signature : */s/ B. Lynne Parshall*

Name : B. Lynne Parshall

Title : Chief Operating Officer

EXHIBIT 10.4

FINAL EXECUTION VERSION

Certain identified information in this exhibit, marked by [***], has been excluded because it is both (i) not material, and (ii) the type that the registrant treats as private or confidential.

AMENDMENT NO.3

This Amendment No.3 ("the "Amendment") to the Collaboration, License and Development Agreement dated December 7th, 2012 (the "Agreement"), is made by and between

(1) ASTRAZENECA AB, a company incorporated in Sweden under no. 556011-7482 with its registered office at 151 85 Södertälje, Sweden and with offices at SE-43 183 Mölndal, Sweden ("AstraZeneca")
(2) IONIS PHARMACEUTICALS, INC., a Delaware corporation, (formally known as Isis Pharmaceuticals, Inc.) having its principal place of business at 2855 Gazelle Court, Carlsbad, CA 92010 ("Ionis")

and is made effective as of the day of January 18th 2016 (the "Amendment Effective Date")

Recitals

WHEREAS, the Parties entered into the Agreement

WHEREAS the Agreement amongst others provides for the Parties to conduct discovery efforts on three targets

WHEREAS these discovery efforts have resulted in the identification of a oligonucleotide drug targeting the [***] gene

WHEREAS the Parties desire to further amend, modify and restate certain terms and conditions of the Agreement with regards to the Parties rights and obligations with regards to the Oncology Research and Development Plan with a view in particular to enable the further development of the [***] targeted drug.

Agreement

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

1. Definitions

Any capitalized term not separately defined in this Amendment shall have the meaning ascribed to it in the Agreement.

2. Modifications

Article 3.3.3 shall be deleted and replaced by the following :

3.3.3 Oncology Development Candidate Selection. Ionis will notify AstraZeneca in writing promptly after designating an Oncology Lead Candidate and, together with such notice, Ionis will provide AstraZeneca the applicable Lead Candidate Data Package. As promptly as possible (but no later than [***] days after AstraZeneca receives such Lead Candidate Data Package) (each such [***]-day deadline, which AstraZeneca has determined is sufficient for AstraZeneca to complete its candidate selection identification criteria analysis, an "***Oncology Development Candidate Decision Deadline***"), AstraZeneca will determine whether to select the Oncology Lead Candidate (or another Oncology Compound) as an Oncology Development Candidate. In addition, during such [***]-day period, AstraZeneca will keep the JSC apprised of AstraZeneca's progress in making a decision regarding which Oncology Compound AstraZeneca may select as the Oncology Development Candidate to enable Ionis to plan as early as possible for manufacturing of the Oncology Development Candidate for IND-Enabling Toxicology Studies. If the JSC determines that any back up Oncology Compound to the proposed Oncology Lead Candidate should be considered alongside the proposed Oncology Lead Candidate, then the JSC may unanimously agree to extend the Oncology Development Candidate Decision Deadline if the JSC determines AstraZeneca should have additional time to consider both candidates before making a decision as to which may be selected as the Oncology Development Candidate. If AstraZeneca selects the Oncology Lead Candidate or any other Oncology Compound as an Oncology Development Candidate, then AstraZeneca will notify Ionis of such selection by the Oncology Development Candidate Decision Deadline and will pay Ionis the Designation of Oncology Development Candidate milestone payment under Section 8.6 within 30 days after AstraZeneca's receipt of an invoice from Ionis. In addition, provided Ionis has supplied the API to AstraZeneca in accordance with Section 4.6.1 (b) (iii) or Section 4.6.1 (b) (iv), as applicable, AstraZeneca will initiate IND-Enabling Toxicology Studies under the applicable Oncology Research and Development Plan no later than [***] days after AstraZeneca pays Ionis the Designation of Oncology Development Candidate milestone payment under Section 8.6. Notwithstanding the foregoing and for the avoidance of doubt, solely for any Oncology Development Candidate targeting [***] ("a [***] Candidate"), the Oncology Development Candidate milestone payment will be due upon the earlier of (i) the completion of [***] and [***] of [***] of the [***] for such [***] Candidate; and (ii) [***], which will be deemed to be the "Oncology Development Candidate Decision Deadline" for any [***] Develpment Candidate. However, the [***] will be extended by one day for every day beyond [***] Ionis delivers API for the GLP toxicology study to AstraZeneca as set forth below (which API will be deemed delivered upon delivery to a carrier designated by AstraZeneca at Ionis manufacturing facility).

If AstraZeneca either (i) does not provide Ionis written notice that AstraZeneca has selected the Oncology Lead Candidate or any other Oncology Compound as the Oncology Development Candidate by the Oncology Development Candidate Decision Deadline, or (ii), provides Ionis written notice that AstraZeneca has not selected the Oncology Lead Candidate or any other Oncology Compound as the Oncology Development Candidate by the Oncology Development Candidate Decision Deadline, then such Oncology Collaboration Program will no longer be a part of this Agreement and AstraZeneca's Option for (and Ionis' obligations with respect to) such Oncology Collaboration Program will terminate and no milestone payments for such Oncology Collaboration Program will be payable.

Article 4.6.1 shall be deleted and replaced by the following:

4.6.1 Collaboration Manufacturing and Supply.

Supplies for Activities under the Collaboration Plans.

(a) **Ionis Conducted Activities**. [***], Ionis will supply API and finished Product sufficient to support the Ionis Conducted Activities designated under a given Collaboration Plan, including but not limited to the API to support the IND Enabling Toxicology Studies for the AR Program.

(b) **AstraZeneca Conducted Activities**. In addition, with respect to the AstraZeneca Conducted Activities, Ionis will supply (the "***Initial Supply***"):

(i) ***STAT3 Program Supply***. API and finished Product sufficient to support the [***] that will be conducted by AstraZeneca under the STAT3 Research and Development Plan;

(ii) ***AR Program Supply***. The quantity of API [***] (which will be set forth in the AR Research and Development Plan) to support the [***] for the AR Development Candidate;

(iii) ***[***] Program Supply***. Up to [***] kilograms of API of the [***] Candidate, to be delivered in [***] [***] the [***] of up to [***] kilogram to support the [***], and other [***] to be delivered by [***], provided and released in the same manner Isis releases API for [***] it conducts, and the [***] of up to [***] kilograms to support the [***], to be delivered by [***], and to be provided under cGMP in the same manner as Isis has supplied API for the STAT3 and AR Programs (AstraZeneca will be responsible for formulation and filling of all API so provided by Ionis), and

(iv) ***Other Oncology Programs***. The quantity of API [***] for each Oncology Development Candidate other than the [***] Candidate, and the quantity of API [***] (which will be set forth in the applicable Oncology Research and Development Plan) for each Oncology Development Candidate.

In each of the foregoing cases in this Section 4.6.1 (b), AstraZeneca will pay Ionis for such API and/or finished Product at [***], within 60 days after AstraZeneca's receipt of the applicable invoice. Notwithstanding the foregoing and for the avoidance of doubt, Ionis will provide AstraZeneca the API outlined in Section 4.6.1(b)(iii) [***]. In the event that AstraZeneca does not [***] the [***] for a [***] Development Candidate, then AstraZeneca will [***] $[***] per kilogram, which is equal to [***] for the [***] API provided by Ionis to AstraZeneca, with such [***]. For the avoidance of doubt, if AstraZeneca has [***] the [***] for the [***] Development Candidate, AstraZeneca shall be under no obligation to [***] for the [***].

Other than the finished Product sufficient to support the [***] in patients under the STAT3 Research and Development Plan, AstraZeneca is responsible for supplying finished Product for all AstraZeneca Conducted Activities. In addition, should AstraZeneca require additional API or research-grade Compound for the STAT3 Program or the AR Program for pre-clinical studies in [***] not covered by the STAT3 or AR Research and Development Plan or in connection with the Oncology Research and Development Plans, then, at AstraZeneca's reasonable request, Ionis will use its reasonable endeavors to provide (A) such API to AstraZeneca at [***], or (B) such research-grade Compound for such [***] studies [***] of such Compound (and for any additional quantities of research-grade Compound, at [***].

It is intended that the API lot used for [***] under a given Collaboration Plan will be of sufficient size to also use in the [***] of the relevant Product.

Article 8.4, Table 3, shall be deleted and replaced by the following:

TABLE 3

Oncology Product Milestone Event	**Oncology Product Milestone Event Payment**
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]

3. Amendment Effective Date

This Amendment shall become effective on the Amendment Effective Date.

4. Entire Agreement

This Amendment, together with the Agreement, constitutes the entire agreement between the Parties with respect to the subject matter of the Agreeement. The Agreeemnt together with this Amendment and any prior Amendments thereto supersedes all prior agreements, whether written or oral, with respect to the subject matter of the Agreeemnet, as amended. Each Party confirms that it is not relying on any representations, warranties or covenants of the other Party except as specifically set out in the Agreement as amended. Nothing in this Agreement is intended to limit or exclude any liability or fraud. All Schedules referred to in this Amendment are intended to be and are hereby specifically incorporated into and made a part of the Agreement. The Parties hereby agree that subject to the modifciations specifically stated in this Amendment, all other terms and conditions of the Agreement shall remain in full force and effect.

5. Execution

THIS AMENDMENT IS EXECUTED by the authorized representatives of the parties as of the date first written above.

ASTRAZENECA AB	**Ionis Pharmaceuticals, Inc.**
Signature : */s/ Marcus Schindler*	Signature: */s/ B. Lynne Parshall*
Name : Marcus Schindler	Name : B. Lynne Parshall
Title : Vice President, Head of CVMD	Title : Chief Operating Officer
iMed AstraZeneca AB	

Exhibit 10.5

Final Execution Version

Certain identified information in this exhibit, marked by [***], has been excluded because it is both (i) not material, and (ii) the type that the registrant treats as private or confidential.

AMENDMENT NO. 4

This Amendment No. 4 (the "Amendment") to the Collaboration, License and Development Agreement dated December 7th, 2012 (the "Agreement"), is made by and between

(1) ASTRAZENECA AB, a company incorporated in Sweden under no. 556011-7482 with its registered office at SE-151 85 Södertälje, Sweden ("AstraZeneca") and

(2) IONIS PHARMACEUTICALS, INC., a Delaware corporation, (formally known as Isis Pharmaceuticals, Inc.) having its principal place of business at 2855 Gazelle Court, Carlsbad, CA 92010 ("Ionis"),

and is made effective as of October 18th, 2018 (the "Amendment Effective Date").

Recitals

WHEREAS, the Parties desire to further amend and restate certain terms and conditions of the Agreement.

Agreement

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

1. **Definitions**

Any capitalized term not separately defined in this Amendment shall have the meaning ascribed to it in the Agreement.

2. **Modifications**

Section 7.1.1 of the Agreement is hereby deleted in its entirety and replaced by the following:

"7.1.1. **Integrated Product Plans**. AstraZeneca will prepare a Development and global integrated Product plan or a comparable document consistent with AstraZeneca's then current internal practices for AstraZeneca's internal programs outlining key aspects of the Development of each Product licensed by AstraZeneca under Section 6.1.1, Section 6.1.2 and Section 6.1.3 through all Approvals as well as, as Development proceeds and when such information is available, key aspects of worldwide regulatory strategy, pricing and market access strategy, market launch, and Commercialization (each plan or other such document, an "Integrated Development Plan" or "IDP"). On a Product-by-Product basis, for each Product licensed by AstraZeneca under Section 6.1.1, Section 6.1.2 or Section 6.1.3, as the case may be, AstraZeneca will prepare each IDP no later than [***] for such Product, and the IDP will contain high level information consistent with AstraZeneca's development and commercialization plans for its similar products at similar stages of development and commercialization in the same AstraZeneca franchise, including material updates, timelines, goals, and the criteria AstraZeneca will use to make internal decisions relating to the Product, provided however that it will be at AstraZeneca's sole discretion whether to and in what format to provide any information which (i) AstraZeneca is required not to share even under confidentiality pursuant to restrictions imposed by any Third Party, or (ii) contains AstraZeneca Confidential Information regarding the use of AstraZeneca's other portfolio compounds used alone or in combination with other AstraZeneca or Third Party products. Once AstraZeneca has prepared an IDP, AstraZeneca will update it consistent with AstraZeneca's standard practice (including if the IDP is updated and presented to an AstraZeneca internal committee) but at least Annually and will provide such updates to Ionis. AstraZeneca and Ionis will meet (through the JSC or as the Parties may otherwise agree) on a yearly basis to discuss the draft of the IDP and AstraZeneca will consider, in good faith, any proposals and comments made by Ionis for incorporation in the final IDP. AstraZeneca and Ionis will [***], to discuss the status of execution of the IDP. Additionally, subject to any restrictions imposed by any Third Party, AstraZeneca may provide more frequent updates in the case of extraordinary material events (e.g. approvals, regulatory feedback, etc.) as deemed appropriate by AstraZeneca. For the avoidance of doubt, information provided by AstraZeneca to Ionis pursuant to this Section 7.1.1 shall be treated by Ionis as AstraZeneca's Confidential Information subject to the provisions in Article 13. Notwithstanding the foregoing, on a Gene Target-by-Gene Target basis, AstraZeneca's obligations to provide Ionis with information or reports under this Section 7.1.1 will terminate if Ionis independently or for or with an Affiliate or Third Party engages in any activity to discover, research or develop an ASO designed to bind to the RNA that encodes such Gene Target in the Field other than in the course of performing its obligations under, or to the extent permitted by, this Agreement."

3. **Amendment Effective Date**

This Amendment shall become effective on the Amendment Effective Date.

4. **Entire Agreement**

This Amendment, together with the Agreement, constitutes the entire agreement between the Parties with respect to the subject matter of the Agreement. The Agreement together with this Amendment and any prior Amendments thereto supersedes all prior agreements, whether written or oral, with respect to the subject matter of the Agreement, as amended. Each Party confirms that it is not relying on any representations, warranties, or covenants of the Party except as specifically set out in the Agreement as amended. Nothing in this Amendment is intended to limit or exclude any liability or fraud. The Parties hereby agree that subject to the modifications specifically stated in this Amendment, all other terms and conditions of the Agreement shall remain in full force and effect.

5. **Execution**

THIS AMENDMENT IS EXECUTED by the authorized representatives of the Parties as of the date first written above.

ASTRAZENECA AB (publ.)	**IONIS PHARMACEUTICALS, INC.**
Signature: /s/Regina Fritsche Danielson	Signature: /s/Brett Monia
Name: Regina Fritsche Danielson	Name: Brett Monia
Title: VP and Head of IMED CVRM	Title: Chief Operating Officer

Exhibit 10.6

Certain identified information in this exhibit, marked by [***], has been excluded because it is both (i) not material, and (ii) the type that the registrant treats as private or confidential.

Strategic Collaboration Agreement

Between

Isis Pharmaceuticals, Inc.,

And

AstraZeneca AB

TABLE OF CONTENTS

STRATEGIC COLLABORATION AGREEMENT

This STRATEGIC COLLABORATION AGREEMENT (the "***Agreement***") is entered into as of the 31st day of July, 2015 (the "***Execution Date***") by and between **Isis Pharmaceuticals, Inc.**, a Delaware corporation, having its principal place of business at 2855 Gazelle Court, Carlsbad, CA 92010 ("***Isis***"), and **AstraZeneca AB**, a company incorporated in Sweden under no. 556011-7482 with its registered office at SE-151 85 Södertälje, Sweden ("***AstraZeneca***"). AstraZeneca and Isis each may be referred to herein individually as a "***Party***" or 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. All attached appendices, exhibits and schedules are a part of this Agreement.

RECITALS

WHEREAS, Isis possesses certain Patent Rights, Know-How, technology and expertise with respect to antisense therapeutics, and has novel and valuable capabilities for the research, discovery, identification, synthesis and development of antisense therapeutics;

WHEREAS, AstraZeneca has expertise in developing and commercializing human therapeutics, and is interested in entering into a strategic relationship with Isis to explore potential targets for the treatment of Metabolic Disorders ([***]), Cardiovascular Diseases, Kidney Diseases [***] (collectively, the "***Primary Diseases***") and to create antisense drugs to such targets;

WHEREAS, AstraZeneca and Isis desire to enter into a new strategic collaboration in the Primary Diseases to include (i) a core technology research program focused on growing the Parties' collective knowledge on ASO interactions in tissues and cell types relevant to Primary Diseases, (ii) a disease research program focused on the identification, validation, and applications of novel targets to treat the Primary Diseases, and (iii) a drug discovery program focused on [***] and up to [***] additional Collaboration Targets that have met certain Target Sanction success criteria;

WHEREAS, with regard to the targets selected as Collaboration Targets for development using an ASO, AstraZeneca desires Isis to (i) identify a Lead Candidate for the JSC to consider designating as a Development Candidate (and for AstraZeneca to consider designating as a Candidate Drug) for each of the Collaboration Targets, and (ii) with respect to Collaboration Targets that are not [***], provide AstraZeneca an exclusive right to obtain an exclusive license under this Agreement to Research, Develop, Manufacture and Commercialize Products in the Field;

WHEREAS, Isis desires to grant to AstraZeneca and AstraZeneca desires to accept from Isis as of the Effective Date an exclusive license to Research, Develop, Manufacture and Commercialize [***] Products;

WHEREAS, Isis also desires to grant to AstraZeneca and AstraZeneca desires to accept from Isis a non-exclusive license under program technology made by Isis under this Agreement and any of Isis' background technology necessary to practice such program technology for AstraZeneca to use in certain fields; and

WHEREAS, Isis and AstraZeneca have other on-going agreements, including the Collaboration, License and Development Agreement effective as of 7 December 2012 (as amended) and the Research Collaboration and License Agreement effective as of 15 October 2014. The strategic collaboration set forth in this Agreement is independent from such other agreements.

NOW, THEREFORE, in consideration of the respective covenants, representations, warranties and agreements set forth herein, the Parties hereto agree as follows:

ARTICLE 1.
RESEARCH COLLABORATION; RIGHT TO OBTAIN EXCLUSIVE LICENSES

1.1. **Research Collaboration Overview**.

1.1.1. The intent of the Research Collaboration is for the Parties to conduct (1) a core technology research program focused on growing the Parties' collective knowledge on systemic delivery of ASO interactions in tissues and cell types relevant to Primary Diseases, (2) a disease research program focused on the identification, validation, and applications of certain novel Targets to treat the Primary Diseases, and (3) a drug discovery program focused on Targets that meet certain Target Sanction success criteria in the disease research program.

1.1.2. At the beginning and throughout the term of the disease research program, the Parties (including through the JSC) will collaboratively discuss and identify Targets that the Parties are potentially interested in pursuing in the disease research program to treat the Primary Diseases. When Targets of interest are identified, the JSC will determine which Targets are eligible for inclusion in the disease research program. AstraZeneca may either add such Eligible Targets directly to the High Interest Target List to commence the work necessary to validate such Targets, or hold a limited number of such Eligible Targets in reserve for a period of time (before deciding whether to add such Targets to the High Interest Target List).

1.1.3. Isis, and in some cases together with AstraZeneca, will perform Target validation activities under the disease research program on Eligible Targets that the JSC (or AstraZeneca) has added to the list of High Interest Targets. Once a High Interest Target reaches Target Sanction, the JSC may select such Target to be the subject of a Collaboration Program under this Agreement.

1.1.4. For each Collaboration Program, Isis will use Commercially Reasonable Efforts to conduct drug discovery activities and generate [***] Lead Candidate for the JSC to consider designating as a Development Candidate.

1.1.5. For each Collaboration Program that is not the [***] Program, on a Collaboration Target-by-Collaboration Target basis, after the JSC or AstraZeneca determines that a Lead Compound has met the success criteria and such Lead Compound is designated a Development Candidate, AstraZeneca will have the right to obtain an exclusive license to further Research, Develop, Manufacture and ultimately Commercialize such Development Candidate (and any other Compounds designed to bind to such Collaboration Target).

1.1.6. [***] is a Collaboration Target (and will be deemed to have been so designated by the JSC on the Effective Date) and the drug discovery program for [***] will be the first Collaboration Program under this Agreement. AstraZeneca has an exclusive license from Isis to further Research, Develop, Manufacture and ultimately Commercialize [***] Compounds.

1.1.7. The purpose of this Section 1.1 is to provide a high-level overview of the roles, responsibilities, rights and obligations of each Party under this Agreement with respect to the Research Collaboration, and therefore this Section 1.1 is qualified in its entirety by the more detailed provisions of this Agreement set forth below.

1.2. **Research Programs**. Subject to and in accordance with the terms of this Agreement, Isis and AstraZeneca will conduct two research programs, each under a separate mutually agreed plan. The data generated from these two research programs will inform the Drug Discovery Programs.

1.2.1. ***Core Research Program***. The core research program will cover research focused on growing the Parties' collective knowledge of systemic delivery of ASO interactions in tissues and cell types relevant to Primary Diseases (such program, the "***Core Research Program***" and the plan for such program, the "***Core Research Plan***"). The Parties will base the Core Research Plan on the preliminary plan attached at SCHEDULE 1.2.1.

1.2.2. ***Disease Research Program***. The disease research program will focus on the identification and validation of High Interest Targets that may be designated as Collaboration Targets (such program, the "***Disease Research Program***" and the plan for such program, the "***Disease Research Plan***"). The Disease Research Plan will include at a minimum, the items set forth on SCHEDULE 1.2.2 and on approval by the JSC will be attached to the JSC minutes. AstraZeneca may, [***], supplement Isis' efforts in the Disease Research Program with AstraZeneca's own scientists at various points throughout the Disease Research Term.

1.2.3. ***Updating the Research Plans***. The Core Research Plan (based on the preliminary plan attached at Schedule 1.2.1) and the Disease Research Plan will be mutually agreed to by the JSC within [***] after the Effective Date and on approval by the JSC will be attached to the JSC minutes. Thereafter, the Parties will update such plans, as needed, and the updated plans will be reviewed and approved by the JSC at least [***] before the beginning of each Calendar Year (to facilitate each Party's budgeting). The first update to the Disease Research Plan will occur after the first High Interest Target is selected. Each update to the Disease Research Plan will include, at a minimum (i) the High Interest Targets to be worked on in the Disease Research Plan in each Calendar Year (or remaining portion thereof) and, if not already commenced, the date on which the JSC anticipates that work on each High Interest Target will commence; and (ii) the activities to support Target Sanction for any High Interest Target included in the Disease Research Plan (including any work on High Interest Targets that is ongoing).

1.2.4. ***Feasibility***. Neither Party will be required to complete any activities under the Core Research Plan or the Disease Research Plan if such Party in good faith believes that such activities are not technically feasible given the then-current state of the art.

1.3. **Core Research Term; Disease Research Term**.

1.3.1. ***Core Research Term***. The term for the conduct of the Core Research Program will begin on the Effective Date and will end on the [***] anniversary of the Effective Date (the "***Core Research Term***").

1.3.2. ***Disease Research Term***. The term for the conduct of the Disease Research Program will begin on the Effective Date and will end on the [***] anniversary of the Effective Date (the "***Disease Research Term***"); *provided, however*, if, by the [***] anniversary of the Effective Date Isis has not completed the activities set forth in the Disease Research Plan to support Target Sanction for [***] High Interest Targets, [***].

1.4. **Collaborative Process to Identify Potentially Eligible Targets – Overview**. Throughout the Disease Research Term, including at the first meeting of the JSC, the Parties will collaboratively discuss and identify Targets that the Parties are potentially interested in pursuing in the Disease Research Program to treat the Primary Diseases. For all of the potential Targets identified through this collaborative process, using the steps identified in Sections 1.5 through 1.7 below, the JSC will first determine whether the Targets being considered are eligible for possible inclusion in the Disease Research Plan, and AstraZeneca may designate Eligible Targets that are of interest to AstraZeneca as High Interest Targets for which activities to support Target Sanction will be conducted, or may choose to hold a limited number of such Eligible Targets in reserve (before deciding whether to add such Targets to the High Interest Target List).

1.5. **Eligible Targets**. AstraZeneca (through the JSC) may consider for designation as High Interest Targets any Targets that are not excluded by any of the Exclusion Criteria (as set forth in Section 1.6.1) (each, an "***Eligible Target***"). The various sources for potential Eligible Targets that may be designated as High Interest Targets include [***]. An Eligible Target may have as its primary disease association a disease that is not a Primary Disease but the focus of each Disease Research Plan will be the Primary Diseases. [***]. To that end, at each JSC meeting, Isis will review with AstraZeneca [***]. Isis' obligations under this paragraph will end on the earlier of (i) [***], and (ii) [***].

1.6. **Exclusion Criteria**.

1.6.1. **List of Exclusion Criteria to Consider for Proposed Targets**. If a Target proposed to be designated as a Reserved Target or High Interest Target meets any of the following criteria listed in items (a) through (g) (such criteria listed in items (a) through (g), the "***Exclusion Criteria***"), such Target is not an Eligible Target and will not be added to the Reserved Target List or the High Interest Target List:

[***];

provided, that [***].

1.6.2. **Notice of Any Applicable Exclusion Criteria**. Isis will (through the JSC) notify AstraZeneca if any of the Exclusion Criteria apply to a Target AstraZeneca requests for consideration as a Reserved Target or High Interest Target ([***]), and shall provide such information as is reasonably necessary to allow the JSC to discuss and verify such conclusion; *provided that* [***]. Upon requesting that a Target be considered as a Reserved Target or a Target that is not a Reserved Target be considered a High Interest Target, AstraZeneca will also notify Isis in writing if AstraZeneca has an internal program (regardless of therapeutic modality) for such Target (or protein product thereof).

1.7. **High Interest Target List; Reserved Target List**. With respect to any Eligible Target, AstraZeneca may either add the Eligible Target directly to the High Interest Target list as described under Section 1.7.1, or hold a limited number of such Eligible Targets in reserve on the Reserved Target List for a period of time as further described in Section 1.7.2 while AstraZeneca considers whether to designate such Eligible Target a High Interest Target.

1.7.1. **High Interest Targets**.

(a) ***High Interest Target List***. Under the Disease Research Plan, the JSC will establish a prioritized list of Eligible Targets to form the basis for the Disease Research Program (each such Target, a "***High Interest Target***" and such list the "***High Interest Target List***"). The JSC will regularly discuss the Eligible Targets the JSC believes may be designated as High Interest Targets, and will establish criteria and a process for selection and prioritization of High Interest Targets, which may include [***]. During the Disease Research Term, an Eligible Target may be included on the High Interest Target List at any time and such inclusion is separate from the decision to commence work on such High Interest Target under the Disease Research Plan.

(b) ***Schedule for Populating the High Interest Target List.*** Given the time needed to research each High Interest Target, the Parties intend that the JSC will name at least [***] High Interest Targets within the [***] of the Disease Research Term, and at least [***] additional High Interest Targets during each consecutive [***] period thereafter during the Disease Research Term; *provided*, the number of High Interest Targets cannot exceed [***]. Each Party may propose updates, if any, to the High Interest Target List at each meeting of the JSC.

(c) ***Substituting or Removing High Interest Targets***. Prior to [***] for a High Interest Target, the JSC may add a new Eligible Target to the High Interest Target List in substitution for such a Target. In addition, if a High Interest Target is invalidated (e.g., published scientific literature demonstrates the invalidity of the High Interest Target) prior to [***] for such Target, as determined by the JSC, then the JSC will replace such invalidated High Interest Target on the High Interest Target List with another Eligible Target selected by the JSC.

1.7.2. **Reserved Targets**.

(a) ***Reserved Target List***. Under the Disease Research Plan, if the JSC (or AstraZeneca) determines that certain Eligible Targets should be held in reserve for consideration as potential High Interest Targets, the JSC will establish and maintain in the JSC minutes such a list of Eligible Targets (the "***Reserved Target List***," and each such listed Eligible Target, a "***Reserved Target***"). AstraZeneca may add Eligible Targets to such list at any time during the Disease Research Term. No Eligible Target can be added to the Reserved Target List if by virtue of such addition the number of Eligible Targets on the Reserved Target List will exceed [***] the number of open High Interest Target slots remaining on the High Interest Target List at any given time. The Reserved Target List will include the date that each such Reserved Target was added to the Reserved Target List and each Reserved Target will be automatically removed from the Reserved Target List (and will no longer be a Reserved Target) [***] after it was put on such list. If, at any time, the number of Targets on the Reserved Target List exceeds the maximum number of allowed Reserved Targets by virtue of a decrease in the number of open slots remaining on the High Interest Target List, no Targets will be required to be removed from the Reserved Target List, except by virtue of the passage of time. AstraZeneca will be precluded from adding any additional Eligible Targets to the Reserved Target List if by virtue of such addition it would increase the size of the Reserved Target List above the maximum permitted number of Reserved Targets.

(b) ***Re-designation as a Reserved Target***. Subject to Section 1.7.2(a) with respect to the maximum number of Reserved Targets, the JSC may add a previously removed Target to the Reserved Target List if such Target is still an Eligible Target, and either (i) the data has changed materially on such Target based on either laboratory work or new information discovered in the literature; or (ii) [***] have passed from the time such Target was removed from the Reserved Target List. On such addition, the Eligible Target shall once again be a Reserved Target until automatically removed from the Reserved Target List in accordance with Section 1.7.2(a).

(c) ***Restrictions on Reserved Targets***. During the Disease Research Term until [***] High Interest Targets have been selected to be included on the High Interest Target List, Isis will not and will ensure that its Affiliates will not offer a Reserved Target to a Third Party or grant to any such Third Party any rights to such Reserved Target or any ASOs designed to bind to such Reserved Target so long as such Target remains a Reserved Target.

(d) ***Dissolution of Reserved Target List***. Once substantial activities are initiated under the Disease Research Plan on [***] High Interest Targets, no additional Targets may be added or substituted on the High Interest Target List, and the Reserved Target List will be dissolved. Isis' obligations and AstraZeneca's rights under this Agreement with respect to any Eligible Targets that were on the Reserved Target List at such dissolution will terminate.

1.8. Activities to Support Target Sanction under the Disease Research Program.

(a) Isis will prepare the Disease Research Plan and any updates to such plan (which will include Target Sanction criteria for each High Interest Target), and the JSC will agree on the Disease Research Plan. AstraZeneca will provide input on the Disease Research Plan through the JSC. The criteria to be met and the activities to be conducted for any High Interest Target to achieve Target Sanction will include the criteria and activities set forth on SCHEDULE 1.8.

(b) The JSC will determine the number of High Interest Targets for which activities to support Target Sanction will be conducted during each Calendar Year (or portion thereof for the initial and final periods) of the Disease Research Term, which number will be approximately [***] High Interest Targets during the first whole Calendar Year of the Disease Research Term, and [***] High Interest Targets per Calendar Year during the remainder of the Disease Research Term for a total of [***] High Interest Targets; *provided, however*, that (i) with the JSC's approval Isis may conduct such activities to support Target Sanction on more High Interest Targets per Calendar Year than was otherwise planned hereunder if Isis identifies that certain High Interest Targets require less work to achieve Target Sanction, and (ii) so long as by the end of the Disease Research Term Isis has conducted activities to support Target Sanction for [***] High Interest Targets, Isis may conduct activities to support Target Sanction on fewer High Interest Targets per Calendar Year than was otherwise planned hereunder if one or more High Interest Targets require an unusually large amount of work ([***]).

(c) The Disease Research Plan will identify which Party will be responsible for each of the activities related to such Targets. In accordance with the Disease Research Plan, Isis will use Commercially Reasonable Efforts to perform the Isis Conducted Activities designated under such plan in accordance with the timelines specified therein. If the JSC agrees that AstraZeneca will conduct activities under the Disease Research Plan to supplement Isis' efforts to achieve Target Sanction, then the JSC will update the Disease Research Plan accordingly and AstraZeneca will use Commercially Reasonable Efforts to conduct such AstraZeneca Conducted Activities designated under the Disease Research Plan in accordance with the timelines specified therein. Each Party will be responsible for the cost of the work it conducts under the Disease Research Program. Unless otherwise mutually agreed by the JSC, neither Party will be required to conduct work using [***] that are not similar in cost or technical feasibility to the models such Party uses for its other programs.

1.9. **Targets that are Outside of the Collaboration**. During the Disease Research Term, either Party may work outside of the Research Collaboration on any Target (or the protein product thereof) that is not (i) a Reserved Target, (ii) a High Interest Target, or (iii) a Collaboration Target.

1.10. **Process for Designating High Interest Targets as Collaboration Targets**.

1.10.1. **Review of Target Sanction Data Package**. Upon completion of the activities in the Disease Research Plan to support Target Sanction for a particular High Interest Target, Isis will deliver a Target Sanction Data Package for such High Interest Target to the JSC for review as soon as reasonably practicable for the JSC to determine whether or not such High Interest Target has achieved Target Sanction and thus is eligible to become a Collaboration Target. Each time Isis delivers to the JSC a Target Sanction Data Package for a High Interest Target under this Section 1.10 the Parties will schedule a meeting of the JSC to occur within [***] following delivery of such Target Sanction Data Package. At such meeting (if possible), or within [***] after such meeting, the JSC (or, if the JSC cannot agree, AstraZeneca) will determine and record in the JSC minutes whether such High Interest Target has achieved Target Sanction. If the JSC (or, if the JSC cannot agree, AstraZeneca), determines that such High Interest Target has achieved Target Sanction, and AstraZeneca designates such High Interest Target a Collaboration Target, then Isis will promptly commence a Collaboration Program for such Collaboration Target under Section 1.13 below.

1.10.2. **Additional Work to Achieve Target Sanction**. If the JSC determines that such High Interest Target has not achieved Target Sanction status, then the JSC will decide whether or not to revise the Target Sanction criteria and/or determine whether additional work will be conducted for such High Interest Target to achieve Target Sanction (and will update the Disease Research Plan accordingly). The allocation of the expense of and budget for any such additional work and the Party best positioned to conduct such work will be discussed and agreed by the JSC, and [***]. The [***] costs of any such additional work incurred by Isis ([***]) will be billed to AstraZeneca ([***]) and will be invoiced to AstraZeneca on a Calendar Quarter basis and paid by AstraZeneca within [***] of AstraZeneca's receipt of such invoice if and to the extent such invoiced costs are within the budget approved by the JSC for such activities. On conclusion of any additional work Isis shall provide the revised data package to the JSC and Section 1.10.1 shall apply.

1.10.3. **Failure to Achieve Target Sanction.** On a High Interest Target-by-High Interest Target basis, if, on first completion of the activities in the Disease Research Plan to support Target Sanction or, if the JSC agrees that further work will be undertaken with respect to such Target, following completion of any agreed additional work, the JSC (or, if the JSC cannot agree, AstraZeneca) determines that a High Interest Target has not achieved Target Sanction, then on the date of such determination (the "***Target Failure Date***"):

(a) such High Interest Target will not be designated a Collaboration Target and will no longer be a High Interest Target under this Agreement, but will still count against the maximum limit of [***] High Interest Targets under this Agreement;

(b) if and when AstraZeneca timely delivers a Release Notice to Isis, AstraZeneca will be free to Exploit ASOs designed to bind to such former High Interest Target. If AstraZeneca does not timely deliver a Release Notice to Isis, then for a period of [***] from the Target Failure Date, AstraZeneca and its Affiliates will not Exploit ASOs designed to bind to such former High Interest Target other than as research tools in connection with its internal programs; and

(c) Isis will be free to Exploit ASOs designed to bind to such former High Interest Target, *provided, however*, that if AstraZeneca does not timely deliver a Release Notice to Isis, for a period of [***] after the Target Failure Date, (x) any work Isis conducts on such former High Interest Target will be undertaken by Isis for itself and not in collaboration with any Third Party partner (other than Isis' subcontractors acting for or on behalf of Isis or Isis' academic collaborators), and (y) if such former High Interest Target achieves Target Sanction (which shall be deemed to have occurred if [***] with respect to such former High Interest Target) within such [***] period, then Isis will provide written notice to AstraZeneca when it [***]. If, within [***] following receipt of such notice, AstraZeneca delivers written notice to Isis that AstraZeneca desires such former High Interest Target to be restored to this Agreement and designated as a Collaboration Target and agrees to reimburse Isis within [***] for [***] ([***]) incurred by Isis to achieve Target Sanction for such Target after the Target Failure Date through the date Isis delivers such notice that Isis initiated drug discovery activities, then such Target will be a Collaboration Target hereunder and Isis will promptly commence drug discovery work on such Collaboration Target under Section 1.13 below.

(d) without limiting Section 4.4.2, Isis will have exclusive rights (and AstraZeneca will, and hereby does grant Isis an exclusive license) to all data, results and information generated with respect to such former High Interest Target to research, develop, manufacture and commercialize ASOs to such High Interest Target and AstraZeneca will promptly transfer to Isis copies of all such data, results and information in AstraZeneca's possession generated under the Disease Research Program.

1.10.4. **JSC Timing**. The process set forth in this Section 1.10 for the JSC (or, if the JSC cannot agree, AstraZeneca) to make a determination regarding whether a High Interest Target has achieved Target Sanction status, whether such High Interest Target is designated a Collaboration Target, whether the Target Sanction criteria will be revised, and/or whether additional work will be conducted for such High Interest Target to achieve Target Sanction, will in no event exceed [***] after the date the JSC first meets to discuss the Target Sanction Data Package or, if the JSC agrees that additional work should be undertaken, the revised Target Sanction Data Package.

1.11. **End of Core Research Term**. At the end of the Core Research Term, (i) neither Isis nor AstraZeneca will have an obligation to perform any activities under the Core Research Program; and (ii) each Party will promptly transfer to the other (to the extent not previously provided) copies of all data, results and information that it has generated under the Core Research Program and each Party shall be entitled to non-exclusively use and disclose such data, results and information in accordance with Section 4.4.

1.12. **End of the Disease Research Term**. At the end of the Disease Research Term, (i) neither Isis nor AstraZeneca will have an obligation to perform any activities under the Disease Research Program; (ii) the High Interest Target List will be dissolved, (iii) Isis will deliver to AstraZeneca a Target Sanction Data Package (completed to the extent possible with the [***] generated prior to expiration of the Disease Research Term) for any High Interest Target that has not yet achieved Target Sanction and the JSC will consider whether any such High Interest Target has achieved Target Sanction, and AstraZeneca may designate such High Interest Target as a Collaboration Target by delivering a written notice to Isis of such designation within [***] after AstraZeneca's receipt of such Target Sanction Data Package, and (iv) the JSC will be deemed to have determined that any High Interest Targets that have not been designated as Collaboration Targets by such expiry (or by the end of such [***] period), have not achieved Target Sanction and Section 1.10.3 shall apply to each such Target. For clarity, the expiration of the Disease Research Term will not affect AstraZeneca's rights or Isis' obligations with respect to Collaboration Programs under this Agreement, including, in the case of Collaboration Programs, Isis' obligation under Section 1.13.1 to use Commercially Reasonable Efforts to identify a Lead Candidate for each applicable Collaboration Program that satisfies the Development Candidate Success Criteria.

1.13. **Collaboration Program Activities and Term**.

1.13.1. **Drug Discovery Plans**.

(a) An initial draft Drug Discovery Plan for [***] is attached to this Agreement at SCHEDULE 1.13.1(a). For each additional Collaboration Program, within [***] after the designation of the applicable Collaboration Target, Isis will provide the JSC an initial draft drug discovery plan for the applicable Collaboration Target. Each such draft plan will detail the drug discovery activities to identify a Development Candidate under the applicable Collaboration Program and on approval by the JSC will be attached to the JSC minutes (each such plan, a "***Drug Discovery Plan***"). Each Drug Discovery Plan will include the success criteria and the activities that will be performed to achieve Development Candidate designation as set forth in SCHEDULE 1.13.1(b), and will be consistent with the scope and timeframe Isis uses for other similar Isis programs.

(b) AstraZeneca will provide input on each Drug Discovery Plan including any additional success criteria for the Development Candidate that AstraZeneca would like to propose for the JSC's consideration; *provided that*, in any event, each Drug Discovery Plan will include project transition criteria consistent with the internal Isis criteria and, to the extent applicable to ASOs and consistent with the scope of Isis' standard drug discovery activities, Isis will endeavor to conduct the Isis Conducted Activities under each Drug Discovery Plan consistent with the AstraZeneca 5R Framework as notified to Isis from time to time (such framework to be consistent with the framework AstraZeneca uses for other drugs in the applicable AstraZeneca franchise). The current version of the AstraZeneca 5R Framework is attached as EXHIBIT 1. The JSC will review such plan and agree on a final Drug Discovery Plan for each Collaboration Program.

(c) The JSC will review, update and approve the [***] Drug Discovery Plan and Isis will initiate the [***] Drug Discovery Plan as soon as practicable but not later than [***] following the Effective Date. Isis estimates the Isis Conducted Activities under the [***] Drug Discovery Plan will be completed within [***] after such activities are initiated.

(d) Isis will use Commercially Reasonable Efforts to carry out its drug discovery activities for each Collaboration Program pursuant to the applicable Drug Discovery Plan in accordance with the timelines specified therein in a manner consistent with its internal practices for other Targets with the goal of identifying a Development Candidate for the applicable Collaboration Program as soon as practicable. Isis will update each Drug Discovery Plan as needed and submit it to the JSC for its review and approval.

(e) If the JSC agrees that AstraZeneca will conduct any activities under a particular Drug Discovery Plan, then the Parties will update such Drug Discovery Plan accordingly for approval by the JSC and, following such approval, AstraZeneca will use Commercially Reasonable Efforts to conduct such AstraZeneca Conducted Activities designated under such Drug Discovery Plan in accordance with the timelines specified therein [***].

(f) If the JSC or the Parties cannot mutually agree on a final Drug Discovery Plan for a given Collaboration Program, such matter will be resolved by the Senior Representatives in accordance with Section 12.1.1.

1.13.2. **Third Party Obligations Applicable to the Compounds**. While the Parties are reviewing technology options to be used under a Drug Discovery Plan for a potential Development Candidate, the Parties will discuss any existing or potential Third Party Obligations they believe apply or may apply to such technology. Isis will disclose to AstraZeneca any such existing or potential Third Party Obligations known by Isis that apply to technology under consideration by the Parties and Isis will identify which technology is (i) [***] (such [***], the "***New Third Party Compound Technology***") and subject to either (A) an Isis In-License Agreement in existence at such time or (B) an agreement that Isis anticipates will be entered into by Isis and such Third Party (and Section 6.9.2 will apply to any such agreement), (ii) subject to a Prior Agreement, or (iii) otherwise subject to an Isis In-License Agreement. Where AstraZeneca agrees to incorporate technology subject to an Isis In-License Agreement into an ASO under the Drug Discovery Plan, AstraZeneca will pay [***]. On such agreement, Isis will update APPENDIX 3 to include any such in-license agreement.

1.13.3. **Collaboration Program Term**. The period during which the Parties will conduct the Collaboration Programs under Drug Discovery Plans (such period, the "***Collaboration Program Term***") will begin on the Effective Date and will end on the [***] anniversary of the Effective Date; *provided that* (a) if the Disease Research Term is extended under Section 1.3.2 and there are uncompleted activities to be performed for a Collaboration Program under a Drug Discovery Plan under this Section 1.13, then, in order to provide sufficient time to perform such additional activities with respect to such Collaboration Program(s), the Collaboration Program Term for all uncompleted Collaboration Programs will be extended to end on the [***] anniversary of the Effective Date; and (b) if a Target is restored to the collaboration in accordance with Section 1.10.3, then the provisions in this Agreement that were operative during the Collaboration Program Term will apply solely with respect to such Target for such period as is necessary to enable the activities specified in the Drug Discovery Plan for such Target to be performed.

1.14. **Process for Designating Development Candidates**.

1.14.1. **Review of Lead Candidate Data Package.** After the activities set forth in the applicable Drug Discovery Plan are completed for a particular Collaboration Program, Isis will deliver to the JSC the applicable Lead Candidate Data Package for review by the JSC as soon as reasonably practicable for the JSC to determine whether or not the Lead Candidate has met the applicable Development Candidate Success Criteria and whether the JSC (or AstraZeneca) wishes to designate a Development Candidate. Each time Isis delivers to the JSC a Lead Candidate Data Package for a Collaboration Program under this Section 1.14 the Parties will schedule a meeting of the JSC to occur within [***] following delivery of such Lead Candidate Data Package. At such meeting (if possible), or within [***] after such meeting, the JSC (or, if the JSC cannot agree, AstraZeneca) will determine and record in the JSC minutes the determination whether such Lead Candidate has met the applicable Development Candidate Success Criteria. If the JSC (or, if the JSC cannot agree, AstraZeneca) determines such Lead Candidate (or any other Compound included in the Lead Candidate Data Package (the "***Other Leads***," and together with the Lead Candidate, the "***Lead Compounds***")) met such criteria and designates a Lead Compound as a Development Candidate, then AstraZeneca will have the right to undertake the evaluation pursuant to Section 1.16.2 to determine whether AstraZeneca wishes to designate such Development Candidate as a Candidate Drug and (i) obtain an exclusive license from Isis to the Compounds from the applicable Collaboration Program in accordance with Section 1.16 below, or (ii) with respect to [***], maintain the exclusive license to [***] Products in accordance with Section 1.16. If Isis believes that a [***] Compound identified in the Lead Candidate Data Package satisfies the [***] Success Criteria, but the JSC fails to designate such [***] Compound a Development Candidate, the matter shall be resolved in accordance with Section 12.1.1 and if applicable Section 12.1.3.

1.14.2. **Additional Work to Achieve Development Candidate Status**. If with respect to a Collaboration Program, the JSC determines that none of the Lead Compounds has met all the applicable Development Candidate Success Criteria, then the JSC will decide whether or not to revise such success criteria (and designate a Development Candidate based on such revised criteria) and/or determine whether additional work will be conducted for one or more Lead Compounds to meet the Development Candidate Success Criteria (and will update the Drug Discovery Plan accordingly). The allocation of the expense of and budget for any such additional work and the Party best positioned to conduct such work will be discussed and agreed by the JSC, and [***]. The [***] costs of any such additional work incurred by Isis ([***]) will be billed to AstraZeneca ([***]) and will be invoiced to AstraZeneca on a Calendar Quarter basis and paid by AstraZeneca within [***] of AstraZeneca's receipt of such invoice. On conclusion of any additional work Isis shall provide the revised data package to the JSC and Section 1.14.1 shall apply.

1.14.3. **Failure to Achieve Development Candidate Status**. On a Collaboration Target-by-Collaboration Target basis, if, following completion of the activities set forth in the applicable Drug Discovery Plan, the JSC (or, if the JSC cannot agree, AstraZeneca or with respect to [***], unless otherwise agreed by the Parties, the Expert in accordance with Section 12.1.3) determines that none of the Lead Compounds have met the applicable Development Candidate Success Criteria, and the JSC determines that such success criteria will not be revised and that no additional work will be conducted for such Lead Compounds, then on the date of such determination (the "***Candidate Failure Date***"):

(a) None of such Lead Compounds (and all other Compounds included in the applicable Collaboration Program) (each, a "***Failed Candidate***") will be designated a Development Candidate and the applicable Collaboration Target will no longer be a Collaboration Target under this Agreement;

(b) AstraZeneca will not have the right to obtain an exclusive license from Isis to any Failed Candidate in accordance with Section 1.16 below;

(c) If the Failed Candidates are [***] Compounds, the license granted to AstraZeneca under Section 4.1.1 with respect to [***] will automatically terminate;

(d) if and when AstraZeneca timely delivers a Release Notice to Isis, AstraZeneca will be free to Exploit ASOs designed to bind to such former Collaboration Target. If AstraZeneca does not timely deliver a Release Notice to Isis, then for a period of [***] (in the case of [***]) and [***] (in the case of any other Failed Candidate), in each case after the Candidate Failure Date (in each case, the "***Carryover Period***"), AstraZeneca and its Affiliates will not Exploit ASOs designed to bind to such former Collaboration Target other than as research tools in connection with its internal programs;

(e) Isis will be free to Exploit ASOs designed to bind to such former Collaboration Target; *provided however*, that if AstraZeneca does not timely deliver a Release Notice to Isis then:

(i) during the Carryover Period (1) any work Isis conducts on a Failed Candidate (or any other ASO designed to bind to the former Collaboration Target) will be undertaken by Isis for itself and not in collaboration with any Third Party (other than Isis' subcontractors acting for or on behalf of Isis or Isis' academic collaborators) and, (2) except as permitted by this Section 1.14.3(e), Isis will not offer a Failed Candidate to a Third Party; and

(ii) if, within the Carryover Period, Isis intends to commence [***] on a Failed Candidate (or a different ASO designed to bind to the applicable former Collaboration Target), Isis shall notify AstraZeneca and will provide AstraZeneca with the Lead Candidate Data Package for such ASO and AstraZeneca will have an exclusive option (the "***Carryover Option***") to obtain from Isis the license under Section 4.1.1 with respect to such former Collaboration Target. If, within [***] following receipt of such data package, AstraZeneca delivers written notice to Isis that AstraZeneca desires such Target to be restored to this Agreement, such ASO will be deemed to have been designated a Development Candidate by the JSC and AstraZeneca may exercise its rights under Section 1.16 and if the Development Candidate is a [***] Compound the license granted to AstraZeneca for [***] Products under Section 4.1.1 will be automatically restored and effective. If AstraZeneca elects to make such designation and exercises the applicable Collaboration Program License Right, without limiting AstraZeneca's obligation to pay Isis the license fee under Section 6.2 or AstraZeneca's obligation to pay the [***] CD Milestone (as applicable), AstraZeneca will reimburse Isis within [***] of such exercise for [***] ([***]) incurred by Isis with respect to such Development Candidate from the Candidate Failure Date to the date Isis delivered to AstraZeneca the applicable Lead Candidate Data Package under this Section 1.14.3(e)(ii).

(f) Subject to any restoration pursuant to Section 1.14.3(e)(ii) and without limiting Section 4.4.2, Isis will have exclusive rights (and AstraZeneca will, and hereby does grant Isis an exclusive license) to use and practice under the AstraZeneca Collaboration Technology (if any) with respect to such Collaboration Target to Exploit ASOs designed to bind to such former Collaboration Target. For clarity, such grant shall not affect AstraZeneca's right to use and practice under the AstraZeneca Collaboration Technology to Exploit compounds and products in the AstraZeneca Field targeting such former Collaboration Target or to Exploit Compounds that are designed to bind to any remaining Exclusive Target.

(g) With regard to the Jointly-Owned Collaboration Technology for such Collaboration Program, AstraZeneca will assign to Isis all of AstraZeneca's right, title and interest in any Jointly-Owned Product-Specific Patents that do not claim any Compound designed to bind to a remaining Exclusive Target and such other Jointly-Owned Product-Specific Patents as may be agreed by the Parties; and any such transferred Jointly-Owned Product-Specific Patents will be included in the licenses granted by Isis to AstraZeneca under (x) Section 4.4.2 and (y) in so far as they are relevant to a remaining Exclusive Target, Section 4.1.1. On a restoration pursuant to Section 1.14.3(e)(ii), any interest assigned to Isis pursuant to this Section 1.14.3(g), will on AstraZeneca's request be assigned back to AstraZeneca.

(h) Each Party will promptly transfer to the other (to the extent not previously provided) copies of all data, results and information relating to such former Collaboration Targets that it has generated under the Drug Discovery Plan and the other Party shall be entitled to non-exclusively use and disclose such data, results and information in accordance with Section 4.4.

1.14.4. **JSC Process**. The process set forth in this Section 1.14 for the JSC to determine whether a Lead Compound has met the Development Candidate Success Criteria, whether any Lead Compound will be designated a Development Candidate, whether the applicable success criteria will be revised, and/or whether additional work will be conducted for a Lead Compound to be designated as a Development Candidate, will in no event exceed [***] after the date the JSC first convenes the meeting to discuss the Lead Candidate Data Package (or if applicable, the revised Lead Candidate Data Package).

1.15. **Expiration of Collaboration Program Term**.

1.15.1. **Failure to Designate a Development Candidate**. On a Collaboration Program-by-Collaboration Program basis, if, despite the Parties' Commercially Reasonable Efforts, by the expiration of the Collaboration Program Term, Isis has not delivered a Lead Candidate Data Package for a particular Collaboration Target or the JSC or AstraZeneca has not designated a Development Candidate for a particular Collaboration Target, then:

(a) the Parties will no longer have an obligation to perform any activities under this ARTICLE 1 with respect to such Collaboration Program;

(b) Isis will deliver a Lead Candidate Data Package (completed to the extent possible with the data, results and information generated prior to expiration of the Collaboration Program Term) and the JSC will consider whether any Lead Compound from such Collaboration Program has met the applicable Development Candidate Success Criteria, and whether or not such criteria are met AstraZeneca may designate such a Compound a Development Candidate by delivering a written notice to Isis of such designation within [***] after AstraZeneca's receipt of such Lead Candidate Data Package;

(c) unless AstraZeneca designates a Development Candidate for a particular Collaboration Program pursuant to Section 1.15.1(b), all Compounds from such Collaboration Program will be deemed to be Failed Candidates and Section 1.14.3 will apply.

1.15.2. **Status of other Collaboration Programs**. For clarity, the expiration of the Collaboration Program Term will not affect the Parties' respective rights and obligations with respect to any Collaboration Program that, at the end of the Collaboration Program Term (a) is a Licensed Program; or (b) is being evaluated by AstraZeneca pursuant to Section 1.16 until the expiry of the applicable Collaboration Program License Right Deadline.

1.16. **Exclusive Right to Obtain or Maintain Exclusive Licenses to Development Candidates**.

1.16.1. **Collaboration Program License Rights**. On a Collaboration Target-by-Collaboration Target basis, AstraZeneca has the exclusive right which it may exercise at any time on or before 5:00 p.m. (Pacific time) on the [***] (each, a "***Collaboration Program License Right Deadline***" and such period the "***Evaluation Period***") following the date [***] (each, a "***Collaboration Program License Right***") to (i) with respect to a Collaboration Target that is not [***], obtain from Isis the license set forth in Section 4.1.1 below, or (ii) with respect to [***], maintain the exclusive license set forth in Section 4.1.1.

1.16.2. **AstraZeneca Evaluation**. During and prior to the Evaluation Period, AstraZeneca may conduct other activities at its expense to supplement the information it uses to determine if it wishes to designate the Development Candidate as a Candidate Drug (in accordance with AstraZeneca's internal procedures) and exercise its Collaboration Program License Right. After designation of a Development Candidate, Isis will provide AstraZeneca as promptly as practicable with [***] of non-GMP research grade API of such Development Candidate (or applicable rodent ASO Isis designed under the applicable Drug Discovery Plan), [***]; *provided, that*, if Isis cannot provide such research grade API to AstraZeneca within [***] after designation of such Development Candidate, the applicable Collaboration Program License Right Deadline and Evaluation Period will be extended for an amount of time equal to the number of days thereafter that it takes Isis to deliver such research grade API to AstraZeneca. If requested by AstraZeneca during the Evaluation Period, and in Isis' possession, Isis will supply further quantities of non-GMP research grade API at [***]. AstraZeneca will notify Isis whether AstraZeneca is exercising its Collaboration Program License Right to license the applicable Collaboration Target or maintain its license to [***] (and in each case all Products included in the applicable Collaboration Program) by notifying Isis in writing on or before the applicable Collaboration Program License Right Deadline. During such Evaluation Period, AstraZeneca will keep Isis apprised of AstraZeneca's progress in making a decision regarding such exercise to enable Isis to plan as early as possible for manufacturing of API under Section 5.5 for the relevant Development Candidate for [***]. For each Collaboration Program being evaluated, during such Evaluation Period Isis will provide such information as AstraZeneca may reasonably request in connection with such evaluation [***].

1.16.3. **Exercise**. If AstraZeneca notifies Isis in writing by the Collaboration Program License Right Deadline that AstraZeneca is exercising the Collaboration Program License Right (on a Collaboration Program-by-Collaboration Program basis, the date of such notice, the "***Collaboration Program Exercise Date***"), AstraZeneca will pay Isis the license fee set forth in Section 6.2 or the [***] CD Milestone set forth in Section 6.3 (as applicable) within [***] after AstraZeneca's receipt of an invoice from Isis for such payment, and, (a) if the Collaboration Program is [***], the license in Section 4.1.1 shall continue and (b) in the case of a Collaboration Program that is not the [***] Program, Isis will, and hereby does, grant to AstraZeneca the license set forth in Section 4.1.1 below with respect to such Collaboration Program.

1.16.4. **No Exercise**. On a Collaboration Program-by-Collaboration Program basis, if AstraZeneca does not provide timely written notice to Isis under Section 1.16.3, then:

(a) AstraZeneca's Collaboration Program License Right will expire and no license fee is payable under Section 6.2, and AstraZeneca will have no further rights to (and Isis will have no further obligations with respect to) such Collaboration Target (including the Development Candidate and all other Compounds included in the applicable Collaboration Program);

(b) the Target to which such Compounds are directed will cease to be a Collaboration Target;

(c) if the Collaboration Target is [***], no [***] CD Milestone is payable, and the license granted to AstraZeneca under Section 4.1.1 for [***] Products will automatically terminate;

(d) Isis will have exclusive rights (and AstraZeneca will, and hereby does grant Isis an exclusive license) to the AstraZeneca Collaboration Intellectual Property (if any) generated by AstraZeneca under this Agreement for such Collaboration Target to Exploit ASOs designed to bind to such Collaboration Target. For clarity, such grant will not affect AstraZeneca's right to use and practice under the AstraZeneca Collaboration Technology to Exploit compounds and products in the AstraZeneca Field targeting such former Collaboration Target or to Exploit Compounds that are designed to bind to any remaining Exclusive Target.

(e) With regard to the Jointly-Owned Collaboration Technology for such Collaboration Program, AstraZeneca will assign to Isis all of AstraZeneca's right, title and interest in any Jointly-Owned Product-Specific Patents that do not claim any Compound designed to bind to a remaining Exclusive Target and such other Jointly-Owned Product-Specific Patents as may be agreed by the Parties; and any such transferred Jointly-Owned Product-Specific Patents will be included in the licenses granted by Isis to AstraZeneca under (x) Section 4.4.2 and (y) in so far as they are relevant to a remaining Exclusive Target, Section 4.1.1.

(f) Each Party will promptly transfer to the other (to the extent not previously provided) copies of all data, results and information relating to such former Collaboration Targets that it has generated under the Drug Discovery Plan and the other Party shall be entitled to non-exclusively use and disclose such data, results and information in accordance with Section 4.4;

(g) for a period of [***] thereafter, AstraZeneca and its Affiliates will not develop or commercialize an ASO designed to bind to the applicable former Collaboration Target other than as research tools in connection with its internal programs; and

(h) to the extent not previously provided, AstraZeneca will promptly transfer to Isis copies of all data, results and information generated by AstraZeneca related to the testing and studies with respect to the applicable Collaboration Target undertaken by AstraZeneca during, and prior to, the Evaluation Period.

ARTICLE 2.
COLLABORATION MANAGEMENT; ADMINISTRATION; COSTS AND EXPENSES AND MANUFACTURING

2.1. Collaboration Management.

2.1.1. JSC. The Parties will establish a joint steering committee ("***JSC***") for the Collaboration Programs within [***] of the Effective Date, to finalize and update the Collaboration Plans and oversee the conduct of activities under the respective Collaboration Plans. The JSC will consist of four representatives appointed by Isis and four representatives appointed by AstraZeneca. Each JSC member will be a senior research or development leader or have similar experience and expertise as a senior research or development leader. Each Party will designate one of its four representatives who are empowered by such Party to make decisions related to the performance of such Party's obligations under this Agreement to act as the co-chair of each JSC. The co-chairs will be responsible for overseeing the activities of its JSC consistent with the responsibilities set forth in Section 2.1.2. SCHEDULE 2.1.1 sets forth certain JSC governance matters agreed to as of the Execution Date. The JSC will determine the JSC operating procedures at its first meeting, including the JSC's policies for replacement of JSC members, policies for participation by additional representatives or consultants invited to attend JSC meetings, and the location of meetings, which will be codified in the written minutes of the first JSC meeting. Each Party will be responsible for the costs of its own employees or consultants attending JSC meetings.

2.1.2. Role of the JSC. Without limiting any of the foregoing, the JSC will perform the following functions in accordance with this Agreement, some or all of which may be addressed directly at any given JSC meeting:

(a) review and agree on the Core Research Plan and any amendments thereto;

(b) review and agree on the Disease Research Plan and any amendments thereto taking into account the outline in SCHEDULE 1.2.2 and the requirement to achieve the criteria and perform the activities listed in SCHEDULE 1.8;

(c) [***];

(d) regularly discuss potential Eligible Targets and the application of the Exclusion Criteria to such Targets and maintain the Reserved Target List in the minutes of the JSC;

(e) establish criteria and a process for selecting and prioritizing High Interest Targets;

(f) maintain the list of High Interest Targets in the minutes of the JSC;

(g) determine the High Interest Targets to be worked on in the Disease Research Plan and when work on a High Interest Target is to commence;

(h) set the Target Sanction criteria for each High Interest Target under the Disease Research Plan; *provided that* unless otherwise agreed by the JSC, such criteria shall include the criteria listed in SCHEDULE 1.8;

(i) evaluate each Target Sanction Data Package and make a determination regarding whether a High Interest Target has achieved Target Sanction status, whether a High Interest Target will be designated a Collaboration Target, whether the Target Sanction criteria will be revised, and/or whether additional work will be conducted for such High Interest Target to achieve Target Sanction as further provided in Section 1.10;

(j) maintain the list of Collaboration Targets that are the subject of the Collaboration Programs;

(k) agree on the Drug Discovery Plan for each Collaboration Program;

(l) prepare Work Plan Reports in accordance with Section 2.7;

(m) evaluate each Lead Candidate Data Package and make a determination regarding whether any Lead Compound has met the Development Candidate Success Criteria, whether a Lead Compound will be designated a Development Candidate, whether such success criteria will be revised, and/or whether additional work will be conducted for such Lead Compound to be designated as a Development Candidate as further provided in Section 1.14;

(n) review the overall progress of the activities under the applicable Collaboration Plan;

(o) review, provide advice on, and amend the applicable Collaboration Plan; and

(p) such other review, approval and advisory responsibilities as may be assigned to the JSC pursuant to this Agreement.

2.1.3. Collaboration Program Decision Making.

(a) If the JSC cannot unanimously agree on a matter to be decided by the JSC, then either Party shall have the right to refer such dispute to the Senior Representatives for resolution by good faith negotiations in accordance with Section 12.1.1. The Parties shall not implement the proposed activity or change pending such decision of the Senior Representatives; *provided that* if the dispute relates to a proposed change to a Collaboration Plan previously agreed by the JSC, Isis may continue the Isis Conducted Activities in accordance with such plan pending resolution of the dispute by the Senior Representatives.

(b) Notwithstanding any provision to the contrary herein, Isis will have no obligation to perform any activity that, after having consulted the JSC, Isis in good faith believes that continuing such activity would (y) [***] or (z) [***].

2.1.4. **Term of the JSC**. Isis' obligation to participate in relation to a Collaboration Plan in the JSC will terminate on the date Isis completes all the Isis Conducted Activities under such Collaboration Plan. Thereafter, Isis will have the right, but not the obligation, to participate in the JSC meetings in relation to such Collaboration Plan upon Isis' request. After [***], the JSC will cease to be responsible for making decisions with respect to such [***] (and for the avoidance of doubt, without limiting the foregoing, the provisions of Section 2.1.3(a) will cease to apply) and AstraZeneca will have full decision making authority with respect to such [***] subject to AstraZeneca's continuing obligation to use Commercially Reasonable Efforts under this Agreement. The JSC will become a forum for the Parties to share information regarding the Licensed Program, and the Parties will decide on the number and frequency of meetings required of the JSC in respect of such Licensed Program in its new role.

2.2. **Alliance Managers**. Promptly after the Effective Date each Party will appoint a representative to act as its alliance manager (each, an "***Alliance Manager***"). Each Alliance Manager will be permitted to attend any meetings of the JSC, and to participate in such meetings as a non-voting observer (unless the Party appointing the Alliance Manager also appoints such person to be a member of the JSC). The Alliance Managers will be responsible for supporting the JSC and performing the activities listed in SCHEDULE 2.2. Each Party may replace its Alliance Manager at any time upon written notice to the other Party in accordance with Section 12.7. During the Collaboration Program Term, the Alliance Managers will meet on a monthly basis (or more frequently as they may determine), in person or telephonically, to discuss the progress of the various activities under the Collaboration Plans.

2.3. **Disclosure of Results**.

2.3.1. **Results under the Collaboration Plans**. Each Party will promptly disclose to the other Party the results of all work performed by the Parties under the Collaboration Plans in a reasonable manner as such results are obtained. Isis and AstraZeneca will provide reports and analyses at each JSC meeting, and more frequently on reasonable request by any member of the JSC, detailing the current status of each Collaboration Plan.

2.3.2. **Reporting by AstraZeneca for Licensed Programs**. For each Licensed Program, AstraZeneca will prepare and maintain reasonably complete and accurate records regarding the Development of each Product and will provide to Isis a reasonably detailed summary report of such activities at least [***], or sooner if [***] (i.e., [***]), a material interaction with a Regulatory Authority occurs with respect to a Product, or [***]. AstraZeneca shall prepare such report in accordance with its internal procedures. AstraZeneca's obligation to provide such information shall cease in accordance with Section 5.2.

2.3.3. **Use of Information**. The results, reports, analyses and other information regarding the Collaboration Plans disclosed by one Party to the other Party pursuant hereto may be used only in accordance with the rights granted and other terms and conditions under this Agreement.

2.3.4. **Format of Reporting**. Any reports required under this Section 2.3 may take the form of and be recorded in minutes of the JSC, which will contain copies of any slides relating to the results as presented to the JSC.

2.4. **Materials Transfer**.

2.4.1. In order to facilitate the activities under the Collaboration Plans, either Party may provide to the other Party certain materials for use by the other Party in furtherance of the Collaboration Plans. All such materials will be used by the receiving Party in accordance with the terms and conditions of this Agreement solely for purposes of exercising its rights and performing its obligations under this Agreement, and the receiving Party will not transfer such materials to any Third Party unless expressly contemplated by this Agreement or upon the written consent of the supplying Party.

2.4.2. The Parties acknowledge and agree that they will exchange information regarding the materials used or generated in connection with the Research Collaboration and if requested by the other Party, each will use reasonable endeavors (subject to its own requirements and any obligations owed to Third Parties) to provide or assist the other to obtain, in the case of AstraZeneca, materials that are Isis Collaboration Intellectual Property, and in the case of Isis, materials that are AstraZeneca Collaboration Intellectual Property, in each case for use in accordance with Section 4.4.

2.4.3. Except as expressly set forth herein, THE MATERIALS ARE PROVIDED "AS IS" AND WITHOUT ANY REPRESENTATION OR WARRANTY, EXPRESS OR IMPLIED, INCLUDING ANY IMPLIED WARRANTY OF MERCHANTABILITY OR OF FITNESS FOR ANY PARTICULAR PURPOSE OR ANY WARRANTY THAT THE USE OF THE MATERIALS WILL NOT INFRINGE OR VIOLATE ANY PATENT OR OTHER PROPRIETARY RIGHTS OF ANY THIRD PARTY. [***]

2.5. **Collaboration Costs**.

2.5.1. **Core Research Program Costs and Disease Research Program Costs**. During the Core Research Term and the Disease Research Term, subject to Section 1.10, Isis will be responsible for all costs associated with the Isis Conducted Activities designated under the Core Research Plan and the Disease Research Plan, and AstraZeneca will be responsible for all costs associated with any AstraZeneca Conducted Activities designated under the Core Research Plan and the Disease Research Plan.

2.5.2. Collaboration Program Costs.

(a) **Drug Discovery Plan Costs Paid by Isis**. Until AstraZeneca exercises the Collaboration Program License Right for a particular Collaboration Program, unless otherwise specified in Section 1.14 and except as otherwise provided under Section 2.5.2(b), Isis will be responsible for all costs associated with the Isis Conducted Activities designated under each Drug Discovery Plan.

(b) **Drug Discovery Plan and Other Costs Paid by AstraZeneca**.

(i) **Before Exercising a Collaboration Program License Right**. Until AstraZeneca exercises the Collaboration Program License Right for a particular Collaboration Program, unless otherwise specified in Section 1.14, AstraZeneca will be responsible for all costs associated with the AstraZeneca Conducted Activities designated under each Drug Discovery Plan.

(ii) **After Exercising a Collaboration Program License Right**. After AstraZeneca exercises the Collaboration Program License Right for a particular Collaboration Program, AstraZeneca will be solely responsible for the costs related to the Research, Development, Manufacture and Commercialization of Products, including all AstraZeneca Conducted Activities.

2.6. **Collaboration Manufacturing and Supply**. [***], Isis will supply API sufficient to support the Isis Conducted Activities and the AstraZeneca Conducted Activities designated under a given Collaboration Plan. [***]

2.7. **JSC Collaboration Summary Work Plan Reports**. On a Calendar Quarter-by-Calendar Quarter basis, beginning with the [***], within [***] after the end of the most recent Calendar Quarter, the JSC (with the assistance of the Alliance Managers) will deliver a written report to AstraZeneca which identifies, for each Collaboration Target, the [***] (each a "***Work Plan Report***") as agreed by the JSC. Where planned activities under the Collaboration Plans for a Collaboration Target have not yet been agreed by the JSC, no data will be provided. The report template is included in SCHEDULE 2.7. The information in the report on [***] will provide the basis for [***]. Such reports will be prepared throughout the Collaboration Program Term until [***]. AstraZeneca will notify the JSC if Work Plan Reports are no longer required during the Collaboration Program Term.

2.8. **Applicable Laws and Bioethics**. The Research to be conducted by each Party (including by its subcontractors) pursuant to this Agreement will be carried out in good scientific manner, and in compliance with all Applicable Laws. In addition, each Collaboration Program will be carried out in compliance with the AstraZeneca bioethics policy attached at Schedule 2.8, to attempt to achieve efficiently and expeditiously the objectives of the applicable Collaboration Plan. In respect of any Isis Conducted Activities to be initiated under a Collaboration Program after the Effective Date, Isis and AstraZeneca will mutually agree on [***] and, prior to award of the work, will work together to secure compliance with AstraZeneca's bioethics policy. Where a [***], the Parties will discuss and agree whether such [***]. Insofar as the requirements of complying with such policy will result in additional [***] costs being charged to Isis for work [***] for Isis Conducted Activities, compared to [***], AstraZeneca agrees to be responsible for such additional costs [***]. The Parties will agree when such costs will be invoiced by Isis and AstraZeneca will pay such costs to Isis within 60 days after AstraZeneca's receipt of an invoice from Isis. The Parties' discussion and agreement under this Section 2.8 can be through the JSC.

ARTICLE 3.
EXCLUSIVITY COVENANTS

3.1. **Exclusivity Covenants**.

3.1.1. **Isis' and AstraZeneca's Exclusivity Covenants**. On an Exclusive Target-by-Exclusive Target basis, except in the performance of its obligations or exercise of its rights under, in the case of AstraZeneca, Section 4.1, and in the case of Isis, Section 10.3.2(a), or as set forth in Section 3.1.2 or Section 3.1.3, Isis and AstraZeneca will not work independently or for or with any of its Affiliates or any Third Party (including the grant of any license to any Third Party) with respect to:

(a) ***High Interest Targets***. The discovery, research or development of an ASO that is designed to bind to any of the High Interest Targets, from the date each such Target becomes a High Interest Target under Section 1.7.1 until [***];

(b) ***Collaboration Targets During the Collaboration Program License Right Period***. The discovery, research or development of an ASO that is designed to bind to any Collaboration Target, from the date each Collaboration Target is or deemed to have been designated by the JSC until [***] (x) [***], (y) [***], or (z) [***]; and

(c) ***Collaboration Targets After Exercising the Collaboration Program License Right***. The development or commercialization, in the Field, of an ASO that is designed to bind to a Collaboration Target for which AstraZeneca has exercised its Collaboration Program License Right in accordance with this Agreement, (A) with respect to development of an ASO that is designed to bind to such Collaboration Target, until [***] or [***], and (B) on a country–by-country basis with respect to commercialization of an ASO that is designed to bind to such Collaboration Target in the Field, until [***].

3.1.2. **Isis Follow-On Products**. Notwithstanding the provisions of Section 3.1.1, on an Exclusive Target-by-Exclusive Target basis, if (A) AstraZeneca does not ask Isis to identify a follow-on product for an Exclusive Target [***] for a Product, or (B) Isis identifies a follow-on product for an Exclusive Target at AstraZeneca's request, but thereafter AstraZeneca does not use Commercially Reasonable Efforts to continue to develop and commercialize such follow-on compound, then Isis (for itself or with or for a Third Party) will be permitted to (i) discover, research and develop an ASO designed to bind to such Exclusive Target that is not the Product being developed by AstraZeneca (an "***Isis Follow-On Product***"), and (ii) after [***] for a Product, commercialize such Isis Follow-On Product.

3.1.3. **Limitations and Exceptions to Each Party's Exclusivity Covenants**.

(a) **Limitations and Exceptions to Isis' Exclusivity Covenants**. Notwithstanding anything to the contrary in this Agreement, Isis' practice of the following will not violate Section 3.1.1 or Section 3.1.2:

(i) Performance of the Isis Conducted Activities;

(ii) With respect to any Collaboration Target, any activities permitted under the Prior Agreements as such agreements are in effect on the date the Target is put on the High Interest Target List and have been disclosed to AstraZeneca (and not as such Prior Agreements may be amended thereafter); and

(iii) The granting of, or performance of obligations under, Permitted Licenses.

(b) **Other Limitations and Exceptions to AstraZeneca's Exclusivity Covenants**. Notwithstanding anything to the contrary in this Agreement, AstraZeneca's performance of the AstraZeneca Conducted Activities will not violate Section 3.1.1 or Section 3.1.2.

3.2. **Additional Exclusivity Covenants**. The Parties acknowledge and agree that the exclusivity covenants set forth in Section 3.1 above are in addition to and do not limit AstraZeneca's covenants set forth in Section 1.10.3, Section 1.14.3 and Section 1.16.4.

3.3. **Corporate Transactions**. Notwithstanding anything to the contrary in this Agreement, Isis will not be in breach of Section 3.1.1 or Section 3.1.2 and AstraZeneca will not be in breach of Section 3.1.1 or the covenants set forth in Section 1.10.3, Section 1.14.3 or Section 1.16.4 as a result of activities relating to an ASO designed to bind to an Exclusive Target (each a "***Competitive ASO***") or a program relating to Competitive ASOs, in each case resulting from the direct or indirect acquisition by a Third Party of a Party or the direct or indirect acquisition by a Party or one of its Affiliates of a Third Party (including through an acquisition of substantially all of its business), in each case after the Execution Date; *so long as:*

3.3.1. in the case where a Party is acquired by a Third Party (the "***Acquiring Party***") with a Competitive ASO, the activities relating to the discovery, research, development or commercialization of the Competitive ASO by the Acquiring Party [***]; or

3.3.2. in the case where a Party or its Affiliate acquires a Third Party (the "***Acquisition Target***") with a Competitive ASO, [***] the acquiring Party or its Affiliate and the Acquisition Target either (i) [***], (ii) [***], (iii) in the case of AstraZeneca, [***], or (iv) [***].

If the Party so acquired or involved in the acquisition of a Competitive ASO is Isis, Section 5.2 will apply (pending, in the case of Section 3.3.2, such [***].

3.4. **Effect of Exclusivity on Indications**. The Compounds are designed to bind to the Exclusive Targets in the Field, which are known to play a role in one or more Primary Diseases. Isis and AstraZeneca are subject to exclusivity obligations under Section 3.1.1 and Section 3.1.2; *however*, the Parties acknowledge and agree that each Party (on its own or with a Third Party) may continue to discover, research, develop, manufacture and commercialize products that are designed to bind to a Target that is ***not*** an Exclusive Target, for any indication, even if such products are designed to treat a Primary Disease.

ARTICLE 4.
LICENSE GRANTS; TECHNOLOGY TRANSFER AND SUPPORT

4.1. **Product License Grants to AstraZeneca**.

4.1.1. **Collaboration Target Development and Commercialization Licenses**. On a Collaboration Target-by-Collaboration Target basis, subject to the terms and conditions of this Agreement:

(a) Isis hereby grants AstraZeneca a worldwide, exclusive (including with regard to Isis and its Affiliates), perpetual and irrevocable (except as otherwise expressly provided in this Agreement), royalty-bearing, sublicensable (in accordance with Section 4.1.2 below) license under the Licensed Technology to Research, Develop, Manufacture, have Manufactured (in accordance with Section 4.1.2 below) and Commercialize [***] Products in the Field; and

(b) in the case of a Collaboration Target that is not [***], grants to AstraZeneca effective upon AstraZeneca's exercise of the Collaboration Program License Right for such Collaboration Target in accordance with Section 1.16, a worldwide, exclusive (including with regard to Isis and its Affiliates), perpetual and irrevocable (except as otherwise expressly provided in this Agreement), royalty-bearing, sublicensable (in accordance with Section 4.1.2 below) license under the Licensed Technology to Research, Develop, Manufacture, have Manufactured (in accordance with Section 4.1.2 below) and Commercialize Products with respect to such Collaboration Target in the Field.

4.1.2. Sublicense Rights.

(a) **Right to Grant Sublicenses**. Subject to the terms and conditions of this Agreement, AstraZeneca will have the right to grant sublicenses through multiple tiers of sublicenses under the licenses granted under Section 4.1.1 above:

(i) under the Licensed Technology (other than Isis Manufacturing and Analytical Patents and Isis Manufacturing and Analytical Know-How), to an Affiliate of AstraZeneca or a Third Party; and

(ii) under the Isis Manufacturing and Analytical Patents and Isis Manufacturing and Analytical Know-How solely to (y) an Affiliate of AstraZeneca or (z) a Third Party with a valid license granted by Isis under the Isis Manufacturing and Analytical Patents and Isis Manufacturing and Analytical Know-How to manufacture Products in a manufacturing facility owned or operated by such Third Party (each, a "***Licensed CMO***");

provided that each such sublicense is for the continued Development, Manufacture and/or Commercialization of a Product, and is subject to, and consistent with, the terms and conditions of this Agreement. AstraZeneca will use reasonable efforts to ensure that all Persons to which it grants sublicenses comply with such terms and conditions to the extent applicable to such sublicense. For clarity, the restrictions in this Section 4.1.2 shall not apply to the appointment of Third Parties who undertake additional manufacturing activities, including testing, and fill/finish using API supplied by or on behalf of AstraZeneca; *provided that* such Third Party is undertaking such activities for AstraZeneca, its Affiliates or Sublicensees and no Licensed Know-How is transferred to such Third Party.

(b) **Enforcing Sublicense Agreements**. If either Party learns of a Sublicensee's breach of the terms of a sublicense granted by AstraZeneca, such Party will promptly notify the other Party in writing and will provide such other Party with any available evidence of such breach, and the Parties will discuss in good faith any applicable cure. AstraZeneca will have the first right to enforce the terms of the sublicense against such Sublicensee and demand the Sublicensee cure such breach. If, within [***] after the discussion with Isis regarding an applicable cure, AstraZeneca fails to take action as discussed by Isis and AstraZeneca to enforce the sublicense terms of a sublicense granted pursuant to this Section 4.1.2 and effect the applicable cure, which failure, in Isis' good faith determination as notified to AstraZeneca in writing, might reasonably be expected to cause a [***], AstraZeneca hereby grants Isis the right to enforce such sublicense terms on AstraZeneca's behalf and will cooperate with Isis (which cooperation will be at AstraZeneca's sole expense and will include, AstraZeneca joining any action before a court or administrative body filed by Isis against such Sublicensee if and to the extent necessary for Isis to have legal standing before such court or administrative body) in connection with enforcing such terms. AstraZeneca will provide Isis with written notice of any sublicense granted pursuant to this Section 4.1.2 that grants a Third Party rights to Commercialize or manufacture a Product, within [***] after the execution thereof, and if requested by Isis, a true and complete copy of any such sublicense or any sublicense that is the subject of a breach of terms sublicensed under this Agreement within 10 days of Isis' request, subject to AstraZeneca being entitled to make appropriate redaction for commercially sensitive information provided it is not relevant to enforcement or is not reasonably necessary for Isis to determine AstraZeneca's compliance with the terms of this Agreement.

(c) **Requests to Grant Sublicenses to CMOs**. In addition, if AstraZeneca provides Isis with a written request that Isis grant a license under the Isis Manufacturing and Analytical Patents and Isis Manufacturing and Analytical Know-How to a CMO designated by AstraZeneca that is not a Licensed CMO, solely for such CMO to manufacture Products for AstraZeneca, its Affiliate or Sublicensee in a manufacturing facility owned or operated by such CMO, Isis will offer to grant such a license to such CMO on terms that are substantially similar to the terms Isis has previously agreed to with its Licensed CMOs. On entering into such an agreement with Isis, such CMO shall become a Licensed CMO for the purpose of Section 4.1.2(a)(ii).

(d) **Effect of Termination on Sublicenses**. If this Agreement terminates for any reason, any Sublicensee will, from the effective date of such termination, automatically become a direct licensee of Isis with respect to the rights sublicensed to the Sublicensee by AstraZeneca; *so long as* (i) such Sublicensee is not in breach of its sublicense agreement, (ii) such Sublicensee agrees in writing to comply with all of the terms of this Agreement to the extent applicable to the rights originally sublicensed to it by AstraZeneca, and (iii) such Sublicensee agrees to pay directly to Isis such Sublicensee's payments under this Agreement to the extent applicable to the rights sublicensed to it by AstraZeneca. AstraZeneca agrees that it will confirm to its knowledge clause (i) of the foregoing in writing at the request and for the benefit of Isis and if requested, the Sublicensee.

(e) **Master Services Agreements and Material Transfer Agreements**. This Section 4.1.2 is not intended to require AstraZeneca to amend the standard terms and conditions of a master services agreement with a Third Party in place as of the Execution Date to conduct preclinical and/or clinical Research and Development on AstraZeneca's behalf, or material transfer agreements with academic collaborators or non-profit institutions, entered into after the Execution Date by AstraZeneca in connection with the Licensed Technology. However, new agreements entered into after the Execution Date will be subject to the approval of the JSC for so long as the JSC has decision making authority, such approval not to be unreasonably withheld or delayed; *provided that* no such approval will be required or given until after the Effective Date.

(f) **Fees Payable by CMOs**. Isis hereby agrees that Licensed CMOs or a CMO licensed pursuant to a request by AstraZeneca pursuant to Section 4.1.2(c) shall not be required to pay any license fees or royalties to Isis in connection with the manufacture of Products for AstraZeneca that are licensed to AstraZeneca under Section 4.1.1.

4.1.3. **Consequence of Natural Expiration of this Agreement**. On a Product-by-Product basis, if with respect to a particular Product for which AstraZeneca has exercised the applicable Collaboration Program License Right, this Agreement expires (i.e., is not terminated early) in a particular country in accordance with Section 10.1 then, in addition to the terms set forth in Section 10.3.1(c), Section 10.3.1(f), Section 10.3.1(g) and Section 10.3.1(h), the applicable license under Section 4.1.1 to the Licensed Know-How for such Product will automatically convert into a perpetual, non-exclusive, worldwide, royalty-free, fully paid-up, sublicensable license under the Licensed Know-How to Manufacture, Research, Develop and Commercialize the Product that is the subject of such expiration in such country.

4.1.4. **No Implied Licenses**. All rights in and to Licensed Technology not expressly licensed to AstraZeneca under this Agreement are hereby retained by Isis or its Affiliates. All rights in and to AstraZeneca Technology not expressly licensed or assigned to Isis under this Agreement, are hereby retained by AstraZeneca or its Affiliates. Except as expressly provided in this Agreement, no Party will be deemed by estoppel or implication to have granted the other Party any license or other right with respect to any intellectual property.

4.1.5. **License Conditions; Limitations**. Subject to Section 6.8 and Section 6.9, on a Collaboration Target-by-Collaboration Target basis, the licenses granted under Section 4.1.1 and the sublicense rights under Section 4.1.2 are subject to and limited by (i) the Prior Agreements as such agreements are in effect on the date such Collaboration Target was designated as a High Interest Target and placed on the High Interest Target List (or, with respect to [***], the Execution Date) and have been disclosed to AstraZeneca prior to such date (and not as such Prior Agreement may be amended thereafter), (ii) the Isis In-License Agreements as such agreements are in effect on the date identified as Isis In-License Agreements and added to Appendix 3 as provided in Section 6.8.5 (and in the form disclosed to AstraZeneca prior to such date and not as such Isis In-License Agreements may be amended thereafter unless such amendment is made with AstraZeneca's prior written consent); and (iii) the granting of, or performance of obligations under, Permitted Licenses.

4.1.6. **Trademarks for Products**. To the extent that (i) Isis owns any trademark(s) specific to a Product licensed under Section 4.1.1, and (ii) AstraZeneca reasonably believes such trademark(s) are necessary or useful for such Product, then upon AstraZeneca's request and at AstraZeneca's sole cost and expense, Isis will assign its rights and title to such trademark(s) to AstraZeneca sufficiently in advance of the First Commercial Sale of a Product. Other than any such trademarks, AstraZeneca is solely responsible for all trademarks, trade dress, logos, slogans, designs, copyrights and domain names used on or in connection with Products licensed under Section 4.1.1.

4.1.7. [***]

4.2. **Assignment of Isis Product-Specific Patents; Grant Back to Isis**.

4.2.1. On a Collaboration Target-by-Collaboration Target basis, with respect to any Collaboration Target for which AstraZeneca has an exclusive license under Section 4.1.1, at any time after completion of the first Phase 2 Study for the applicable Product, after discussion by the IP Managers, Isis will assign to AstraZeneca (and AstraZeneca will accept from Isis), Isis' ownership interest in all Isis Product-Specific Patents within the Licensed Patents that are owned by Isis (whether solely owned or jointly owned with one or more Third Parties); *provided that*, if either Party reasonably determines that such assignment would be likely to adversely affect the applicable Licensed Patent (including diminishing the scope, term, validity or enforceability of such Licensed Patent), then, [***].

4.2.2. AstraZeneca grants to Isis a worldwide, exclusive, sublicensable license under any Patent Rights assigned to AstraZeneca under Section 4.2.1 (i) for all purposes outside of the Field (except to license or Commercialize a compound claimed by the Product-Specific Patents that specifically claim the Product being Developed and Commercialized by AstraZeneca), and (ii) to research, develop, manufacture, have manufactured, register, market and commercialize Isis Follow-On Products in accordance with Section 3.1.2, in each case to the extent permitted by this Agreement.

4.3. **Non-Exclusive Technology License Grant to AstraZeneca**. As of the Effective Date, subject to the terms and conditions of this Agreement, Isis hereby grants to AstraZeneca a worldwide, non-exclusive, non-sublicenseable, non-transferrable, royalty-free, fully-paid up, license under the Isis Collaboration Intellectual Property and Isis Background Intellectual Property, for the sole purpose of AstraZeneca (i) performing the AstraZeneca Conducted Activities and effectively participating in the JSC under this Agreement, (ii) to understand and retain some capabilities with regard to Isis' technology in furtherance of AstraZeneca's continuation of the Development of Products under this Agreement after expiration of Isis' input (e.g., post-AstraZeneca exercise of each Collaboration Program License Right) (but expressly excluding the right to Manufacture or Commercialize such Products), (iii) conducting research activities outside the scope of this Agreement that are not human clinical studies or designed to support an IND and do not involve any Compounds being developed or commercialized by Isis, its Affiliates or sublicensees on its or their own behalf, and (iv) solely with respect to Product-Specific Patents within the Isis Technology and Isis Background Technology, conducting research and development activities in the AstraZeneca Field. Except as expressly provided in clauses (i) and (ii) of this Section 4.3, the foregoing license granted to AstraZeneca in this Section 4.3 does not include the right to Develop, Manufacture or Commercialize a Compound.

4.4. **Cross-Licenses Under Collaboration Intellectual Property**.

4.4.1. **Enabling Technology Licenses from AstraZeneca to Isis**. Subject to the terms and conditions of this Agreement (including Isis' exclusivity obligations under Section 3.1), AstraZeneca hereby grants Isis a fully-paid, royalty-free (except as otherwise provided under Section 10.3.2(g) and Section 10.3.2(h)), irrevocable, worldwide, non-exclusive, sublicenseable license under any AstraZeneca Collaboration Intellectual Property (including AstraZeneca's interest in any Jointly-Owned Collaboration Technology) to research, develop, manufacture, have manufactured and commercialize products (other than any ASO designed to bind to an Exclusive Target) in the Isis Field.

4.4.2. **Enabling Technology Licenses from Isis to AstraZeneca**. Subject to the terms and conditions of this Agreement, Isis hereby grants AstraZeneca a fully-paid, royalty-free, irrevocable, worldwide, non-exclusive, sublicenseable license under any Isis Collaboration Intellectual Property (including Isis' interest in any Jointly-Owned Collaboration Technology) to research, develop, manufacture, have manufactured and commercialize products in the AstraZeneca Field.

4.5. **Interaction of Licenses.** For the avoidance of doubt, the licenses granted in Section 4.3 and Section 4.4 are not intended to undermine the exclusivity covenants or the exclusive nature of any exclusive licenses granted to a Party under this Agreement, or any of the royalty-bearing licenses granted by one Party to the other Party under Section 4.1.1 or Section 10.3.2(a). As such, a Party cannot attempt to exercise a right granted under Section 4.3 or Section 4.4 to avoid complying with an applicable exclusivity covenant, or paying a milestone payment, royalty or other payment that would be due under this Agreement as a result of exercising rights under the licenses granted under Section 4.1.1 or Section 10.3.2(a).

4.6. **Subcontracting**. Subject to the terms of this Section 4.6, each Party will have the right to engage Third-Party subcontractors to perform certain of its obligations under this Agreement. Any subcontractor to be engaged by a Party to perform a Party's obligations set forth in this Agreement will meet the qualifications typically required by such Party for the performance of work similar in scope and complexity to the subcontracted activity and will enter into such Party's standard nondisclosure agreement consistent with such Party's standard practices. Any Party engaging a subcontractor hereunder will remain responsible and obligated for such activities and will not grant rights to such subcontractor that interfere with the rights of the other Party under this Agreement.

4.7. **[***] Initial Technology Transfer.** To the extent not previously provided, within [***] of the Effective Date, Isis will deliver or otherwise make available (through site visits or access to shared electronic portals) to AstraZeneca the Licensed Know-How relating to the [***] Program as conducted by Isis prior to the Effective Date, for use solely in accordance with the licenses granted under Section 4.1.1(a) and Section 4.3.

4.8. **Technology Transfer**. On a Collaboration Target-by-Collaboration Target basis, after the Collaboration Program Exercise Date, Isis will deliver to AstraZeneca the following Licensed Know-How pursuant to a technology transfer plan to be mutually agreed by Isis and AstraZeneca:

4.8.1. **Licensed Know-How - Generally**. Copies of Licensed Know-How (other than the Isis Manufacturing and Analytical Know-How) in the Field in Isis' possession that has not previously been provided hereunder, for use solely in accordance with the licenses granted under Section 4.1.1 and Section 4.3, to AstraZeneca together with all regulatory documentation (including drafts, if any) related to each Product. To assist with the transfer of such Licensed Know-How, Isis will make its personnel reasonably available to AstraZeneca during normal business hours for up to a total (i.e., not on a Collaboration Target-by-Collaboration Target basis) of [***] ([***]) of Isis' time under this Agreement to transfer such Licensed Know-How under this Section 4.8.1. Thereafter, if requested by AstraZeneca, Isis will provide AstraZeneca with a reasonable level of assistance in connection with such transfer, which AstraZeneca will reimburse Isis for its time incurred in providing such assistance at the FTE Rate, and any of Isis' reasonable travel expenses for travel requested by AstraZeneca, and any outside consultants' costs and consultants' reasonable travel expenses incurred by Isis agreed in advance by AstraZeneca.

4.8.2. **Isis Manufacturing and Analytical Know-How**. Solely for use by AstraZeneca, its Affiliates or a Third Party acting on AstraZeneca's behalf to Manufacture API for AstraZeneca, its Affiliates or Sublicensees, in AstraZeneca's own, or an Affiliate's, or up to two mutually agreed Licensed CMO's manufacturing facility, copies of the Isis Manufacturing and Analytical Know-How relating to Products in Isis' possession that has not previously been provided hereunder, which is necessary for the exercise by AstraZeneca, its Affiliates or a Third Party of the Manufacturing rights granted under Section 4.1.1. Isis will make its personnel reasonably available to AstraZeneca during normal business hours and AstraZeneca will reimburse Isis for its time incurred in performing such technology transfer at the FTE Rate, and any of Isis' reasonable travel expenses for travel requested by AstraZeneca, and any of its outside consultants' costs and consultants' reasonable travel expenses incurred by Isis agreed in advance by AstraZeneca.

ARTICLE 5.
DEVELOPMENT, MANUFACTURING AND COMMERCIALIZATION

5.1. **AstraZeneca Diligence**. On a Collaboration Target-by-Collaboration Target basis, commencing on the Collaboration Program Exercise Date, except as expressly provided otherwise in this Agreement, AstraZeneca is solely responsible for the Development, Manufacture and Commercialization of Products with respect to such Collaboration Target, and will be solely responsible for all costs associated therewith. With respect to each Licensed Program, AstraZeneca will use Commercially Reasonable Efforts (i) to Develop a Product and to seek Approval for such Product for use in humans [***], (ii) following Approval, to Commercialize such Product for use in humans [***], (iii) to Develop and Commercialize a Product for use in humans worldwide (outside of [***]) to the extent consistent with the global commercialization strategy and efforts AstraZeneca would use for AstraZeneca's similar products in the same franchise, and (iv) to Develop and Commercialize each Product substantially in accordance with the applicable IPP.

5.1.1. **Specific Performance Milestone Events**. On a Licensed Program-by-Licensed Program basis, within [***] after the Collaboration Program Exercise Date, AstraZeneca will identify and provide to Isis specific performance milestone events ("***Specific Performance Milestone Events***") for the first Product from such Licensed Program and the [***] based on the information then available to AstraZeneca and its then-current practices, and in all cases consistent with AstraZeneca's then current internal specific performance milestone event metrics for the applicable AstraZeneca franchise. AstraZeneca shall consider in good faith and will not unreasonably refuse to incorporate any proposals and comments made by Isis in connection with such Specific Performance Milestone Events and [***] and once the Specific Performance Milestone Events and [***] are set by AstraZeneca for a given Product, such Specific Performance Milestone Events and [***] will be attached hereto and made a part hereof as SCHEDULE 5.1.1. AstraZeneca will use Commercially Reasonable Efforts to achieve the Specific Performance Milestone events. If regulatory or Development issues arise that impede commencement of activities as anticipated, AstraZeneca will notify Isis and if requested by Isis meet to discuss such delays.

5.1.2. **Integrated Product Plans**. For each Licensed Program, AstraZeneca will prepare a global integrated Product plan or a comparable document consistent with AstraZeneca's then current internal practices for AstraZeneca's internal programs outlining key aspects of the Development of the Product being Developed from such Program as well as, as Development proceeds, and such information is available, key aspects of worldwide regulatory strategy, pricing and market access strategy, market launch, and Commercialization (each plan or other such document, an "***Integrated Product Plan***" or "***IPP***"). AstraZeneca will prepare each IPP no later than [***] for the relevant Product, and the IPP will contain high level information consistent with AstraZeneca's development and commercialization plans for its similar products at similar stages of development and commercialization in the same AstraZeneca franchise. Once AstraZeneca has prepared an IPP, AstraZeneca will update it consistent with AstraZeneca's standard practice (including if the IPP is updated and presented to an AstraZeneca internal committee) but at least Annually and will provide such updates to Isis. AstraZeneca and Isis will meet (through the JSC or as the Parties may otherwise agree) on an Annual basis to discuss the draft of the IPP and AstraZeneca will consider, in good faith, any proposals and comments made by Isis for incorporation in the IPP.

5.1.3. **Investigator's Brochure**. Subject to Section 5.2, AstraZeneca will keep Isis reasonably informed with respect to the status, activities and progress of Development of Products licensed by AstraZeneca hereunder and will provide updated versions of the Investigator's Brochure when requested by Isis (but no more frequently than Annually) or when Development of the Products results in any substantive change to the safety or risk to the Products.

5.2. **Isis Competitive Product**. Notwithstanding Section 2.1, Section 2.3.2, Section 5.1.2, Section 5.1.3, and Section 5.3, on a Product-by-Product basis, if Isis independently or with an Affiliate or Third Party (i) commences a [***] for any product (and has not ceased all development of such product) for the same Indication as AstraZeneca is Developing or Commercializing a Product, or (ii) commercializes any product for the same Indication as AstraZeneca is Developing or Commercializing a Product, then AstraZeneca may at its discretion, following written notice to Isis, cease to provide, or reduce the information, communications, reports or plans provided to Isis pursuant to this Agreement for the affected Product; and unless otherwise agreed by AstraZeneca, Isis will [***], for such affected Product; *provided, however*, that AstraZeneca will continue to (v) provide Isis the information described under Section 5.4 for the Isis Internal ASO Safety Database, (w) provide Isis the royalty reports to be delivered in accordance with Section 6.9, (x) provide Isis with advance notice under Section 11.5 of any material announcements regarding such Product, (y) deliver to Isis on an Annual basis a high-level summary of the IPP for such Product, and (z) meet with Isis through the JSC (or, if the JSC does not exist, with Isis) in accordance with Section 2.1 for Collaboration Programs that do not involve such Product.

5.3. Regulatory Interactions.

5.3.1. Participation in Regulatory Meetings. Each Party will provide the other Party with as much advance written notice as practicable of any meetings such Party has or plans to have with a Regulatory Authority regarding pre-approval or Approval matters for a Product (or, in the case of Isis as the invitee, that relate to Isis' antisense oligonucleotide platform), and, subject to Section 5.2, will allow one representative of the invited Party to participate (as an observer) in any such meeting that is [***] (e.g., meetings regarding [***]). The costs associated with such observer attendance will be met by the invitee Party, except if Isis' presence has been specifically requested by AstraZeneca, in which case AstraZeneca will reimburse Isis for its time incurred in attending at the FTE Rate. To the extent that AstraZeneca has not fully used the [***] available to it pursuant to Section 4.8.1 or Section 5.3.3, then AstraZeneca will be entitled to allocate such [***] to the activities to be performed by Isis pursuant to this Section 5.3.1.

5.3.2. Regulatory Communications. Subject to Section 5.2, each Party will provide the other Party with copies of documents and communications submitted to (including such drafts as the providing Party considers reasonably practicable but to include at least one pre-finalization draft thereof) and received from Regulatory Authorities that materially impact the Development or Commercialization of Products for the other Party's review and comment, and the submitting Party will consider in good faith including any comments provided by the reviewing Party to such documents and communications.

5.3.3. Assistance with Regulatory Filings. On a Collaboration Target-by-Collaboration Target basis, after the Collaboration Program Exercise Date, upon AstraZeneca's written request [***], Isis will prepare the reports pertaining to Isis Conducted Activities as required for inclusion in INDs for the Product. AstraZeneca and Isis will co-ordinate to ensure that the content of such reports is suitable for submission to the applicable Regulatory Authorities using AstraZeneca's then-current template for products in the same franchise; *so long as* Isis is able to use such template without incurring more than [***]. If use of such template would require Isis to incur such costs (e.g. in connection with the purchase of software), the Parties shall discuss and agree on the appropriate format for such reports. In addition, Isis will assist AstraZeneca in preparing regulatory filings for the Products (including INDs and other regulatory filings) and, except with respect to regulatory filing-related activities outlined in Section 5.3.1 and Section 5.3.2, such additional regulatory filings assistance will be [***]. Thereafter, upon AstraZeneca's written request, Isis will provide such additional assistance in preparing such regulatory filings for the Products at the FTE Rate, and any of Isis' reasonable travel expenses for travel requested by AstraZeneca, and any of its outside consultants' costs and consultants' reasonable travel expenses incurred by Isis agreed in advance by AstraZeneca. An estimate of such costs and expenses will be provided to AstraZeneca before initiation of agreed work.

5.3.4. **Class Generic Claims**. To the extent AstraZeneca intends to make any claims in a Product label or regulatory filing that are class generic to ASOs or any of Isis' technology incorporated into a Product, AstraZeneca will provide such claims and regulatory filings to Isis in advance and will consider in good faith any proposals and comments made by Isis.

5.3.5. **Applicable Laws**. Each of Isis and AstraZeneca will perform its activities pursuant to this Agreement in compliance with good laboratory and clinical practices and cGMP, in each case as applicable under the laws and regulations of the country and the state and local government wherein such activities are conducted.

5.4. **Isis' Antisense Safety Database**.

5.4.1. Isis maintains an internal database that includes information regarding the tolerability of its drug compounds, individually and as a class, including information discovered during pre-clinical and clinical development (the "***Isis Internal ASO Safety Database***"), *provided that* AstraZeneca's obligations pursuant to this Section 5.4.1 are subject to Applicable Laws and in particular AstraZeneca will not be required to disclose any information in contravention of Applicable Laws relating to data privacy. In an effort to maximize understanding of the safety profile and pharmacokinetics of Isis compounds, AstraZeneca will cooperate in connection with populating the Isis Internal ASO Safety Database. To the extent collected by AstraZeneca and, in the form in which AstraZeneca uses/stores such information for its own purposes, AstraZeneca will provide Isis with material information concerning toxicology, pharmacokinetics, safety pharmacology study(ies), serious adverse events and other safety information related to Products licensed by AstraZeneca under this Agreement as soon as practicable following the date such information is available to AstraZeneca (but not later than [***] after AstraZeneca's receipt of such information). In connection with any reported serious adverse event, AstraZeneca will provide Isis all serious adverse event reports, including initial, interim, follow-up, amended, and final reports. In addition, with respect to Products, AstraZeneca will provide Isis with copies of Annual safety updates filed with each IND and the safety sections of any final Clinical Study reports. Furthermore, AstraZeneca will promptly provide Isis with any supporting data and answer any follow-up questions reasonably requested by Isis to conduct analyses to keep Isis and its partners informed regarding class generic properties of ASOs, including with respect to safety. All such information disclosed by AstraZeneca to Isis will be AstraZeneca Confidential Information; *provided*, *however*, that so long as Isis does not disclose the identity of a Product (or the relevant Target) or AstraZeneca's identity, Isis may disclose any such AstraZeneca Confidential Information to Regulatory Authorities and Isis' other partners pursuant to Section 5.4.2 below if such information is regarding class generic properties of ASOs and, with respect to Isis' partners, such partners have agreed to a similar provision permitting the disclosure of their Confidential Information relating to ASOs to Isis' partners. AstraZeneca will deliver all such information to Isis for the Isis Internal ASO Safety Database to Isis Pharmaceuticals, Inc., 2855 Gazelle Court, Carlsbad, California 92010, Attention: Chief Medical Officer (or to such other address/contact designated in writing by Isis). AstraZeneca will also cause its Affiliates and Sublicensees to comply with this Section 5.4.1.

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

5.5. Manufacturing and Supply.

5.5.1. Initial Supply to AstraZeneca.

(a) With respect to the [***] Licensed Programs, in support of AstraZeneca's further Development of Products to such Collaboration Targets, upon AstraZeneca's written request at least [***] in advance of the requested delivery date, Isis will manufacture and supply up to [***] of API for a Product from each such Licensed Program. If requested by AstraZeneca, Isis will use reasonable endeavors to manufacture and supply API on less than [***] notice to the extent Isis has available capacity.

(b) AstraZeneca will pay Isis for such API at [***], within [***] after AstraZeneca's receipt of the applicable invoice. Subject to Section 5.5.1(c), any request from AstraZeneca for Isis to manufacture API under this Section 5.5.1 will be submitted to Isis within [***] after AstraZeneca's exercise of its Collaboration Program License Right for the applicable Product under this Agreement.

(c) AstraZeneca may place orders for API pursuant to Section 5.5.1(a) prior to exercise of its Collaboration Program License Right for a given Collaboration Target but Isis will not be required to deliver the API until after such exercise. In such circumstances, Isis may invoice AstraZeneca for [***] for such API when such order is placed and the balance [***] on delivery; *provided that* (a) if AstraZeneca does not exercise its Collaboration Program License Right for such Collaboration Target, AstraZeneca shall not be required to [***]; and (b) if Isis continues development of the relevant Product, Isis shall [***].

(d) After AstraZeneca's exercise of its Collaboration Program License Right for the applicable Product under this Agreement, in addition to the supply set forth in this Section 5.5, Isis will sell to AstraZeneca, if AstraZeneca desires, any other inventory of cGMP API and finished drug Product in Isis' possession at [***].

5.5.2. **Manufacturing Services Agreement**. Each of the Parties agrees and acknowledges that a mutually agreed manufacturing services agreement ("***MSA***") is required to be put in place to govern the supply arrangements by Isis under Section 5.5.1, which will be negotiated in good faith between the Parties following the Effective Date and will be in a form substantially similar to that certain Manufacturing and Services Agreement between Isis and AstraZeneca dated March 7, 2013. The Parties' objective is that the MSA will be entered into within [***] after the Effective Date.

5.5.3. AstraZeneca is responsible for supplying finished drug Product for AstraZeneca's Research, Development and Commercialization of Products under this Agreement, and API for the sixth and each subsequent Licensed Program.

ARTICLE 6.
FINANCIAL PROVISIONS

6.1. **Up-Front Fee**. Within 15 days following the Effective Date, AstraZeneca will pay Isis an up-front fee of US$65,000,000 allocated as follows:

6.1.1. $[***] in consideration for the exclusive license granted under Section 4.1.1 to AstraZeneca for [***] Products; and

6.1.2. $[***] in consideration for (i) [***], (ii) [***], and (iii) [***].

6.2. **Product License Fees**. On a Collaboration Program License Right-by-Collaboration Program License Right basis (for Collaboration Programs that are not the [***] Program), following AstraZeneca's written notice to Isis stating that AstraZeneca is exercising such Collaboration Program License Right in accordance with this Agreement, AstraZeneca will pay Isis a license fee of:

6.2.1. For each of the [***] such Collaboration Programs, $[***] within [***] after AstraZeneca's receipt from Isis of an invoice for such license fee; and

6.2.2. For the [***] and each subsequent Collaboration Program, $[***] within [***] after AstraZeneca's receipt from Isis of an invoice for such license fee.

6.3. **[***] Candidate Drug Designation Milestone.** Following AstraZeneca's written notice to Isis stating that AstraZeneca is exercising its Collaboration Program License Right with respect to [***] in accordance with this Agreement, AstraZeneca will pay Isis a milestone payment of $[***] (the "**[***]** ***CD Milestone***") within [***] after AstraZeneca's receipt from Isis of an invoice for such milestone payment.

6.4. **Milestone Payments for Achievement of Milestone Events by a Product**. On a Licensed Program-by-Licensed Program basis, in accordance with Section 6.5.5, AstraZeneca will pay to Isis the milestone payments as set forth in TABLE 1 below when a milestone event listed in TABLE 1 is first achieved by AstraZeneca, its Affiliates or Sublicensees with respect to a Product under such Licensed Program:

TABLE 1	
Product Milestone Event	**Product Milestone Event Payment**
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]

6.5. **Limitations on Milestone Payments; Exceptions; Notice**.

6.5.1. Each milestone payment set forth in TABLE 1 above will be paid only once per Licensed Program upon the first achievement of the milestone event regardless of how many Products for such Licensed Program achieve such milestone event.

6.5.2. If the [***] is a [***], the milestone otherwise payable on "[***]" will not be payable unless and until [***].

6.5.3. If a particular milestone event is not achieved because Development or Commercial activities transpired such that achievement of such earlier milestone event was unnecessary or did not otherwise occur, then upon achievement of a later milestone event the milestone event payment applicable to such earlier milestone event will also be due. For example, if a Party proceeds directly to "[***]" without achieving the "[***]," then upon achieving the "[***]" milestone event, each of the "[***]," "[***]" and "[***]" milestone event payments are due. As an additional example, if, after achieving the "[***]" milestone event [***], then both the "[***]" and "[***]" milestone event payments are due. Similarly, if a Party proceeds directly to "[***]" without achieving the "[***]," then upon achieving the "[***]" milestone event, both the "[***]" and "[***]" milestone event payments are due.

6.5.4. In addition, if a particular milestone event is achieved contemporaneously or in connection with another milestone event, then upon achievement of one such milestone event the other milestone event will also be deemed achieved and the milestone payments for both milestone events are due. For example, if AstraZeneca achieves the "[***]" milestone event and the [***] ([***]) that was the subject of such milestone event [***], then both the "[***]" and the "[***]" milestone event payments are due. Similarly, if AstraZeneca achieves the "[***]" milestone event and the [***] ([***]) that was the subject of such milestone event [***], then both the "[***]" and the "[***]" milestone event payments are due.

6.5.5. Each time a milestone event is achieved under this ARTICLE 6, AstraZeneca will send Isis a written notice thereof promptly (but no later than ten Business Days) following the date of achievement of such milestone event. Thereafter, Isis will promptly invoice AstraZeneca for the achievement of any milestone event under this ARTICLE 6 and such milestone payment will be due within [***] after AstraZeneca's receipt of such invoice.

6.6. [***].

6.6.1. [***]

6.6.2. [***]

6.6.3. ***Examples of*** [***] ***under Section 6.6.2***

6.6.4. [***]

6.7. Royalty Payments to Isis.

6.7.1. AstraZeneca Full Royalty. On a Licensed Program-by-Licensed Program basis, as partial consideration for the rights granted to AstraZeneca hereunder, subject to the provisions of this Section 6.7.1 and Section 6.7.2, AstraZeneca will pay to Isis royalties on Annual worldwide Net Sales of Products sold by AstraZeneca, its Affiliates or Sublicensees, on a country-by-country and Product-by-Product basis, in each case in the amounts as follows in TABLE 2 below (the "***AstraZeneca Full Royalty***"):

TABLE 2

Royalty Tier	Annual Worldwide Net Sales of Products from a Licensed Program	Royalty Rate
1	For the portion of Annual Worldwide Net Sales < $[***]	[***]%
2	For the portion of Annual Worldwide Net Sales ≥ $[***] but < $[***]	[***]%
3	For the portion of Annual Worldwide Net Sales ≥ $[***]	[***]%

Subject to Section 6.7.2(d), annual worldwide Net Sales will be calculated by taking the aggregate sum of Net Sales of Products (under the applicable Licensed Program) for all countries worldwide.

(a) During the Royalty Period, AstraZeneca will pay Isis royalties on Net Sales of Products arising from named patient and other similar programs under Applicable Laws, and AstraZeneca will provide reports and payments to Isis consistent with Section 6.9. No royalties are due on Net Sales of Products arising from compassionate use and other programs providing for the delivery of Product at no cost. The sales of Products arising from named patient, compassionate use, or other similar programs will not be considered a First Commercial Sale for purposes of calculating the Royalty Period or determining whether an Approval milestone event listed in TABLE 1 of Section 6.4 has been achieved.

(b) For purposes of clarification, any Isis Product-Specific Patents assigned to AstraZeneca as set forth in Section 4.2.1 will still be considered Isis Product-Specific Patents for determining the royalty term and applicable royalty rates under this ARTICLE 6.

6.7.2. **Application of Royalty Rates**. All royalties set forth under Section 6.7.1 are subject to the provisions of this Section 6.7.2, and are payable as follows:

(a) **Royalty Period**. AstraZeneca's obligation to pay Isis the AstraZeneca Full Royalty above with respect to a Product will continue on a country-by-country and Product-by-Product basis from the date of First Commercial Sale of such Product until the later of the date of expiration of (i) the last Valid Claim within the Licensed Patents Covering such Product in the country in which such Product is made, used or sold, (ii) the data exclusivity period conferred by the applicable Regulatory Authority in such country with respect to such Product (e.g., such as in the case of an orphan drug), and (iii) the [***] ([***]) anniversary of the First Commercial Sale of the first Product to contain the relevant Compound in such country (such royalty period, the "***Royalty Period***"); *provided*, if, following such [***] ([***]) anniversary of such First Commercial Sale, the only remaining Valid Claim of a Licensed Patent Covering such Product in a country where such Product is made or sold is an Isis Manufacturing and Analytical Patent, then AstraZeneca will pay Isis a reduced royalty for such Product in such country at royalty rates equal to [***] until such Isis Manufacturing and Analytical Patent expires.

(b) **Allocation of Reduction**. The Parties acknowledge that the applicable royalty rate in TABLE 2 is dependent on Annual worldwide Net Sales of Products and any royalty rate reduction in the proviso of Section 6.7.2(a) applies on a country-by-country and Product-by-Product basis. The Parties will apply appropriate mechanisms to apportion any such reduction proportionally across the royalty tiers in TABLE 2.

(c) **Limitation on Aggregate Reduction for AstraZeneca Royalties**.

(i) If the offset under Section 6.7.2(a) does not apply, in no event will the aggregate royalty offsets under Section 6.8.3(b) and Section 6.8.4(b) reduce the royalties payable to Isis on Net Sales of a Product in any given period to an amount that is less than the greater of (A) [***], and (B) [***].

(ii) If the offset under Section 6.7.2(a) applies, in no event will the aggregate royalty offsets under Section 6.7.2(a), Section 6.8.3(b) and Section 6.8.4(b) reduce the royalties payable to Isis on Net Sales of a Product in any given period to an amount that is less than [***].

(d) **End of Royalty Obligation**. On a country-by-country and Product-by-Product basis, other than [***], AstraZeneca's obligation to make royalty payments hereunder in such country will end on the expiration of the Royalty Period in such country. Any sales of a Product made after the expiration of the Royalty Period for such Product in a country shall not be included in the Annual worldwide Net Sales for the purposes of calculating royalties under Section 6.7.1.

(e) **Compulsory Licenses**. If a court or a governmental agency of competent jurisdiction requires AstraZeneca or any of its Affiliates or Sublicensees to grant a compulsory license to a Third Party (each, a "***Compulsory Sublicensee***") permitting such Third Party to make and sell a Product in a country, (i) such Compulsory Sublicensee will not be considered a Sublicensee for the purpose of this Agreement, and (ii) such grant will be permitted and deemed consented to by Isis under Section 4.1.2. At such time as AstraZeneca or any of its Affiliates or Sublicensees enters into a sublicense with a Compulsory Sublicensee, [***]; *provided that* [***].

6.8. **Third Party Payment Obligations that are Not Relevant to New Third Party Compound Technology**. Any Third Party Obligations that become payable by Isis or AstraZeneca under an agreement such Party has entered into to license or otherwise acquire Third Party Patent Rights or other intellectual property rights, in each case that are not New Third Party Compound Technology will be paid by a Party or shared by the Parties as expressly set forth in this Section 6.8:

6.8.1. **Existing Technology In-License Agreements**.

(a) ***Isis' Existing Technology In-License Agreements***. Certain of the Licensed Technology that may be licensed to AstraZeneca under Section 4.1.1 is in-licensed or was acquired by Isis under the agreements with Third Party licensors or sellers listed in APPENDIX 3, and certain milestone or royalty payments and license maintenance fees may become payable by Isis to such Third Parties under the Isis In-License Agreements based on the Development or Commercialization of a Product by AstraZeneca, its Affiliate or Sublicensee under this Agreement. Any such payment obligations arising under the Isis In-License Agreements listed on APPENDIX 3 to the extent not applicable to New Third Party Compound Technology:

(i) as they apply to (x) any Patent Right or Know-How claiming [***], or (y) [***], in each case licensed by Isis to AstraZeneca in connection with the applicable Product, will be paid by [***] as [***], and

(ii) as they apply to [***] and [***], in each case licensed by Isis to AstraZeneca in connection with the applicable Product, will be paid by [***] as [***].

(b) ***AstraZeneca's Existing In-License Agreements***. AstraZeneca will be solely responsible for any Third Party Obligations that become payable by AstraZeneca to Third Parties under any agreements or arrangements AstraZeneca has with such Third Parties as of the Effective Date, based on the Development or Commercialization of a Product by AstraZeneca, its Affiliate or Sublicensee under this Agreement. Any such payment obligations will be paid by AstraZeneca as AstraZeneca Supported Pass-Through Costs under this Agreement.

6.8.2. New In-Licensed Additional Product-Specific Patents.

(a) **Prior to Exercise of a Collaboration Program License Right**. On a Collaboration Target-by-Collaboration Target basis, if, prior to AstraZeneca's exercise of its Collaboration Program License Right, Isis obtains Third Party Patent Rights necessary to Develop or Commercialize a Product where such Patent Right would have satisfied the definition of an Isis Product-Specific Patent had Isis Controlled such Patent Rights on the Effective Date, then to the extent Controlled by Isis, Isis will include such Third Party Patent Rights in the license to be granted to AstraZeneca under Section 4.1.1 if [***]. Isis will consult with AstraZeneca before entering into such Third Party agreement and will take into consideration any reasonable comments made by AstraZeneca. On such agreement by AstraZeneca, such in-license agreement shall be an Isis In-License Agreement and Appendix 3 shall be updated accordingly.

(b) **After Exercise of Collaboration Program License Right**.

(1) On a Collaboration Target-by-Collaboration Target basis, after AstraZeneca exercises its Collaboration Program License Right, AstraZeneca or Isis, as the case may be, will promptly provide the other Party written notice of any additional Third Party Patent Rights necessary to practice an Isis Product-Specific Patent to Develop or Commercialize a Product ("***Additional Product-Specific Patents***") it believes it has identified and AstraZeneca will have the first right, but not the obligation, to negotiate with, and obtain a license from the Third Party Controlling such Additional Product-Specific Patents. If AstraZeneca obtains any such Additional Product-Specific Patents then any and all Third Party Obligations arising under such Third Party agreement will be paid by [***] as [***].

(2) If, however, AstraZeneca elects not to obtain such a license to such Additional Product-Specific Patents, AstraZeneca will so notify Isis, and Isis may obtain such a license to such Additional Product-Specific Patents and will include such Additional Product-Specific Patents in the license granted to AstraZeneca under Section 4.1.1 [***]. On such agreement by AstraZeneca, such in-license agreement shall be an Isis In-License Agreement and APPENDIX 3 shall be updated accordingly.

6.8.3. Additional Core IP In-License Agreements.

(a) AstraZeneca will promptly provide Isis written notice of any intellectual property controlled by a Third Party that is necessary to [***] that *is not* New Third Party Compound Technology ("***Additional Core IP***") that AstraZeneca believes it has identified, and Isis will have the first right, but not the obligation, to negotiate with, and obtain a license from the Third Party controlling such Additional Core IP. For clarity, Additional Core IP does not include any Patent Rights claiming (or intellectual property related to) [***] or New Third Party Compound Technology. If Isis obtains such a Third Party license, Isis will include such Additional Core IP in the license granted to AstraZeneca under Section 4.1.1, and [***] will pay any financial obligations under such Third Party agreement as [***]. Provided that AstraZeneca has agreed the terms of such agreement, such agreement shall be an Isis In-License Agreement and APPENDIX 3 shall be updated accordingly.

(b) If, however, Isis elects not to obtain such a license to such Additional Core IP, Isis will so notify AstraZeneca, and AstraZeneca may obtain such a Third Party license and AstraZeneca may offset an amount equal to [***] against [***].

6.8.4. Disputes Regarding Additional Core IP.

(a) If Isis does not agree that certain intellectual property identified by AstraZeneca pursuant to Section 6.8.3(a) is Additional Core IP, Isis will send written notice to such effect to AstraZeneca, and the Parties will engage a mutually agreed upon independent Third Party intellectual property lawyer with expertise in the patenting of oligonucleotides, and appropriate professional credentials in the relevant jurisdiction, to determine the question of whether or not such Third Party intellectual property is Additional Core IP. The determination of the Third Party expert engaged under the preceding sentence will be binding on the Parties solely for purposes of determining whether [***]. The costs of any Third Party expert engaged under this Section 6.8.4 will be paid by the Party against whose position the Third Party lawyer's determination is made.

(b) Notwithstanding the determination of the Third Party lawyer under Section 6.8.4(a), if a Third Party Controlling Additional Core IP is awarded a judgment from a court of competent jurisdiction arising from its claim against AstraZeneca asserting that [***], AstraZeneca will be permitted to (i) [***] and (ii) [***].

6.8.5. **Isis In-License Agreements**. The Isis In-License Agreements in existence at the Execution Date are listed in APPENDIX 3. After the Effective Date APPENDIX 3 will be updated in accordance with Section 1.13.2, Section 6.8.2(a), Section 6.8.2(b)(2), Section 6.8.3(a), Section 6.9, and Section 8.4.2. Any such update will on a Collaboration Target-by-Collaboration Target basis, identify the relevant intellectual property rights, any AstraZeneca Supported Pass Through Costs and any Isis Supported Pass Through Costs.

6.8.6. ***Minimum Third Party Payments***. Any Minimum Third Party Payments AstraZeneca is obligated to pay under this Agreement will be satisfied by [***].

6.9. New Third Party Compound Technology.

6.9.1. **Existing New Third Party Compound Technology**. Where AstraZeneca agrees to incorporate New Third Party Compound Technology into an ASO under the Drug Discovery Plan in accordance with Section 1.13.2, Isis will include such technology in the license granted to AstraZeneca under Section 4.1.1 and, subject to Section 6.9.3, [***] will pay [***] to the extent triggered by the Manufacturing, Development or Commercialization of a Product by Isis in the conduct of the Drug Discovery Plan or by or on behalf of AstraZeneca.

6.9.2. **Additional New Third Party Compound Technology**. If, (i) in order to grant a license to AstraZeneca to New Third Party Compound Technology that the Parties agree to incorporate into an ASO in accordance with Section 1.13.2, it is necessary for Isis to obtain a license from the Third Party controlling such New Third Party Compound Technology, or (ii) at any time after the Parties decide to incorporate New Third Party Compound Technology into an ASO pursuant to Section 1.13.2, either Party becomes aware of any intellectual property controlled by a Third Party that is necessary to practice such New Third Party Compound Technology to Develop, Manufacture or Commercialize a Product, then (A) Isis will consult with AstraZeneca before entering into an agreement with such Third Party for access to such New Third Party Compound Technology or such intellectual property necessary to practice such New Third Party Compound Technology, (B) Isis will take into consideration any reasonable comments made by AstraZeneca to such agreement, and (C) to the extent the economic terms of such Third Party agreement are Third Party Obligations that will be paid by [***] as [***], such economic terms will be [***] prior to Isis executing such agreement with such Third Party. On such agreement by [***] to pay such [***] as [***], Isis will include such technology in the license granted to AstraZeneca under Section 4.1.1, such in-license agreement shall be an Isis In-License Agreement, and APPENDIX 3 shall be updated accordingly. If Isis elects not to obtain such a license to New Third Party Compound Technology, Isis will so notify AstraZeneca, and AstraZeneca may obtain such a Third Party license [***].

6.9.3. AstraZeneca will not be responsible for any [***] paid by Isis with respect to New Third Party Compound Technology and if any [***] with respect to New Third Party Compound Technology are triggered prior to exercise of the applicable Collaboration Program Exercise Date, AstraZeneca will not be required to pay such amount unless and until such exercise.

6.10. Payments.

6.10.1. Commencement. Beginning with the Calendar Quarter in which the First Commercial Sale for a Product is made and for each Calendar Quarter thereafter, AstraZeneca will make royalty payments to Isis under this Agreement within [***] following the end of each such Calendar Quarter. Each royalty payment will be accompanied by a report, summarizing Net Sales for Products during the relevant Calendar Quarter and the calculation of royalties due thereon, including country, units, sales price and the exchange rate used. If no royalties are payable in respect of a given Calendar Quarter, AstraZeneca will submit a written royalty report to Isis so indicating together with an explanation as to why no such royalties are payable. In addition, beginning with the Calendar Quarter in which the First Commercial Sale for a Product is made and for each Calendar Quarter thereafter, within [***] following the end of each such Calendar Quarter, AstraZeneca will provide Isis a preliminary, non-binding Product sales estimate for such Calendar Quarter.

6.10.2. Mode of Payment. All payments under this Agreement will be (i) payable in full in U.S. dollars, regardless of the country(ies) in which sales are made, (ii) made by wire transfer of immediately available funds to an account designated by Isis in writing, and (iii) non-creditable (except as otherwise provided in Section 6.6 or Section 6.11), and non-refundable. Whenever for the purposes of calculating the royalties payable under this Agreement conversion from any foreign currency will be required, all amounts will first be calculated in the currency of sale and then converted into United States dollars by AstraZeneca in accordance with the rates of exchange for the relevant month for converting such other currency into US Dollars used by AstraZeneca's internal accounting systems, which are independently audited on an annual basis and which are in accordance with generally accepted accounting principles, fairly applied and as employed on a consistent basis throughout AstraZeneca's operations.

6.10.3. Records Retention. Commencing with the First Commercial Sale of a Product, AstraZeneca will keep complete and accurate records pertaining to the sale of Products for a period of [***] after the year in which such sales occurred, and in sufficient detail to permit Isis to confirm the accuracy of the Net Sales or royalties paid by AstraZeneca hereunder.

6.11. **Audits**. During the Agreement Term and for a period of [***] thereafter, at the request and expense of Isis, AstraZeneca will permit an independent certified public accountant of nationally recognized standing appointed by Isis and reasonably acceptable to AstraZeneca, at reasonable times and upon reasonable notice, but in no case more than [***] per Calendar Year, to examine such records as may be necessary for the purpose of verifying the accrual of any milestone payments, the calculation and reporting of Net Sales, the correctness of any milestone or royalty payment made under this Agreement, and any calculation contemplated by Section 6.7.2(e) for any period within the preceding [***]. As a condition to examining any records of AstraZeneca, such auditor will sign a nondisclosure agreement reasonably acceptable to AstraZeneca in form and substance. Any and all records of AstraZeneca examined by such independent certified public accountant will be deemed AstraZeneca's Confidential Information. Upon completion of the audit, the accounting firm will provide both AstraZeneca and Isis with a written report disclosing whether the milestone or royalty payments and any calculation contemplated by Section 6.7.2(e) made by AstraZeneca are correct or incorrect and the specific details concerning any discrepancies ("***Audit Report***"). If, as a result of any inspection of the books and records of AstraZeneca, it is shown that AstraZeneca's payments under this Agreement were more or less than the milestone or royalty amount which should have been paid, then the relevant Party will make all payments required to be made by paying the other Party the difference between such amounts to eliminate any discrepancy revealed by said inspection within 45 days of receiving the Audit Report, with interest calculated in accordance with Section 6.13; *provided, however*, that any such payment by Isis to AstraZeneca will be [***]. Isis will pay for such audit, except that if AstraZeneca is found to have underpaid Isis by more than [***]% of the amount that should have been paid for the audited period, AstraZeneca will reimburse Isis the reasonable fees and expenses charged by the accounting firm for the audit.

6.12. **Taxes**.

6.12.1. **Taxes On Income**. Each Party alone will be solely responsible for paying any and all Taxes (other than withholding taxes required by Applicable Law to be paid by AstraZeneca or Isis (as the case may be) levied on account of, or measured in whole or in part by reference to, the income of such Party.

6.12.2. **Indirect Taxes**. All payments are exclusive of Indirect Taxes. If any Indirect Taxes are chargeable in respect of any payments, the paying Party will pay such Indirect Taxes at the applicable rate in respect of such payments following receipt, where applicable, of an Indirect Taxes invoice in the appropriate form issued by the receiving Party in respect of those payments.

The Parties will issue invoices for all amounts payable under this Agreement consistent with Indirect Tax requirements and irrespective of whether the sums may be netted for settlement purposes. If such amounts of Indirect Taxes are refunded by the applicable Governmental Authority or other fiscal authority subsequent to payment, the Party receiving such refund will transfer such amount to the paying Party within 45 days of receipt. The Parties agree to reasonably cooperate to provide any information required by the Party pursuing a refund of Indirect Taxes paid.

6.12.3. **Withholding Tax**. To the extent the paying Party is required to deduct and withhold taxes on any payment, the paying Party will pay the amounts of such taxes to the proper governmental authority for the account of the receiving Party and remit the net amount to the receiving Party in a timely manner. The paying Party will promptly furnish the receiving Party with proof of payment of such taxes. If documentation is necessary in order to secure an exemption from, or a reduction in, any withholding taxes, the Parties will provide such documentation to the extent they are entitled to do so. In accordance with the procedures set forth in Section 9.3 and Section 9.4, (i) the receiving Party will also indemnify the paying Party for any tax, interest or penalties imposed on the paying Party if the paying Party improperly reduces or eliminates withholding tax based upon representations made by the receiving Party, and (ii) Isis will indemnify AstraZeneca for any withholding tax incurred on AstraZeneca Supported Pass-Through Costs paid by AstraZeneca to Isis that arises because these costs are deemed to not be beneficially owned by Isis.

6.12.4. **Tax Cooperation**. At least 15 days prior to the date a given payment is due under this Agreement, the non-paying Party will provide the paying Party with any and all tax forms that may be reasonably necessary in order for the paying Party to lawfully not withhold tax or to withhold tax at a reduced rate with respect to such payment under an applicable bilateral income tax treaty. Following the paying Party's timely receipt of such tax forms from the non-paying Party, the paying Party will not withhold tax or will withhold tax at a reduced rate under an applicable bilateral income tax treaty, if appropriate under the Applicable Laws. The non-paying Party will provide any such tax forms to the paying Party upon request and in advance of the due date. Each Party will provide the other with reasonable assistance to enable the recovery, as permitted by Applicable Law, of withholding taxes resulting from payments made under this Agreement, such recovery to be for the benefit of the Party who would have been entitled to receive the money but for the application of withholding tax under this Section 6.12.

The provisions of this Section 6.12 are to be read in conjunction with the provisions of Section 12.3 below.

6.13. **Interest**. Any undisputed payments to be made hereunder that are not paid on or before the date such payments are due under this Agreement, and any payments that are pending resolution of any dispute unless the dispute is ruled in favor of the paying Party, will bear interest at a rate per annum equal to the lesser of (i) the rate announced by Bank of America (or its successor) as its prime rate in effect on the date that such payment would have been first due plus 1% or (ii) the maximum rate permissible under applicable law.

ARTICLE 7.
INTELLECTUAL PROPERTY

7.1. Ownership.

7.1.1. Isis Technology and AstraZeneca Technology. As between the Parties, Isis will own and retain all of its rights, title and interest in and to the Licensed Know-How and Licensed Patents and AstraZeneca will own and retain all of its rights, title and interest in and to the AstraZeneca Background Intellectual Property, AstraZeneca Know-How and AstraZeneca Patents, subject to any assignments, rights or licenses expressly granted by one Party to the other Party under this Agreement. For clarity, except as otherwise expressly provided in this Agreement, the scope of licenses granted by AstraZeneca under this Agreement will not include AstraZeneca Background Intellectual Property.

7.1.2. Collaboration Technology. As between the Parties, each Party shall own and retain all right, title and interest in and to any and all Know-How that is conceived, discovered, developed or otherwise made by or on behalf of such Party (or its Affiliates) under or in connection with this Agreement, whether or not patented or patentable and any and all Patent Rights and other intellectual property rights with respect thereto.

7.1.3. Disclosure of Collaboration Technology.

(a) AstraZeneca will promptly disclose to Isis, and will cause its Affiliates to so disclose, the discovery, development, or creation of any AstraZeneca Collaboration Intellectual Property.

(b) Isis will promptly disclose to AstraZeneca, and will cause its Affiliates to so disclose, the discovery, development, or creation of any Isis Collaboration Intellectual Property.

7.1.4. Jointly Owned Collaboration Technology. The Parties shall each own an equal, undivided interest in any and all such Know-How and Patent Rights that are conceived, discovered, developed or otherwise made jointly by or on behalf of the Parties under or in connection with this Agreement. Inventorship will be determined in accordance with Section 7.1.5(b). Each Party shall, without additional compensation, cooperate to make any necessary assignments to fully effect the ownership provided for in this Section 7.1.4. Except as expressly provided in this Agreement, without limiting the exclusive licenses granted under Section 4.1.1 or the exclusivity covenants under Section 3.1, neither Party will have any obligation to account to the other for profits with respect to, or to obtain any consent of the other Party to license or exploit, Jointly-Owned Collaboration Technology by reason of joint ownership thereof, and each Party hereby waives any right it may have under the laws of any jurisdiction to require any such consent or accounting; *provided that* [***].

7.1.5. IP Managers.

(a) Each Party will appoint one of its in-house patent attorneys to serve as the primary contact with respect to intellectual property matters arising under this Agreement (the "***IP Managers***") and will cooperate with respect to the activities set forth in this ARTICLE 7. A strategy will be discussed with regard to (x) prosecution and maintenance, defense and enforcement of Isis Product-Specific Patents, AstraZeneca Product-Specific Patents and Jointly-Owned Collaboration Patents that would be or are licensed to AstraZeneca under Section 4.1.1, (y) defense against allegations of infringement of Third Party Patent Rights, and (z) licenses to Third Party Patent Rights or Know-How, in each case to the extent such matter would be reasonably likely to have a material impact on this Agreement or the licenses granted hereunder. In addition, the IP Managers will ensure that all Patent Rights claiming (i) the specific composition of matter (the exact sequence and chemistry) of a prospective or designated Lead Candidate or Development Candidate, and/or (ii) methods of using such Compound as a prophylactic, therapeutic or diagnostic, will be separated into their own patent applications separate from other subject matter to ensure any such claims are initially licensed to AstraZeneca under Section 4.1.1 and then assigned as Isis Product Specific Patents under Section 4.2.1.

(b) In addition, the IP Managers will be responsible for the determination of inventorship. The determination of inventorship will be made in accordance with United States patent laws and therefore this will determine if the invention is solely or jointly owned by the relevant Party or Parties. To the extent reasonably requested by either Party, the IP Managers will solicit the involvement of more senior members of their respective legal departments (up to the most senior intellectual property attorney, where appropriate) with respect to critical issues, and may escalate issues to the Senior Representatives for input and resolution pursuant to Section 12.1.1. Each Party's IP Mangers will consider comments and suggestions made by the other in good faith. If either Party deems it reasonably advisable, the Parties will enter into a mutually agreeable common interest agreement covering the matters contemplated by this Agreement.

7.2. Prosecution and Maintenance of Patents.

7.2.1. Patent Filings. The Party responsible for Prosecution and Maintenance of any Patent Rights as set forth in Section 7.2.2 or Section 7.2.3 will endeavor to obtain patent protection for the Product as it Prosecutes and Maintains its other patents Covering products in development, using counsel of its own choice (but with respect to Patent Rights licensed to AstraZeneca under Section 4.1.1, counsel reasonably acceptable to AstraZeneca), in such countries as the responsible Party sees fit.

7.2.2. Licensed Patents and AstraZeneca Patents.

(a) **Isis Core Technology Patents and Isis Manufacturing and Analytical Patents**. During the Agreement Term, Isis will control and be responsible for all aspects of the Isis Core Technology Patents and Isis Manufacturing and Analytical Patents.

(b) **Isis Product-Specific Patents and Jointly-Owned Collaboration Patents**. On a Collaboration Target-by-Collaboration Target basis, following the Collaboration Program Exercise Date (so long as the applicable license to AstraZeneca under Section 4.1.1 is in effect), AstraZeneca will control and be responsible for all aspects of the Prosecution and Maintenance of the (i) Isis Product-Specific Patents and (ii) Jointly-Owned Collaboration Patents that are not Isis Core Technology Patents or Isis Manufacturing and Analytical Patents, in each case (i) and (ii) to the same extent Isis had the right to control and was responsible for such Prosecution and Maintenance immediately prior to such license (or such milestone payment), subject to Section 7.2.3.

(c) **AstraZeneca Patents**. AstraZeneca will control and be responsible for all aspects of the Prosecution and Maintenance of all AstraZeneca Patents, subject to Section 7.2.3 and Section 7.2.4.

7.2.3. Jointly-Owned Collaboration Patents. Isis will control and be responsible for all aspects of the Prosecution and Maintenance of Jointly-Owned Collaboration Patents (i) that are Isis Core Technology Patents or Isis Manufacturing and Analytical Patents, (ii) that do not Cover Products, and (iii) for Collaboration Targets prior to the applicable Collaboration Program Exercise Date. AstraZeneca will control and be responsible for all aspects of the Prosecution and Maintenance of Jointly-Owned Collaboration Patents licensed to AstraZeneca under Section 4.1.1 (and with respect to [***], following the Collaboration Program Exercise Date) that Cover Products and are not Isis Core Technology Patents or Isis Manufacturing and Analytical Patents.

7.2.4. Other Matters Pertaining to Prosecution and Maintenance of Patents.

(a) Each Party will keep the other Party informed through the IP Managers as to material developments with respect to the Prosecution and Maintenance of the Product-Specific Patents or Jointly-Owned Collaboration Patents for which such Party has responsibility for Prosecution and Maintenance pursuant to Section 7.2.2, Section 7.2.3, or this Section 7.2.4, including by providing copies of material data as it arises, any office actions or office action responses or other correspondence that such Party provides to or receives from any patent office, including notice of all interferences, reissues, re-examinations, oppositions or requests for patent term extensions, and all patent-related filings, and by providing the other Party the timely opportunity to have reasonable input into the strategic aspects of such Prosecution and Maintenance.

(b) If AstraZeneca elects (i) not to file and prosecute patent applications for the Jointly-Owned Collaboration Patents or Isis Product-Specific Patents that have been licensed or assigned to AstraZeneca under this Agreement or the AstraZeneca Product-Specific Patents ("***AstraZeneca-Prosecuted Patents***") in a particular country, (ii) not to continue the prosecution (including any interferences, oppositions, reissue proceedings, re-examinations, and patent term extensions, adjustments, and restorations) or maintenance of any AstraZeneca-Prosecuted Patent in a particular country, or (iii) not to file and prosecute patent applications for the AstraZeneca-Prosecuted Patent in a particular country following a written request from Isis to file and prosecute in such country, then AstraZeneca will so notify Isis promptly in writing of its intention (including a reasonably detailed rationale for doing so) in good time to enable Isis to meet any deadlines by which an action must be taken to establish or preserve any such Patent Right in such country; and Isis will have the right, but not the obligation, to file, prosecute, maintain, enforce, or otherwise pursue such AstraZeneca-Prosecuted Patent in the applicable country at its own expense with counsel of its own choice. In such case, AstraZeneca will cooperate with Isis to file for, or continue to Prosecute and Maintain or enforce, or otherwise pursue such AstraZeneca-Prosecuted Patent in such country in Isis' own name, but only to the extent that AstraZeneca is not required to take any position with respect to such abandoned AstraZeneca-Prosecuted Patent that would be reasonably likely to adversely affect the scope, validity or enforceability of any of the other Patent Rights being prosecuted and maintained by AstraZeneca under this Agreement. Notwithstanding anything to the contrary in this Agreement, if Isis assumes responsibility for the Prosecution and Maintenance of any such AstraZeneca-Prosecuted Patent under this Section 7.2.4(b), Isis will have no obligation to notify AstraZeneca if Isis intends to abandon such AstraZeneca-Prosecuted Patent.

(c) The Parties, through the IP Managers, will cooperate in good faith to determine if and when any divisional or continuation applications will be filed with respect to any Jointly-Owned Collaboration Patents or Product-Specific Patents, and where a divisional or continuation patent application filing would be practical and reasonable, then such a divisional or continuation filing will be made.

(d) If the Party responsible for Prosecution and Maintenance pursuant to Section 7.2.3 intends to abandon such Jointly-Owned Collaboration Patent without first filing a continuation or substitution, then such Party will notify the other Party of such intention at least 60 days before such Jointly-Owned Collaboration Patent will become abandoned, and such other Party will have the right, but not the obligation, to assume responsibility for the Prosecution and Maintenance thereof at its own expense (subject to Section 7.3.1) with counsel of its own choice, in which case the abandoning Party will, and will cause its Affiliates to, assign to the other Party (or, if such assignment is not possible, grant a fully-paid exclusive license in) all of their rights, title and interest in and to such Jointly-Owned Collaboration Patents. If a Party assumes responsibility for the Prosecution and Maintenance of any such Jointly-Owned Collaboration Patents under this Section 7.2.4(d), such Party will have no obligation to notify the other Party of any intention of such Party to abandon such Jointly-Owned Collaboration Patents.

(e) In addition, the Parties will consult, through the IP Managers, and take into consideration the comments of the other Party for all matters relating to interferences, reissues, re-examinations and oppositions with respect to those Patent Rights in which such other Party (i) has an ownership interest, (ii) has received a license thereunder in accordance with this Agreement, or (iii) may in the future, in accordance with this Agreement, obtain a license or sublicense thereunder.

7.3. Patent Costs.

7.3.1. Jointly-Owned Collaboration Patents. Unless the Parties agree otherwise, Isis and AstraZeneca will share equally the Patent Costs associated with the Prosecution and Maintenance of Jointly-Owned Collaboration Patents; *provided that,* either Party may decline to pay its share of costs for filing, prosecuting and maintaining any Jointly-Owned Collaboration Patents in a particular country or particular countries, in which case the declining Party will, and will cause its Affiliates to, assign to the other Party (or, if such assignment is not possible, grant a fully-paid exclusive license in) all of their rights, titles and interests in and to such Jointly-Owned Collaboration Patents.

7.3.2. Licensed Patents and AstraZeneca Patents. Except as set forth in Section 7.2.3 and Section 7.3.1, each Party will be responsible for all Patent Costs incurred by such Party prior to and after the Effective Date in all countries in the Prosecution and Maintenance of Patent Rights for which such Party is responsible under Section 7.2.

7.4. Defense of Claims Brought by Third Parties.

7.4.1. Products – Prior to AstraZeneca Exercising a Collaboration Program License Right. If a Third Party initiates a Proceeding claiming a Patent Right owned by or licensed to such Third Party is infringed by the Development, Manufacture or Commercialization of any Product with respect to which AstraZeneca has not yet exercised its Collaboration Program License Right, Isis will have the first right, but not the obligation, to defend against any such Proceeding at its sole cost and expense. If Isis elects to defend against such Proceeding, then Isis will have the sole right to direct the defense and to elect whether to settle such claim; *provided, however*, Isis will not settle such Proceeding without the prior written consent of AstraZeneca (such consent not to be unreasonably withheld, conditioned or delayed). AstraZeneca will reasonably assist Isis in defending such Proceeding and cooperate in any such litigation at the request and expense of Isis. Isis will provide AstraZeneca with prompt written notice of the commencement of any such Proceeding that is of the type described in this Section 7.4.1, and Isis will keep AstraZeneca apprised of the progress of such Proceeding. If Isis elects not to defend against such a Proceeding, then Isis will so notify AstraZeneca in writing within 60 days after Isis first receives written notice of the initiation of such Proceeding, and AstraZeneca will have the right, but not the obligation, to defend against such Proceeding at its sole cost and expense and thereafter AstraZeneca will have the sole right to direct the defense thereof, including the right to settle such claim (but only with the prior written consent of Isis, which consent will not be unreasonably withheld, delayed or conditioned). In any event, the Party not defending such Proceeding will reasonably assist the other Party and cooperate in any such litigation at the request and expense of the Party defending such Proceeding. Each Party may at its own expense and with its own counsel join any defense initiated or directed by the other Party under this Section 7.4. Each Party will provide the other Party with prompt written notice of the commencement of any such Proceeding under this Section 7.4, and such Party will promptly furnish the other Party with a copy of each communication relating to the alleged infringement that is received by such Party.

7.4.2. Products After AstraZeneca Exercises a Collaboration Program License Right. If a Third Party initiates a Proceeding claiming a Patent Right owned by or licensed to such Third Party is infringed by the Development, Manufacture or Commercialization of any Product being Developed or Commercialized by AstraZeneca under a license granted under Section 4.1.1, then AstraZeneca will have the first right, but not the obligation, to defend against any such Proceeding at its sole cost and expense. If AstraZeneca elects to defend against such Proceeding, then AstraZeneca will have the sole right to direct the defense and to elect whether to settle such claim (but only with the prior written consent of Isis, not to be unreasonably withheld, conditioned or delayed). Isis will reasonably assist AstraZeneca in defending such Proceeding and cooperate in any such litigation at the request and expense of AstraZeneca. AstraZeneca will provide Isis with prompt written notice of the commencement of any such Proceeding that is of the type described in this Section 7.4.2, and AstraZeneca will keep Isis apprised of the progress of such Proceeding. If AstraZeneca elects not to defend against a Proceeding, then AstraZeneca will so notify Isis in writing within 60 days after AstraZeneca first receives written notice of the initiation of such Proceeding, and Isis will have the right, but not the obligation, to defend against such a Proceeding at its sole cost and expense and thereafter Isis will have the sole right to direct the defense thereof, including the right to settle such claim (but only with the prior written consent of AstraZeneca, which consent will not be unreasonably withheld, delayed or conditioned). Notwithstanding the foregoing, if [***]; *provided, however*, [***]. In any event, the Party not defending such Proceeding will reasonably assist the other Party and cooperate in any such litigation at the request and expense of the Party defending such Proceeding. Each Party may at its own expense and with its own counsel join any defense initiated or directed by the other Party under this Section 7.4. Each Party will provide the other Party with prompt written notice of the commencement of any such Proceeding under this Section 7.4, and such Party will promptly furnish the other Party with a copy of each communication relating to the alleged infringement that is received by such Party.

7.4.3. **Discontinued Product**. If a Third Party initiates a Proceeding claiming that any Patent Right or Know-How owned by or licensed to such Third Party is infringed by the Development, Manufacture or Commercialization of a Discontinued Product, Isis will have the first right, but not the obligation, to defend against and settle such Proceeding at its sole cost and expense. AstraZeneca will reasonably assist Isis in defending such Proceeding and cooperate in any such litigation at the request and expense of Isis. Each Party may at its own expense and with its own counsel join any defense directed by the other Party. Isis will provide AstraZeneca with prompt written notice of the commencement of any such Proceeding, or of any allegation of infringement of which Isis becomes aware and that is of the type described in this Section 7.4.3, and Isis will promptly furnish AstraZeneca with a copy of each communication relating to the alleged infringement received by Isis.

7.4.4. **Interplay Between Enforcement of IP and Defense of Third Party Claims**. Notwithstanding the provisions of Section 7.4.1 and Section 7.4.3, to the extent that a Party's defense against a Third Party claim of infringement under this Section 7.4 involves (i) the enforcement of the other Party's Know-How or Patent Rights, or (ii) the defense of an invalidity claim with respect to such other Party's Know-How or Patent Rights, then, in each case, the general concepts of Section 7.5 will apply to the enforcement of such other Party's Know-How or Patent Rights or the defense of such invalidity claim (i.e., each Party has the right to enforce its own intellectual property, except that the relevant Commercializing Party will have the initial right, to the extent provided in Section 7.5, to enforce such Know-How or Patent Rights or defend such invalidity claim, and the other Party will have a step-in right, to the extent provided in Section 7.5, to enforce such Know-How or Patent Rights or defend such invalidity claim).

7.5. **Enforcement of Patents Against Competitive Infringement**. With respect to infringement, unauthorized use, misappropriation or threatened infringement by a Third Party of any Product-Specific Patents by reason of the development, manufacture, use or commercialization of a product that binds to a Collaboration Target in the Field ("***Competitive Infringement***"), prior to the applicable Collaboration Program Exercise Date, Isis will have the sole right (with no obligation to discuss with AstraZeneca), but not the obligation, to institute, prosecute, and control a Proceeding with respect thereto. With respect to any Competitive Infringement after the applicable Collaboration Program Exercise Date, the Parties will handle such Competitive Infringement in accordance with the remainder of this Section 7.5.

7.5.1. **Duty to Notify of Competitive Infringement**. If either Party learns of a Competitive Infringement by a Third Party to which such Party does not owe any obligation of confidentiality, such Party will promptly notify the other Party in writing and will provide such other Party with available evidence of such Competitive Infringement; *provided, however*, that for cases of Competitive Infringement under Section 7.5.6 below, such written notice will be given within 10 days.

7.5.2. **Control of Competitive Infringement Proceedings**. For any Competitive Infringement with respect to a Product licensed to AstraZeneca under Section 4.1.1 that occurs after the applicable Collaboration Program Exercise Date, so long as part of such Proceeding AstraZeneca also enforces any Patent Rights Controlled by AstraZeneca (including any Isis Product-Specific Patents assigned by Isis to AstraZeneca under this Agreement) being infringed that Cover such Product, then AstraZeneca will have the first right, but not the obligation, to institute, prosecute, and control a Proceeding with respect thereto by counsel of its own choice at its own expense, and Isis will have the right, at its own expense, to be represented in that action by counsel of its own choice, *however,* AstraZeneca will have the right to control such litigation. If AstraZeneca fails to initiate a Proceeding within a period of 90 days after receipt of written notice of such Competitive Infringement (subject to a 90 day extension to conclude negotiations, if AstraZeneca has commenced good faith negotiations with an alleged infringer for elimination of such Competitive Infringement within such 90 day period), Isis will have the right to initiate and control a Proceeding with respect to such Competitive Infringement by counsel of its own choice, and AstraZeneca will have the right to be represented in any such action by counsel of its own choice at its own expense. Notwithstanding the foregoing, if [***]; *provided, however*, [***].

7.5.3. **Joinder**.

(a) If a Party initiates a Proceeding in accordance with this Section 7.5, the other Party agrees to be joined as a party plaintiff where necessary and to give the first Party reasonable assistance and authority to file and prosecute the Proceeding. Subject to Section 7.5.4, the costs and expenses of each Party incurred pursuant to this Section 7.5.3(a) will be borne by the Party initiating such Proceeding; *provided* AstraZeneca will only be requested to join such a Proceeding if such Proceeding relates to a Patent Right or Product licensed to AstraZeneca under Section 4.1.1.

(b) If one Party initiates a Proceeding in accordance with this Section 7.5.3, the other Party may join such Proceeding as a party plaintiff where necessary for such other Party to seek lost profits with respect to such infringement.

7.5.4. **Share of Recoveries**. Any damages or other monetary awards recovered with respect to a Proceeding brought pursuant to this Section 7.5 will be shared as follows:

(a) the amount of such recovery will first be applied to the Parties' reasonable out-of-pocket costs incurred in connection with such Proceeding (which amounts will be allocated *pro rata* if insufficient to cover the totality of such expenses); then

(b) any remaining proceeds will be allocated as follows: (A) if Isis initiates or controls the defense of the Proceeding pursuant to Section 7.4.1, Section 7.4.2, Section 7.4.3 or Section 7.5.2 [***]; (B) if AstraZeneca initiates or controls the defense of the Proceeding pursuant to Section 7.4.1, AstraZeneca will receive and retain [***]% of the remaining proceeds and Isis will receive and retain [***]% of the remaining proceeds; and (C) if AstraZeneca initiates or controls the defense of the Proceeding pursuant to Section 7.4.2 or 7.5.2, [***].

7.5.5. **Settlement**. Notwithstanding anything to the contrary in this ARTICLE 7, neither Party may enter a settlement, consent judgment or other voluntary final disposition of a suit under this ARTICLE 7 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.

7.5.6. **35 USC 271(e)(2) Infringement**. Notwithstanding anything to the contrary in this Section 7.5, solely with respect to Licensed Patents that have not been assigned to AstraZeneca under this Agreement for a Competitive Infringement under 35 USC 271(e)(2), the time period set forth in Section 7.5.2 during which a Party will have the initial right to bring a Proceeding will be shortened to a total of 25 days, so that, to the extent the other Party has the right, pursuant to such Section to initiate a Proceeding if the first Party does not initiate a Proceeding, such other Party will have such right if the first Party does not initiate a Proceeding within 25 days after such first Party's receipt of written notice of such Competitive Infringement.

7.6. Other Infringement.

7.6.1. Jointly-Owned Collaboration Patents. With respect to the infringement in the Field of a Jointly-Owned Collaboration Patent which is not a Competitive Infringement, the Parties will cooperate in good faith to bring suit together against such infringing party or the Parties may decide to permit one Party to solely bring suit. Any damages or other monetary awards recovered with respect to a Proceeding brought pursuant to this Section 7.6.1 will be shared as follows: (i) the amount of such recovery will first be applied to the Parties' reasonable out-of-pocket costs incurred in connection with such Proceeding (which amounts will be allocated *pro rata* if insufficient to cover the totality of such expenses); (ii) (A) if the Parties jointly initiate a Proceeding pursuant to this Section 7.6.1, [***]; and (B) if only one Party initiates the Proceeding pursuant to this Section 7.6.1, [***].

7.6.2. Patents Solely Owned by Isis. Isis will retain all rights to pursue an infringement of any Patent Right solely owned by Isis which is other than a Competitive Infringement and Isis will retain all recoveries with respect thereto.

7.6.3. Patents Solely Owned by AstraZeneca. AstraZeneca will retain all rights to pursue an infringement of any Patent Right solely owned by AstraZeneca which is other than a Competitive Infringement and AstraZeneca will retain all recoveries with respect thereto.

7.7. Patent Listing.

7.7.1. AstraZeneca's Obligations. AstraZeneca will promptly, accurately and completely list, with the applicable Regulatory Authorities during the Agreement Term, all applicable Patent Rights that Cover a Product licensed to AstraZeneca under Section 4.1.1. Prior to such listings, the Parties will meet, through the IP Managers, to evaluate and identify all applicable Patent Rights, and AstraZeneca will have the right to review, where reasonable, original records relating to any invention for which Patent Rights are being considered by the IP Managers for any such listing. Notwithstanding the preceding sentence, AstraZeneca will retain final decision-making authority as to the listing of all applicable Patent Rights for a Product that are not Isis Core Technology Patents or Isis Manufacturing and Analytical Patents, regardless of which Party owns such Patent Rights.

7.7.2. Isis' Obligations. Isis will promptly, accurately and completely list, with the applicable Regulatory Authorities, all applicable Patent Rights that Cover a Discontinued Product. Prior to such listings, the IP Managers will meet to evaluate and identify all applicable Patent Rights, and Isis will have the right to review, where reasonable, original records relating to any invention for which Patent Rights are being considered by the IP Managers for any such listing. Notwithstanding the preceding sentence, Isis will retain final decision-making authority as to the listing of all applicable Patent Rights for such Discontinued Products, as applicable, regardless of which Party owns such Patent Rights.

7.8. **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, it will notify the other Party and neither Party will make an election under such provision when exercising its rights under this ARTICLE 7 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 such Party with respect to any submissions, filings or other activities in support thereof. The Parties acknowledge and agree that this Agreement is a "joint research agreement" as defined in 35 U.S.C. § 100(h).

7.9. **Obligations to Third Parties**. Notwithstanding any of the foregoing, each Party's rights and obligations with respect to Licensed Technology under this ARTICLE 7 will be subject to the Third Party rights and obligations under any (i) Third Party agreements the restrictions and obligations of which AstraZeneca has agreed to under Section 1.13.2, Section 6.8.2(a) or Section 6.8.2(b)(2), (ii) Prior Agreements as such agreements are in effect on the date such Collaboration Target was designated as a High Interest Target and placed on the High Interest Target List (or, with respect to [***], the Execution Date) (and not as such Prior Agreement may be amended thereafter), and (iii) Isis In-License Agreements as such agreements are in effect on the date identified as Isis In-License Agreements and added to APPENDIX 3 in accordance with Section 6.8.5 and have been disclosed to AstraZeneca prior to such date (and in the form disclosed to AstraZeneca prior to such date and not as such Isis In-License Agreements may be amended thereafter unless such amendment is made with AstraZeneca's prior written consent); *provided*, *however*, that, to the extent that Isis has a non-transferable right to prosecute, maintain or enforce any Patent Rights licensed to AstraZeneca hereunder and this Agreement purports to grant any such rights to AstraZeneca, Isis will act in such regard with respect to such Patent Rights at AstraZeneca's direction.

7.10. **Additional Rights and Exceptions**. Notwithstanding any provision of this ARTICLE 7, but subject to Section 7.4.4, Isis retains the sole right to Prosecute and Maintain Isis Core Technology Patents and Isis Manufacturing and Analytical Patents during the Agreement Term and to control any enforcement of Isis Core Technology Patents and Isis Manufacturing and Analytical Patents, and will take the lead on such enforcement solely to the extent that the scope or validity of any Patent Rights Controlled by Isis and Covering the Isis Core Technology Patents or Isis Manufacturing and Analytical Patents is at risk.

7.11. **Patent Term Extension.** The Parties will cooperate with each other in gaining patent term extension wherever applicable to a Product, and AstraZeneca will determine which Isis Product-Specific Patents will be extended. For clarity, with respect to any Isis Product-Specific Patent for which AstraZeneca has an exclusive license under Section 4.1.1, as between AstraZeneca and any Third Party granted a license by Isis outside the Field under any such Isis Product-Specific Patents, AstraZeneca will determine which Isis Product-Specific Patents will be extended.

7.12. **UPC**. With respect to any Isis Product-Specific Patents, AstraZeneca will have the right to determine whether to opt in or opt out (and to opt in again) of the Unified Patent Court system and if requested by AstraZeneca, Isis will promptly do all things reasonably necessary and execute all documents required to give effect to such decision(s), *provided that* [***].

ARTICLE 8.
REPRESENTATIONS AND WARRANTIES

8.1. **Representations, Warranties and Covenants of Both Parties**. Each Party hereby represents and warrants as of the Effective Date, and covenants, to the other Party that:

8.1.1. it has the power and authority and the legal right to enter into this Agreement and perform its obligations hereunder, and that it has taken all necessary action on its part required to authorize the execution and delivery of this Agreement and the performance of its obligations hereunder;

8.1.2. this Agreement has been duly executed and delivered on behalf of such Party and constitutes a legal, valid and binding obligation of such Party and is enforceable against it in accordance with its terms subject to the effects of bankruptcy, insolvency or other laws of general application affecting the enforcement of creditor rights and judicial principles affecting the availability of specific performance and general principles of equity, whether enforceability is considered a proceeding at law or equity;

8.1.3. all necessary consents, approvals and authorizations of all Regulatory Authorities and other parties required to be obtained by such Party in connection with the execution and delivery of this Agreement and the performance of its obligations hereunder have been obtained;

8.1.4. the execution and delivery of this Agreement and the performance of such Party's obligations hereunder (a) do not conflict with or violate any requirement of Applicable Law or any provision of the certificate of incorporation, bylaws or any similar instrument of such Party, as applicable, in any material way, and (b) do not conflict with, violate, or breach or constitute a default or require any consent not already obtained under, any contractual obligation or court or administrative order by which such Party is bound;

8.1.5. all employees, consultants, or (sub)contractors (except (i) academic collaborators, (ii) Third Parties under the Permitted Licenses or Prior Agreements and (iii) in relation to AstraZeneca and its Affiliates, any Third Parties appointed on the terms of agreements described in Section 4.1.2(e)); of such Party or Affiliates performing Development activities hereunder on behalf of such Party are, and such Party hereby covenants to the other Party that they will be, obligated to assign all right, title and interest in and to any inventions developed by them, whether or not patentable, to such Party or Affiliate, respectively, as the sole owner thereof;

8.1.6. such Party will, and such Party hereby covenants to the other Party that it will, perform its activities pursuant to this Agreement in compliance with good laboratory and clinical practices and cGMP and Applicable Law, in each case as applicable under the laws and regulations of the country and the state and local government wherein such activities are conducted, and with respect to the care, handling and use in Development activities hereunder of any non-human animals by or on behalf of such Party, will at all times comply (and will ensure compliance by any of its subcontractors) with all applicable national, federal, state and local laws, regulations and ordinances in performing its obligations under this Agreement; and

8.1.7. such Party is not debarred under the United States Federal Food, Drug and Cosmetic Act or comparable Applicable Laws and it does not, and will not during the Agreement Term, employ or use the services of any person or entity who is debarred, in connection with the Development, manufacture or commercialization of the Products. If either Party becomes aware of the debarment or threatened debarment of any person or entity providing services to such Party, including the Party itself and its Affiliates or Sublicensees, which directly or indirectly relate to activities under this Agreement, the other Party will be immediately notified in writing.

8.2. **Representations, Warranties and Covenants of Isis**. Isis hereby represents and warrants to AstraZeneca, as of the Effective Date, that:

8.2.1. Isis is the owner of, or otherwise has the right to grant all rights and licenses it purports to grant to AstraZeneca with respect to the Licensed Technology under this Agreement for Compounds identified by Isis on or before the Effective Date or any Collaboration Programs as they exist on the Effective Date;

8.2.2. to Isis' Knowledge, all Licensed Patents have been filed and maintained properly and correctly in all material respects.

8.2.3. Isis has not previously entered into any agreement, whether written or oral, with respect to, or otherwise assigned, transferred, licensed, conveyed or otherwise encumbered its right, title or interest in or to, the Licensed Technology (including by granting any covenant not to sue with respect thereto) in such a way as to make the representation set forth in Section 8.2.1 not true, and it will not enter into any such agreements or grant any such right, title or interest to any Person that is inconsistent with the rights and licenses granted to AstraZeneca under this Agreement;

8.2.4. to Isis' Knowledge, each of the Licensed Patents properly identifies each and every inventor of the claims thereof as determined in accordance with the laws of the jurisdiction in which such Patent Right is issued or such application is pending;

8.2.5. Isis has not received any written claim alleging, and does not have Knowledge of any fact or circumstance indicating, that any of the Licensed Patents are invalid or unenforceable, including any Licensed Patents required in order for Isis to conduct its obligations under the Collaboration Plans as they exist on the Effective Date (or the applicable Bring-Down Date), in each case with respect to the Collaboration Targets, Compounds and Products identified by Isis on or before the Effective Date;

8.2.6. Isis has not received any written claim alleging, and does not have Knowledge of any fact or circumstance indicating, that any of Isis' activities relating to the Collaboration Targets, Compounds and Products identified by Isis on or before the Effective Date infringe any intellectual property rights of a Third Party;

8.2.7. to Isis' Knowledge, (i) the Isis In-License Agreements and the licenses granted to Isis under the Isis In-License Agreements are in full force and effect, (ii) Isis has not received any written notice, and has no Knowledge, of any breach by any party to any Isis In-License Agreement, and (iii) Isis' performance of its obligations under this Agreement (including the Collaboration Plans as they exist on the Effective Date or the applicable Bring-Down Date) will not constitute a breach of Isis' obligations under the Isis In-License Agreements and the licenses granted to Isis thereunder;

8.2.8. to Isis' Knowledge, Isis does not require any additional licenses or other intellectual property rights in order for Isis to conduct its obligations under the Collaboration Plans as they exist on the Effective Date (or the applicable Bring-Down Date), in each case with respect to the Collaboration Targets and Compounds identified by Isis on or before the Effective Date;

8.2.9. to Isis' Knowledge, in respect of the pending United States patent applications included in the Licensed Patents, Isis has submitted all material prior art of which it is aware in accordance with the requirements of the United States Patent and Trademark Office;

8.2.10. to Isis' Knowledge, (i) neither Isis nor its Affiliates owns or Controls any Patent Rights or Know How covering formulation or delivery technology as of the Effective Date and (ii) there are no additional licenses (beyond those that would be granted to AstraZeneca under Section 4.1.1 upon the exercise of the Collaboration Program License Right for a Collaboration Target) under any intellectual property owned or Controlled by Isis or its Affiliates as of the Effective Date, in each case (i) and (ii) that would be necessary or useful in order for AstraZeneca to further Develop, Manufacture or Commercialize Compounds contemplated under the Collaboration Plans as they exist on the Effective Date (or the applicable Bring-Down Date);

8.2.11. APPENDIX 7 (Prior Agreements) is a complete and accurate list of all Isis In-License Agreements and all agreements between Isis and Third Parties as of the Effective Date with respect to the Exclusive Targets included in this Agreement as of the Effective Date, that create material Third Party Obligations that affect the rights granted by Isis to AstraZeneca under this Agreement. The Prior Agreements have not been materially amended or extended since first being placed in the Isis data room to which AstraZeneca was given access during the negotiation of this Agreement and subject to redactions represent a true and complete and accurate copy thereof, and any such redactions are of information not necessary to disclose to understand the implications of such Prior Agreements to this Agreement; and

8.2.12. Isis has not conducted any clinical studies with the Compounds and has conducted, and has required its contractors and consultants to conduct, any and all preclinical studies related to the Compounds in compliance with good laboratory and clinical practices and cGMP and Applicable Law, in each case as applicable under the laws and regulations of the country and the state and local government wherein such activities were conducted.

8.3. **Update to Warranties**. On a Collaboration Target-by-Collaboration Target basis, if at the time Isis delivers a Lead Candidate Data Package under Section 1.14.1 or at any time during the Evaluation Period with respect to such Target (each, a "***Bring-Down Date***"), Isis has Knowledge that any of the representations or warranties set forth in Section 8.2 are not true and accurate as at such Bring-Down Date with respect to such Target or any then existing Compounds for such Target (including any identified after the Effective Date), Isis will notify AstraZeneca of the relevant facts or circumstances as soon as practicable but no later than [***]` before the applicable Collaboration Program License Right Deadline.

8.4. **Additional Covenants of Isis**. Isis hereby covenants to AstraZeneca that, during the Agreement Term:

8.4.1. Isis will promptly amend APPENDIX 4 (Isis Core Technology Patents), APPENDIX 5 (Isis Manufacturing and Analytical Patents), APPENDIX 6 (Isis Product-Specific Patents and submit such amended Appendix to AstraZeneca if Isis becomes aware that any Isis Core Technology Patents, Isis Manufacturing and Analytical Patents or Isis Product-Specific Patents are not properly identified on such Appendices.

8.4.2. Isis will promptly notify AstraZeneca if it becomes aware of any agreement that should have been identified as a Prior Agreement or an Isis In-License Agreement and shall provide AstraZeneca with a copy of such agreement. With AstraZeneca's written consent, APPENDIX 3 (Isis In-License Agreements) or APPENDIX 7 (Prior Agreements) will be amended to include any such omitted agreement.

8.4.3. Isis will maintain and not breach any Isis In-License Agreement or any other agreement with Third Parties entered into after the Execution Date that provide a grant of rights from such Third Party to Isis that are Controlled by Isis and are licensed or that Isis believes may become subject to a license from Isis to AstraZeneca for any Exclusive Target, Lead Candidate or Product and will not amend, modify or terminate any such agreement in a manner that would adversely affect AstraZeneca's rights hereunder without first obtaining AstraZeneca's written consent, which consent may be withheld in AstraZeneca's sole discretion.

8.5. **DISCLAIMER OF WARRANTY. EXCEPT FOR THE EXPRESS WARRANTIES SET FORTH IN THIS ARTICLE 8, ASTRAZENECA AND ISIS MAKE NO REPRESENTATIONS AND GRANT NO WARRANTIES, EXPRESS OR IMPLIED, EITHER IN FACT OR BY OPERATION OF LAW, BY STATUTE OR OTHERWISE, AND ASTRAZENECA AND ISIS EACH SPECIFICALLY DISCLAIM ANY WARRANTIES, WHETHER WRITTEN OR ORAL, OR EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OF QUALITY, MERCHANTABILITY OR FITNESS FOR A PARTICULAR USE OR PURPOSE OR ANY WARRANTY AS TO THE VALIDITY OF ANY PATENT RIGHTS OR THE NON-INFRINGEMENT OF ANY INTELLECTUAL PROPERTY RIGHTS OF THIRD PARTIES.**

ARTICLE 9.
INDEMNIFICATION; INSURANCE

9.1. **Indemnification by AstraZeneca**. AstraZeneca agrees to defend Isis, its Affiliates and their respective directors, officers, stockholders, employees and agents, and their respective successors, heirs and assigns (collectively, the "***Isis Indemnitees***"), and will indemnify and hold harmless the Isis Indemnitees, from and against any liabilities, losses, costs, damages, fees or expenses payable to a Third Party, and reasonable attorneys' fees and other legal expenses with respect thereto (collectively, "***Losses***") arising out of any claim, action, lawsuit or other proceeding by a Third Party (collectively, "***Third Party Claims***") brought against any Isis Indemnitee and resulting from or occurring as a result of: (a) any activities conducted by an AstraZeneca employee, consultant or (sub)contractor in the performance of the AstraZeneca Conducted Activities, (b) the Development, Manufacture or Commercialization of any Product by AstraZeneca or its Affiliates, Sublicensees, Distributors, Compulsory Sublicensees (but only to the extent AstraZeneca is indemnified by such Compulsory Sublicensee) or contractors, (c) any breach by AstraZeneca of any of its representations, warranties or covenants pursuant to this Agreement, or (d) the negligence or willful misconduct of AstraZeneca or any AstraZeneca Affiliate or Sublicensee in the performance of this Agreement; *except* in any such case to the extent such Losses result from: (i) the negligence or willful misconduct of any Isis Indemnitee, (ii) any breach by Isis of any of its representations, warranties, covenants or obligations pursuant to this Agreement or the MSA, or (iii) any breach of Applicable Law by any Isis Indemnitee.

9.2. **Indemnification by Isis**. Isis agrees to defend AstraZeneca, its Affiliates and their respective directors, officers, stockholders, employees and agents, and their respective successors, heirs and assigns (collectively, the "***AstraZeneca Indemnitees***"), and will indemnify and hold harmless the AstraZeneca Indemnitees, from and against any Losses arising out of Third Party Claims brought against any AstraZeneca Indemnitee and resulting from or occurring as a result of: (a) any activities conducted by an Isis employee, consultant or (sub)contractor in the performance of the Isis Conducted Activities; (b) any breach by Isis of any of its representations, warranties or covenants pursuant to this Agreement, (c) the negligence or willful misconduct of any Isis Indemnitee or any (sub)contractor of Isis in the performance of this Agreement, or (d) the Development, Manufacture or Commercialization of any Discontinued Product by Isis or its Affiliates, Sublicensees, Distributors or contractors; *except* in any such case to the extent such Losses result from: (i) the negligence or willful misconduct of any AstraZeneca Indemnitee, (ii) any breach by AstraZeneca of any of its representations, warranties, covenants or obligations pursuant to this Agreement or the MSA, or (iii) any breach of Applicable Law by any AstraZeneca Indemnitee.

9.3. **Notice of Claim**. All indemnification claims provided for in Section 6.12.3, Section 9.1, Section 9.2 and Section 10.3.2(a) will be made solely by such Party to this Agreement (the "***Indemnified Party***"). The Indemnified Party will give the indemnifying Party prompt written notice (an "***Indemnification Claim Notice***") of any Losses or the discovery of any fact upon which the Indemnified Party intends to base a request for indemnification under Section 9.1 or Section 9.2, but in no event will the indemnifying Party be liable for any Losses to the extent such Losses result from any delay in providing such notice. Each Indemnification Claim Notice must contain a description of the claim and the nature and amount of such Loss (to the extent that the nature and amount of such Loss is known at such time). The Indemnified Party will furnish promptly to the indemnifying Party copies of all papers and official documents received in respect of any Losses and Third Party Claims.

9.4. **Defense, Settlement, Cooperation and Expenses**.

9.4.1. **Control of Defense**. At its option, the indemnifying Party may assume the defense of any Third Party Claim by giving written notice to the Indemnified Party within 30 days after the indemnifying Party's receipt of an Indemnification Claim Notice. The assumption of the defense of a Third Party Claim by the indemnifying Party will not be construed as an acknowledgment that the indemnifying Party is liable to indemnify the Indemnified Party in respect of the Third Party Claim, nor will it constitute a waiver by the indemnifying Party of any defenses it may assert against the Indemnified Party's claim for indemnification. Upon assuming the defense of a Third Party Claim, the indemnifying Party may appoint as lead counsel in the defense of the Third Party Claim any legal counsel selected by the indemnifying Party. In the event the indemnifying Party assumes the defense of a Third Party Claim, the Indemnified Party will as soon as is reasonably possible deliver to the indemnifying Party all original notices and documents (including court papers) received by the Indemnified Party in connection with the Third Party Claim. Should the indemnifying Party assume the defense of a Third Party Claim, except as provided in this Section 9.4.1, the Indemnified Party will be responsible for the legal costs or expenses subsequently incurred by such Indemnified Party in connection with the analysis, defense or settlement of the Third Party Claim.

9.4.2. **Right to Participate in Defense**. Without limiting Section 9.4.1, any Indemnified Party will be entitled to participate in, but not control, the defense of such Third Party Claim and to employ counsel of its choice for such purpose; *provided, however*, that such employment will be at the Indemnified Party's own cost and expense unless (a) the employment thereof has been specifically authorized by the indemnifying Party in writing, (b) the indemnifying Party has failed to assume the defense and employ counsel in accordance with Section 9.4.1 (in which case the Indemnified Party will control the defense), or (c) the interests of the Indemnified Party and the indemnifying Party with respect to such Third Party Claim are sufficiently adverse to prohibit the representation by the same counsel of both Parties under Applicable Law, ethical rules or equitable principles in which case the indemnifying Party will be responsible for any such costs and expenses of counsel for the Indemnified Party.

9.4.3. **Settlement**. With respect to any Third Party Claims relating solely to the payment of money damages in connection with a Third Party Claim and that will not admit liability or violation of Law on the part of the Indemnified Party or result in the Indemnified Party's becoming subject to injunctive or other relief or otherwise adversely affecting the business of the Indemnified Party in any manner (such as granting a license or admitting the invalidity of a Patent Right Controlled by an Indemnified Party), and as to which the indemnifying Party will have acknowledged in writing the obligation to indemnify the Indemnified Party hereunder, the indemnifying Party will have the sole right to consent to the entry of any judgment, enter into any settlement or otherwise dispose of such Loss, on such terms as the indemnifying Party, in its sole discretion, will deem appropriate. With respect to all other Losses in connection with Third Party Claims, where the indemnifying Party has assumed the defense of the Third Party Claim in accordance with Section 9.4.1, the indemnifying Party will have authority to consent to the entry of any judgment, enter into any settlement or otherwise dispose of such Loss provided it obtains the prior written consent of the Indemnified Party (which consent will not be unreasonably withheld). The indemnifying Party will not be liable for any settlement, consent to entry of judgment, or other disposition of a Loss by an Indemnified Party that is reached without the written consent of the indemnifying Party. Regardless of whether the indemnifying Party chooses to defend or prosecute any Third Party Claim, no Indemnified Party will admit any liability with respect to or settle, compromise or discharge, any Third Party Claim without the prior written consent of the indemnifying Party, such consent not to be unreasonably withheld.

9.4.4. **Cooperation**. Regardless of whether the indemnifying Party chooses to defend or prosecute any Third Party Claim, the Indemnified Party will, and will cause each other Indemnified Party to, cooperate in the defense or prosecution thereof and will furnish such records, information and testimony, provide such witnesses and attend such conferences, discovery proceedings, hearings, trials and appeals as may be reasonably requested in connection therewith. Such cooperation will include access during normal business hours afforded to indemnifying Party to, and reasonable retention by the Indemnified Party of, records and information that are reasonably relevant to such Third Party Claim, and making Indemnified Parties and other employees and agents available on a mutually convenient basis to provide additional information and explanation of any material provided hereunder, and the indemnifying Party will reimburse the Indemnified Party for all its reasonable out-of-pocket costs and expenses in connection therewith.

9.4.5. **Costs and Expenses**. Except as provided above in this Section 9.4, the costs and expenses, including attorneys' fees and expenses, incurred by the Indemnified Party in connection with any claim will be reimbursed on a Calendar Quarter basis by the indemnifying Party, without prejudice to the indemnifying Party's right to contest the Indemnified Party's right to indemnification and subject to refund in the event the indemnifying Party is ultimately held not to be obligated to indemnify the Indemnified Party.

9.5. **Insurance**.

9.5.1. **Isis' Insurance Obligations**. Isis will maintain, at its cost, reasonable insurance against liability and other risks associated with its activities contemplated by this Agreement, including but not limited to its indemnification obligations herein, in such amounts and on such terms as are customary for prudent practices for biotech companies of similar size and with similar resources in the pharmaceutical industry for the activities to be conducted by it under this Agreement taking into account the scope of development of products. Isis will furnish to AstraZeneca evidence of any insurance required under this Section 9.5.1, upon request.

9.5.2. **AstraZeneca's Insurance Obligations**. AstraZeneca hereby represents and warrants to Isis that it will maintain, at its cost, reasonable insurance against liability and other risks associated with its activities contemplated by this Agreement (including product liability), including but not limited to its indemnification obligations herein, in such amounts and on such terms as are customary for prudent practices for large companies in the pharmaceutical industry for the activities to be conducted by AstraZeneca under this Agreement. AstraZeneca will maintain such insurance or self-insurance throughout the Agreement Term and for five years thereafter, and will furnish to Isis evidence of such insurance, upon request.

9.6. **LIMITATION OF CONSEQUENTIAL DAMAGES. EXCEPT FOR (a) CLAIMS OF A THIRD PARTY THAT ARE SUBJECT TO INDEMNIFICATION UNDER THIS ARTICLE 9 OR SECTION 10.3.2(a), (b) CLAIMS ARISING OUT OF A PARTY'S WILLFUL MISCONDUCT, (c) A PARTY'S BREACH OF ARTICLE 3, OR A BREACH OF SECTION 10.3.1(a) BY ASTRAZENECA OR ITS AFFILIATES OR (d) CLAIMS ARISING OUT OF A PARTY'S BREACH OF ITS CONFIDENTIALITY OBLIGATIONS UNDER THIS AGREEMENT, NEITHER PARTY NOR ANY OF ITS AFFILIATES WILL BE LIABLE TO THE OTHER PARTY TO THIS AGREEMENT OR ITS AFFILIATES FOR ANY INCIDENTAL, CONSEQUENTIAL, SPECIAL, PUNITIVE OR OTHER INDIRECT DAMAGES OR LOST OR IMPUTED PROFITS OR ROYALTIES, LOST DATA OR COST OF PROCUREMENT OF SUBSTITUTE GOODS OR SERVICES, WHETHER LIABILITY IS ASSERTED IN CONTRACT, TORT (INCLUDING NEGLIGENCE AND STRICT PRODUCT LIABILITY), INDEMNITY OR CONTRIBUTION, AND IRRESPECTIVE OF WHETHER THAT PARTY OR ANY REPRESENTATIVE OF THAT PARTY HAS BEEN ADVISED OF, OR OTHERWISE MIGHT HAVE ANTICIPATED THE POSSIBILITY OF, ANY SUCH LOSS OR DAMAGE.**

9.7. **Anti-Bribery and Corruption Compliance**.

9.7.1. Each Party agrees, on behalf of itself, its officers, directors and employees and on behalf of its Affiliates that it will, and will use its diligent efforts to procure that its agents, representatives, consultants and subcontractors hired for activities undertaken for or in connection with the performance of this Agreement, (together with such Party, the "***Party Representatives***") for the performance of its obligations hereunder:

Party Representatives will not directly or indirectly pay, offer or promise to pay, or authorize the payment of any money, or give, offer or promise to give, or authorize the giving of anything else of value, to:

(1) any Government Official in order to influence official action;

(2) any Person (whether or not a Government Official) (i) to influence such Person to act in breach of a duty of good faith, impartiality or trust ("acting improperly"), (ii) to reward such Person for acting improperly, or (iii) where such Person would be acting improperly by receiving the money or other thing of value;

(3) any other Person while knowing or having reason to know that all or any portion of the money or other thing of value will be paid, offered, promised or given to, or will otherwise benefit, a Government Official in order to influence official action for or against either Party in connection with the matters that are the subject of this Agreement; or

(4) any Person to reward that Person for acting improperly or to induce that Person to act improperly.

9.7.2. Each Party will not and will use diligent efforts to procure that its Party Representatives will not, directly or indirectly, solicit, receive or agree to accept any payment of money or anything else of value in violation of the Anti-Corruption Laws.

9.7.3. Each Party acknowledges that its undertakings given in Sections 9.7.1 and 9.7.2 are material to the other Party in entering into a relationship with such Party.

9.7.4. Each Party, on behalf of itself and its Party Representatives, represents and warrants to the other Party that for the term of this Agreement and six years thereafter, it will and will use diligent efforts to procure that its Party Representatives keep and maintain accurate books and reasonably detailed records in connection with the performance of its obligation under this Agreement including all records required to establish compliance with Sections 9.7.1 and 9.7.2 above.

9.7.5. Each Party will promptly provide the other Party with written notice of the following events: (A) upon becoming aware of any material breach or violation by it or its Party Representatives of any representation, warranty or undertaking set forth in Sections 9.7.1 and 9.7.2; and (B) upon receiving a formal notification that it is the target of a formal investigation by a Relevant Authority for a Material Anti-Corruption Law Violation or upon receipt of information from any of its Party Representatives connected with this Agreement that any of them is the target of a formal investigation by a Relevant Authority for a Material Anti-Corruption Law Violation.

9.7.6. For the term of this Agreement and six years thereafter, each Party will for the purpose of auditing and monitoring the performance of its compliance with the Agreement and particularly this Section 9.7 permit the other Party, its Affiliates, any auditors of any of them and any Regulatory Authority to have access to any premises of such Party and to the extent that such Party is able to secure such access, its Party Representatives in each case used in connection with this Agreement, together with a right to access personnel and records that relate to this Agreement ("***Audit***").

9.7.7. Each Party will be responsible for any breach of any representation, warranty or undertaking in this Section 9.7 or of the Anti-Corruption Laws by any of its Party Representatives.

9.7.8. Each Party may disclose the terms of this Agreement or any action taken under this Section 9.7 to prevent a potential violation or continuing violation of applicable Anti-Corruption Laws, including the identity of the other Party and the payment terms, to any governmental authority if such Party determines, upon advice of counsel, that such disclosure is necessary.

ARTICLE 10.
TERM; TERMINATION

10.1. **Agreement Term; Expiration**. This Section 10.1, ARTICLE 11 and ARTICLE 12 of this Agreement will become effective on the Execution Date and the remainder of this Agreement will become effective as of the Effective Date and, unless earlier terminated pursuant to the other provisions of this ARTICLE 10, will continue in full force and effect until this Agreement expires as follows:

10.1.1. where there are no Collaboration Targets designated under Section 1.10 by the later of (i) the expiration of the Disease Research Term or (ii) the last date on which any former High Interest Target could become a Collaboration Target pursuant to Section 1.10.3(c);

10.1.2. where there are no Development Candidates designated under Section 1.14 by the later of (i) the expiration of the Collaboration Program Term, and (ii) the last date on which the exercise of a Carryover Option could occur;

10.1.3. where all Collaboration Program License Rights (including those that could arise pursuant to Section 1.10.3(c) and Section 1.14.3(e)) have expired unexercised;

10.1.4. on a country-by-country and Product-by-Product basis, on the date of expiration of all payment obligations by AstraZeneca under this Agreement with respect to such Product in such country; or

10.1.5. in its entirety upon the expiration of all payment obligations by AstraZeneca under this Agreement with respect to the last Product in all countries pursuant to Section 10.1.4.

The period from the Effective Date until the date of expiration of this Agreement pursuant to this Section 10.1 or earlier termination of this Agreement pursuant to Section 10.2, is the "***Agreement Term***." If any antitrust clearance required in accordance with Section 12.5 is not obtained by December 31, 2015, this Agreement, including this Section 10.1, ARTICLE 11 and ARTICLE 12 will automatically expire.

10.2. **Termination of the Agreement**.

10.2.1. **AstraZeneca's Termination for Convenience or Change of Control**.

(a) **Termination for Convenience or with respect to** [***]. At any time following payment by AstraZeneca of the upfront fee under Section 6.1, subject to Section 10.3.1 below, AstraZeneca will be entitled to terminate this Agreement:

(i) in its entirety or in part on a Collaboration Target-by-Collaboration Target basis for convenience by providing 90 days written notice to Isis of such termination; or

(ii) with respect to the [***] Program as set forth in Section 6.6.2 on written notice to Isis of such termination.

(b) **Change of Control Event**.

(i) Prior to the Collaboration Program License Right Deadline for a Collaboration Target, AstraZeneca will have the right to terminate this Agreement in whole or in part with respect to one or more Collaboration Targets for which AstraZeneca has not exercised its Collaboration Program License Right, immediately upon written notice to Isis provided at any time within 30 Business Days following notification by Isis to AstraZeneca of the closing of a Change of Control Event (and Isis will be obliged to give notice on such closing, and in the event it fails to do so, AstraZeneca's right to terminate may be exercised within 90 Business Days of such closing coming to AstraZeneca's Knowledge), if such closing occurs during the Collaboration Program Term.

(ii) If at AstraZeneca's discretion, AstraZeneca decides not to terminate this Agreement with respect to a particular Collaboration Target pursuant to this Section 10.2.1(b) following the closing of a Change of Control Event during the Collaboration Program Term, then, subject to the below provisions in this Section 10.2.1, Isis' and AstraZeneca's obligations under ARTICLE 1 to perform the relevant program on such Collaboration Target will remain and Isis (or its successor) will use Commercially Reasonable Efforts to perform the relevant program on such Collaboration Target in accordance with this Agreement while, to the extent reasonably practicable, maintaining confidentiality of AstraZeneca's Confidential Information from any entity acquiring Isis as a result of the Change of Control Event. As soon as reasonably possible after the public announcement of such a Change of Control Event, Isis (or its successor) and AstraZeneca will meet to discuss in good faith how Isis (or its successor) will continue to perform its obligations under this Agreement with respect to any Collaboration Targets for which AstraZeneca has not exercised its Collaboration Program License Right so that AstraZeneca can consider whether to exercise its rights of termination under this Section 10.2.1(b).

(iii) If AstraZeneca does not exercise its right of termination, AstraZeneca will have the right, by providing Isis with written notice within 30 Business Days following notification by Isis to AstraZeneca of the closing of a Change of Control Event, to require that Isis ceases performing any or certain activities and co-operate and take such measures as may be requested to ensure a prompt and smooth transition of such activities to AstraZeneca or its designee. AstraZeneca will be entitled to deduct an amount equal to the [***] from its next applicable milestone or license fee payment as applicable. Without prejudice to the foregoing, if requested by AstraZeneca such measures will include a technology transfer pursuant to the provisions of Section 4.8 and/or Section 4.1.2(c), in either case without charge to AstraZeneca.

(iv) Furthermore, if the surviving entity following such Change of Control Event is clinically developing or commercializing a product that is directly competing with a Product under this Agreement, then subject to Section 3.3, (i) the development or commercialization of such directly competing product by such surviving entity will not be a violation of Isis' exclusivity covenants under Section 3.1 if such product was being developed or commercialized by the Acquiring Party prior to the Change of Control Event, and (ii) solely with respect to the Product that is subjected to such competition, Section 5.2 shall apply.

10.2.2. Termination for Material Breach.

(a) **AstraZeneca's Right to Terminate**. If AstraZeneca has reason to believe that Isis is in material breach of this Agreement (other than with respect to a failure to use Commercially Reasonable Efforts under ARTICLE 1, which is governed by Section 10.2.3 below), then AstraZeneca may deliver notice of such material breach to Isis. If the breach is curable, Isis will have 60 days to cure such breach. If Isis fails to cure such breach within the 60 day period, or if the breach is not subject to cure, AstraZeneca may terminate this Agreement in its entirety if such breach relates to this Agreement in its entirety, or in relevant part on a Product-by-Product, Collaboration Target-by-Collaboration Target basis if such breach does not relate to this Agreement in its entirety, by providing written notice to Isis.

(b) **Isis' Right to Terminate**. If Isis has reason to believe that AstraZeneca is in material breach of this Agreement (other than with respect to a failure to use Commercially Reasonable Efforts under ARTICLE 1 or Section 5.1, which is governed by Section 10.2.3 below), then Isis may deliver notice of such material breach to AstraZeneca. If the breach is curable, AstraZeneca will have 60 days to cure such breach (except to the extent such breach involves the failure to make a payment when due, which breach must be cured within 30 days following such notice). If AstraZeneca fails to cure such breach within the 60 day or 30 day period, as applicable, or if the breach is not subject to cure, Isis may terminate this Agreement in its entirety if such breach relates to this Agreement in its entirety, or in relevant part on a Product-by-Product, Collaboration Target-by-Collaboration Target basis if such breach does not relate to this Agreement in its entirety, by providing written notice to AstraZeneca.

10.2.3. Remedies for Failure to Use Commercially Reasonable Efforts.

(a) If Isis fails to use Commercially Reasonable Efforts as contemplated in ARTICLE 1 (as determined in accordance with Section 12.1), AstraZeneca will notify Isis and, within 30 days thereafter, Isis and AstraZeneca will meet and confer to discuss and resolve the matter in good faith, and attempt to devise a mutually agreeable plan to address any outstanding issues related to Isis' use of Commercially Reasonable Efforts in ARTICLE 1. Following such a meeting, if Isis fails to use Commercially Reasonable Efforts as contemplated in ARTICLE 1 and such failure constitutes a material breach of this Agreement, then subject to Section 10.2.4 below, AstraZeneca will have the right, at its sole discretion, to terminate this Agreement in whole or in part on a Collaboration Target-by-Collaboration Target basis.

(b) If AstraZeneca fails to use Commercially Reasonable Efforts as contemplated in ARTICLE 1 or Section 5.1 (as determined in accordance with Section 12.1), Isis will notify AstraZeneca and, within 30 days thereafter, Isis and AstraZeneca will meet and confer to discuss and resolve the matter in good faith, and attempt to devise a mutually agreeable plan to address any outstanding issues related to AstraZeneca's use of Commercially Reasonable Efforts in ARTICLE 1 or Section 5.1. Following such a meeting, if AstraZeneca fails to use Commercially Reasonable Efforts as contemplated in ARTICLE 1 or Section 5.1, and such failure constitutes a material breach of this Agreement then subject to Section 10.2.4 below, Isis will have the right, at its sole discretion, to terminate this Agreement in part on a Collaboration Target-by-Collaboration Target basis.

10.2.4. Disputes Regarding Material Breach. Notwithstanding the foregoing, if the Breaching Party in Section 10.2.2 or Section 10.2.3 disputes in good faith the existence, materiality, or failure to cure of any such breach which is not a payment breach, and provides notice to the Non-Breaching Party of such dispute within respectively such 60 day cure period or 30 day notice period, the Non-Breaching Party will not have the right to terminate this Agreement in accordance with Section 10.2.2 or Section 10.2.3, unless and until it has been determined in accordance with Section 12.1 that this Agreement was materially breached by the Breaching Party and the Breaching Party fails to cure such breach within 30 days following such determination. It is understood and acknowledged that during the pendency of such dispute, all the terms and conditions of this Agreement will remain in effect and the Parties will continue to perform all of their respective obligations hereunder, including satisfying any payment obligations.

10.2.5. **Termination of a Licensed Program**. Once AstraZeneca has exercised its Collaboration Program License Rights with respect to a Collaboration Target, neither Party shall be entitled to terminate that Licensed Program pursuant to Sections 10.2.2 or 10.2.3 unless the material breach or failure to use Commercially Reasonable Efforts is with respect to such Licensed Program and any such breach or failure shall be determined on a Licensed Program-by-Licensed Program basis.

10.2.6. **Termination for Insolvency**.

(a) Either Party may terminate this Agreement if, at any time, the other Party files in any court or agency pursuant to any statute or regulation of any state or country a petition in bankruptcy or insolvency or for the appointment of a receiver or trustee of the Party or of substantially all of its assets; or if the other Party proposes a written agreement of composition or extension of substantially all of its debts; or if the other Party will be served with an involuntary petition against it, filed in any insolvency proceeding, and such petition will not be dismissed within 90 days after the filing thereof; or if the other Party will propose or be a party to any dissolution or liquidation; or if the other Party will make an assignment of substantially all of its assets for the benefit of creditors.

(b) All rights and licenses granted under or pursuant to any section of this Agreement are and will otherwise be deemed to be for purposes of Section 365(n) of Title 11, United States Code (the "***Bankruptcy Code***") or analogous provisions of Applicable Law outside the US licenses of rights to "intellectual property" as defined in Section 101(56) of the Bankruptcy Code or analogous provisions of Applicable Law outside the US. The Parties will retain and may fully exercise all of their respective rights and elections under the Bankruptcy Code or analogous provisions of Applicable Law outside the US. Upon the commencement of a bankruptcy proceeding of any Party, the non-bankrupt Party will further be entitled to a complete duplicate of, or complete access to, any such intellectual property, and all embodiments which, if not already in its possession, will be promptly delivered to the non-bankrupt Party upon written request.

10.2.7. **Termination for Patent Challenge**. Isis may terminate this Agreement if AstraZeneca disputes, or assists any Third Party to dispute, the validity of any Licensed Patent, in a patent re-examination, inter-partes review, post grant or other patent-office proceeding, opposition, litigation, or other court proceeding and, within 30 days written notice from Isis, AstraZeneca fails to rescind any and all of such actions, *provided however* that, nothing in this clause prevents AstraZeneca from taking any of the actions referred to in this clause and *provided further* that Isis will not have the right to terminate if AstraZeneca:

(a) asserts invalidity as a defense in any court proceeding brought by Isis asserting infringement of a Licensed Patent; or

(b) Acquires a Third Party that has an existing challenge, whether in a court or administrative proceeding, against a Licensed Patent; or

(c) licenses a product for which Isis has an existing challenge, whether in a court or administrative proceeding, against a Licensed Patent.

10.3. **Consequences of Expiration or Termination of this Agreement**.

10.3.1. **Consequence of Termination of this Agreement**. If this Agreement is terminated by a Party in accordance with Section 10.2, in its entirety or on a Collaboration Target-by-Collaboration Target basis at any time and for any reason, the following terms will apply to any such termination, but only to the extent of any such termination (i.e., with respect to the terminated Collaboration Program or Licensed Program (the "***Terminated Program***" and its Target, the "***Terminated Target***" and the Products under such Terminated Program at the termination Date, the "***Discontinued Products***"), or in its entirety):

(a) **Licenses**. The licenses granted by Isis to AstraZeneca under this Agreement will terminate and, AstraZeneca and its Affiliates and, subject to Section 4.1.2(d), its Sublicensees will cease selling Discontinued Products under such licenses; *provided, that* (i) AstraZeneca and its Affiliates and Sublicensees will have the right to sell any remaining inventory of Discontinued Product over a period of no greater than six months after the effective date of such termination, and AstraZeneca will pay Isis royalties in accordance with Section 6.7 on the Net Sales of such inventory of such Products, to the extent not already paid; and (ii) if there are any Clinical Studies being conducted at the date of termination, AstraZeneca shall be entitled to continue Developing and Manufacturing Compounds and Products to the extent and for the period necessary to effect an orderly transfer or wind down of such Clinical Studies in a timely manner and in accordance with all Applicable Laws.

(b) **Collaboration Program License Rights**. If not exercised prior to the date of termination, AstraZeneca's Collaboration Program License Right will terminate with respect to any Terminated Target.

(c) **Exclusivity**. Neither Party will have any further obligations under Section 3.1 of this Agreement insofar as it relates to a Terminated Target.

(d) **Collaboration Plans**. Except as expressly stated to survive under Section 10.3.1(h), neither Party will have any further obligations with respect to the Terminated Program under the Collaboration Plan(s).

(e) **Responsibility for Discontinued Products**. If a Product becomes a Discontinued Product, except as expressly provided in this Section 10.3, AstraZeneca will have no further obligations or responsibilities with respect to such Product and except for any activities undertaken by AstraZeneca, its Affiliates, Sublicensees or Distributors pursuant to Section 10.3.1(a) or prior to the date of termination, Isis will be responsible for all liabilities relating to the Development, Manufacture and Commercialization of a Discontinued Product by or on behalf of Isis, its Affiliates, Sublicensees or distributors following the date of such termination.

(f) **Return of Information and Materials**. The Parties will return (or destroy, as directed by the other Party) all data, files, records and other materials containing or comprising the other Party's Confidential Information to which it does not retain rights under the surviving provisions of this Agreement. Notwithstanding the foregoing, the Parties will be permitted to retain one copy of such data, files, records, and other materials for archival and legal compliance purposes. Each Party will also be permitted to retain such additional copies of or any computer records or files containing the other Party's Confidential Information that have been created solely by automatic archiving and back-up procedures, to the extent created and retained in a manner consistent with the retaining Party's standard archiving and back-up procedures, but not for any other use or purpose. All Confidential Information shall continue to be subject to the terms of this Agreement for the period set forth in Section 11.1.

(g) **Accrued Rights**. Termination of this Agreement for any reason will be without prejudice to any rights or financial compensation that will have accrued to the benefit of a Party prior to such termination. Such termination will not relieve a Party from obligations that are expressly indicated to survive the termination of this Agreement. For purposes of clarification, milestone payments under ARTICLE 6 accrue as of the date the applicable milestone event is achieved even if the payment is not due at that time.

(h) **Survival**. The following provisions of this Agreement will survive the expiration or earlier termination of this Agreement: Section 1.10 (Process for Designating High Interest Targets as Collaboration Targets) (but only with respect to the Parties' rights and obligations related to restoring a Target to this Agreement as a Collaboration Target and the exclusivity covenants in effect as of the date of such expiration or earlier termination of this Agreement), Section 1.11 (End of Core Research Term) (but only with respect to the licenses and other rights granted therein), Section 1.12 (End of the Disease Research Term) (but only with respect to the provisions of Section 1.10 referenced therein), Section 1.14 (Process for Designating Development Candidates) (but only with respect to the Parties' rights and obligations related to restoring a Target and Compounds to this Agreement, the licenses and other rights granted therein and the exclusivity covenants in effect as of the date of such expiration or earlier termination of this Agreement), Section 1.15 (Expiration of Collaboration Program Term) (but only with respect to the provisions of Section 1.14 referenced therein), Section 1.16 (Exclusive Right to Obtain or Maintain Exclusive Licenses to Development Candidates) (but only with respect to Development Candidates restored to this Agreement), Section 1.16.4 (No Exercise) (but only with respect to the licenses and other rights granted therein and AstraZeneca's exclusivity covenants in effect as of the date of such expiration or earlier termination of this Agreement), Section 4.1.2(d) (Effect of Termination on Sublicenses), Section 4.1.3 (Consequence of Natural Expiration of this Agreement), Section 4.1.4 (No Implied Licenses), Section 4.2.2 (Grant-Back to Isis of Isis Product-Specific Patents), Section 4.3 (Non-Exclusive Technology License Grant to AstraZeneca), Section 4.4 (Cross Licenses Under Collaboration Intellectual Property), Section 4.5 (Interaction of Licenses), Section 6.7.2(d) (End of Royalty Obligation), Section 6.10.3 (Records Retention), Section 6.11 (Audits), Section 6.12 (Taxes), Section 6.13 (Interest), Section 7.1.1 (Isis Technology and AstraZeneca Technology), Section 7.1.2 (Collaboration Technology), Section 7.1.4 (Jointly Owned Collaboration Technology), Section 7.2.3 (Jointly-Owned Collaboration Patents) (but subject to Section 10.3.2(e), if applicable), Section 7.3.1 (Jointly-Owned Collaboration Patents) (but subject to Section 10.3.2(e), if applicable) ARTICLE 9 (Indemnification; Insurance) (but excluding Section 9.7), Section 10.3 (Consequences of Expiration or Termination of this Agreement), ARTICLE 11 (Confidentiality), ARTICLE 12 (Miscellaneous) and APPENDIX 1 (Definitions) (to the extent definitions are embodied in the foregoing listed Articles and Sections).

10.3.2. **Isis: Special Consequences of Certain Terminations**. If (A) AstraZeneca terminates the Agreement under Section 10.2.1 or (B) Isis terminates this Agreement under Section 10.2.2(b), Section 10.2.3(b), Section 10.2.6, or Section 10.2.7, then, in addition to the terms set forth in Section 10.3.1, the following additional terms will also apply but only with respect to the Terminated Program, Terminated Target and Discontinued Product:

(a) Subject to Section 10.3.2(g) and Section 10.3.2(h), AstraZeneca will and hereby does grant to Isis:

(1) a sublicensable, worldwide, exclusive license or sublicense, as the case may be, under all AstraZeneca Technology (excluding AstraZeneca Background Intellectual Property) Controlled by AstraZeneca as of the date of such reversion that Covers the Discontinued Product as Developed or Commercialized by AstraZeneca or its Affiliates as at such date; and

(2) a sublicensable, worldwide, non-exclusive license or sublicense, as the case may be, under all AstraZeneca Background Intellectual Property Controlled by AstraZeneca as of the date of such reversion that Covers the Discontinued Product as Developed or Commercialized by AstraZeneca or its Affiliates as at such date;

in each case solely to Develop, make, have made, use, sell, offer for sale, have sold, import and otherwise Commercialize the Discontinued Product in the Field (such licenses will be sublicensable by Isis in accordance with Section 4.1.2, *mutatis mutandis*); and *provided that* Isis will, (y) in accordance with ARTICLE 9, indemnify and hold harmless AstraZeneca and its Affiliates and Sublicensees from any Losses arising out of Third Party Claims with respect to the Exploitation of such Discontinued Product; and (z) be responsible for (and to the extent paid by AstraZeneca, indemnify and hold harmless AstraZeneca and its Affiliates for) all licensing costs and payments payable to Third Parties for technology used in a Discontinued Product of which AstraZeneca has made Isis aware unless Isis notifies AstraZeneca that it does not wish a license under such technology and Isis ceases to use such technology on or prior to such notification, in each case (x) and (y) with respect to the Exploitation of such Discontinued Product under such licenses that accrue after the date of such termination.

(b) AstraZeneca will assign back to Isis any Patent Rights that relate to the Discontinued Product previously assigned by Isis to AstraZeneca under this Agreement;

(c) AstraZeneca will transfer to Isis for use with respect to the Development and Commercialization of the Discontinued Product, any Know-How, data, results, regulatory information, pricing and market access strategy information, health economic study information, material communications with payors, filings, and files in the possession of AstraZeneca, or copies thereof, as of the date of such termination or reversion that relate solely to such Discontinued Product;

(d) AstraZeneca will grant to Isis a non-exclusive, royalty-free, fully paid up license under any trademarks that are specific to a Discontinued Product solely for use with such Discontinued Product; *provided, however*, that in no event will AstraZeneca have any obligation to license to Isis any trademarks used by AstraZeneca both in connection with the Product and in connection with the sale of any other product or service, including any AstraZeneca- or AstraZeneca-formative marks;

(e) Isis will control and be responsible for all aspects of the Prosecution and Maintenance of all Jointly-Owned Collaboration Patents and AstraZeneca will provide Isis with (and will instruct its counsel to provide Isis with) all of the information and records in AstraZeneca's and its counsel's possession related to the Prosecution and Maintenance of such Jointly-Owned Collaboration Patents, in each case only in respect of the Discontinued Product;

(f) upon Isis' written request pursuant to a mutually agreed supply agreement, AstraZeneca will sell to Isis any bulk API and finished Product in AstraZeneca's possession related to the Compounds that are the subject of the termination at the time of such termination, at a price equal to AstraZeneca's cost at the time such material was produced;

(g) If Isis or any of its Affiliates or Sublicensees Commercializes a Discontinued Product for which AstraZeneca has paid Isis the license fee under Section 6.2 (or, with respect to [***], the [***] CD Milestone) for a Product, then in each such case, following the First Commercial Sale of such Discontinued Product by Isis or its Affiliates or Sublicensees, Isis will pay AstraZeneca a royalty of [***]% of Annual worldwide Net Sales of such Discontinued Product until [***];

(h) If there are any licensed rights granted by AstraZeneca to Isis under Section 10.3.2(a)(2), the Parties will negotiate in good faith regarding a reasonable royalty for such Discontinued Product (not to exceed [***]%) of Annual worldwide Net Sales of such Discontinued Product) to be paid by Isis to AstraZeneca for Discontinued Products covered by such licensed rights, with such royalty payments beginning on the date [***] and ending on the earlier of (y) [***], or (z) [***];

(i) for the purposes of clauses (g) and (h), Net Sales shall mean Net Sales by Isis, its Affiliates and Sublicensees, *provided, that* any definition of "net sales" agreed to by Isis and a Sublicensee in an arms-length sublicense agreement for the Commercialization of a Discontinued Product will be used to calculate net sales of such Discontinued Product sold by Isis' Sublicensees on which royalties are payable by Isis to AstraZeneca hereunder; and

(j) for clarity, the licenses granted by AstraZeneca pursuant to this Section 10.3.2 do not include any intellectual property rights relating to compounds that are not Compounds.

10.3.3. AstraZeneca: Special Consequences of Certain Terminations.

(a) If AstraZeneca terminates this Agreement under Section 10.2.2(a), Section 10.2.3(a) or Section 10.2.6, all of the provisions of Section 10.3.1 will apply, *except that* AstraZeneca, its Affiliates, Sublicensees and Distributors will have the right to sell any remaining inventory of Product, and AstraZeneca will pay Isis royalties in accordance with Section 6.7 on the Net Sales of such inventory of such Products to the extent not already paid.

(b) If AstraZeneca has the right to terminate this Agreement under Section 10.2.2(a), Section 10.2.3(a) or Section 10.2.6, but elects to continue the Agreement, the following provisions which will be effective upon AstraZeneca's notice of such election, will apply:

(i) AstraZeneca may require that Isis ceases performing any activities and co-operate and take such measures as may be requested to ensure a prompt and smooth transition of such activities to AstraZeneca or its designee; and may require that Isis cease to participate in the JSC. Without prejudice to the foregoing, if requested by AstraZeneca such measures will include a technology transfer pursuant to the provisions of Section 4.8 or Section 4.1.2(c), in either case without charge to AstraZeneca; and

(ii) any money damages that may be awarded to AstraZeneca arising from the circumstances which gave rise to the right to terminate, and any costs (the amount of such costs as mutually agreed in good faith by the Parties) incurred by AstraZeneca in connection with the transition of Isis' responsibilities under this Agreement to AstraZeneca or its designee may be set off against any monies owed by AstraZeneca to Isis as provided in Section 12.2.2.

10.3.4. The provisions of this Section 10.3 will not preclude any 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 any Party's right to obtain performance of any obligation; *provided that* in assessing the remedies available to Isis, the rights transferred to Isis following a termination of this Agreement (in its entirety or with respect to a Termination Program and Discontinued Product) shall be taken into account. The Parties acknowledge and agree that the only rights that permit a Party to terminate this Agreement are set out in this ARTICLE 10.

ARTICLE 11.
CONFIDENTIALITY

11.1. **Confidentiality; Exceptions**. Except to the extent expressly authorized by this Agreement or otherwise agreed in writing, the Parties agree that, during the Agreement Term and for five years thereafter, the receiving Party (the "***Receiving Party***") and its Affiliates will keep confidential and will not publish or otherwise disclose or use for any purpose other than as provided for in this Agreement any Confidential Information disclosed by the other Party or its Affiliates (the "***Disclosing Party***").

11.2. **Prior Confidentiality Agreement**. The Mutual Confidential Disclosure Agreement executed by Isis and AstraZeneca on April 11, 2011 (including any and all amendments thereto) (the "***CDA***") will govern disclosures of Confidential Information (as defined in the CDA) between the Parties prior to the Execution Date in connection with the subject matter of this Agreement. All Confidential Information exchanged between the Parties on or after the Execution Date under this Agreement will be subject to the terms of this ARTICLE 11.

11.3. **Authorized Disclosure**. Except as expressly provided otherwise in this Agreement, a Receiving Party or its Affiliates may use and disclose to Third Parties Confidential Information of the Disclosing Party as follows: (i) solely in connection with the performance of its obligations or exercise of rights granted or reserved in this Agreement under confidentiality provisions no less restrictive than those in this Agreement, *provided,* that Confidential Information may be disclosed by a Receiving Party to a governmental entity or agency without requiring such entity or agency to enter into a confidentiality agreement; (ii) to the extent reasonably necessary to file or prosecute patent, copyright and trademark applications (subject to Section 11.4 below), complying with applicable governmental regulations, obtaining Approvals, conducting Pre-Clinical Studies or Clinical Studies, marketing the Product, or as otherwise required by applicable law, regulation, rule or legal process (including the rules of the SEC and any stock exchange); *provided, however*, that if a Receiving Party or any of its Affiliates is required by law or regulation to make any such disclosure of a Disclosing Party's Confidential Information it will, except where impracticable for necessary disclosures, give reasonable advance notice to the Disclosing Party of such disclosure requirement and will use its reasonable efforts to secure confidential treatment of such Confidential Information required to be disclosed; (iii) in communication with actual or potential lenders, investors, merger partners, acquirers, Sublicensees, consultants, or professional advisors on a need-to-know basis, in each case under confidentiality provisions no less restrictive than those of this Agreement; (iv) to the extent such disclosure is required to comply with existing expressly stated contractual obligations owed to such Party's or its Affiliates' licensor with respect to any intellectual property licensed to the other Party under this Agreement; (v) subject to the terms of any protective order the Disclosing Party is using to protect its own Confidential Information, to prosecute or defend litigation as permitted by this Agreement, or (vi) as mutually agreed to in writing by the Parties.

11.4. **Licensed Know-How**. Isis acknowledges AstraZeneca's interest in maintaining the confidentiality of Confidential Information that is Isis Know-How and specific to an Exclusive Target, Product and will take reasonable steps to protect such Confidential Information from unauthorized use or disclosure.

11.5. **Press Release; Publications; Disclosure of Agreement**.

11.5.1. **Public Announcements – Generally**. On or promptly after each of the Execution Date and the Effective Date, the Parties will issue a joint press release announcing the existence of this Agreement in a form and substance agreed to in writing by the Parties. Except to the extent required to comply with Applicable Law, regulation, rule or legal process or as otherwise permitted in accordance with this Section 11.5, each Party agrees not to issue any other press release or other public statement disclosing other information relating to this Agreement or the terms of this Agreement or the transactions contemplated hereby without the prior written consent of the other Party, which consent will not be unreasonably withheld or delayed.

11.5.2. **Use of Name**. Except as set forth in Section 11.5.8, neither Party will use the other Party's name in a press release or other publication without first obtaining the prior consent of the Party to be named.

11.5.3. **Notice of Significant Events**. Each Party will promptly notify (and where it has advance warning provide advance notice to) the other of any significant event related to a Product in a Major Market (including any data or regulatory advice or approval or reimbursement decision) so that the Parties may analyze the need to or desirability of publicly disclosing or reporting such event. Notwithstanding Section 11.5.1 above, any press release or other similar public communication (i) by Isis related to a Product will be submitted to AstraZeneca for review and approval at least three Business Days in advance of such proposed public disclosure, which approval will not be unreasonably withheld or delayed; and (ii) by AstraZeneca related to a Product's efficacy or safety data and/or results, regulatory advice or an approval or reimbursement decision in a Major Market, will be submitted to Isis for review (but shall not be subject to approval by Isis) at least three Business Days in advance of such proposed public disclosure.

11.5.4. **Disclosure of Information Related to Products**. The Party that has primary control of a Product (i.e., as of the Effective Date, Isis, with respect to all Products for which AstraZeneca has not exercised its Collaboration Program License Right, and with respect to any Licensed Program, AstraZeneca) has the sole right, consistent with its practice with its other products, to issue press releases or other similar public communications to disclose the progress and results regarding such Product to the public in order to satisfy its disclosure obligations under Applicable Law or to remain consistent with its normal public disclosure practices (but for clarity, in connection with the Collaboration Programs, such disclosure would not involve disclosing a Collaboration Target or a Development Candidate until such Development Candidate is in a Phase 1 Study); *provided, that* any proposed press release or other similar public communication by such controlling Party disclosing regulatory discussions, the efficacy or safety data or results related to the Product, (i) such controlling Party will submit such proposed communication to the non-controlling Party for review at least two Business Days in advance of such proposed public disclosure, (ii) the non-controlling Party will have the right to review and recommend changes to such communication, and (iii) the controlling Party will in good faith consider any changes that are timely recommended by the non-controlling Party. In addition, if at any time during such two Business Day review period, the other Party informs such Party that its proposed public disclosure discloses inventions made by either Party in the course of the Research or Development under this Agreement that have not yet been protected through the filing of a patent application, or the public disclosure could be expected to have a material adverse effect on any Patent Rights or Know-How solely owned or Controlled by such other Party, then such Party will either (x) delay such proposed publication for a period of time reasonably necessary to permit the timely preparation and first filing of patent application(s) on the information involved, or (y) to the extent permitted by Applicable Law, remove the identified information prior to disclosure. While the Parties acknowledge that it may be interpreted that there is overlap between this Section 11.5.4 and Section 11.5.5, for clarity, the Parties intend for this Section 11.5.4 to address public disclosures that are not primarily of a scientific or scholarly nature (which are meant to be disclosed in accordance with Section 11.5.5 below) but rather this Section 11.5.4 is designed to address more urgent disclosures required under Applicable Law or to provide investors with material information regarding Products or this Agreement in a timely manner so that they may make informed investment decisions in Isis' or AstraZeneca's stock.

11.5.5. **Scientific or Clinical Presentations**. Regarding any proposed scientific publications or public presentations related to summaries of results from the Collaboration Plans or any Clinical Studies generated by Isis or AstraZeneca for a Product, the Parties acknowledge that scientific lead time is a key element of the value of a Product under this Agreement and further agree to use Commercially Reasonable Efforts to control public scientific disclosures of the results of the Research or Development activities under this Agreement to prevent any potential adverse effect of any premature public disclosure of such results, for example, without limitation, intellectual property protection, competitive intelligence, prejudicing the optimal presentation at major meetings. For clarity, in connection with the Collaboration Programs, such disclosure would not involve disclosing a Collaboration Target or a Development Candidate until such Development Candidate is in a Phase 1 Study, unless agreed otherwise by the Parties. The IP Managers will establish a procedure for publication review and each Party will first submit to the other Party's IP Manger an early draft of all such publications or presentations, whether they are to be presented orally or in written form, at least 30 days prior to submission for publication including to facilitate the publication of any summaries of Clinical Studies data and results as required on the clinical trial registry of each respective Party. Each Party will review such proposed publication in order to avoid the unauthorized disclosure of a Party's Confidential Information and to preserve the patentability of inventions arising from the Collaboration Plans. If, during such 30 day period, the other Party informs such Party that its proposed publication contains Confidential Information of the other Party, then such Party will delete such Confidential Information from its proposed publication. In addition, if at any time during such 30 day period, the other Party informs such Party that its proposed publication discloses inventions made by either Party in the course of the Research or Development under this Agreement that have not yet been protected through the filing of a patent application, or the public disclosure of such proposed publication could be expected to have a material adverse effect on any Patent Rights or Know-How solely owned or Controlled by such other Party, then such Party will either (i) delay such proposed publication for up to 60 days from the date the other Party informed such Party of its objection to the proposed publication, to permit the timely preparation and first filing of patent application(s) on the information involved or (ii) remove the identified disclosures prior to publication.

11.5.6. **SEC Filings**. Each Party will give the other Party a reasonable opportunity to review all material filings with the SEC describing the terms of this Agreement prior to submission of such filings, and will give due consideration to any reasonable comments by the non-filing Party relating to such filing.

11.5.7. **Subsequent Disclosure**. Notwithstanding the foregoing, to the extent information regarding this Agreement or the Product has already been publicly disclosed, either Party (or its Affiliates) may subsequently disclose the same information to the public without the consent of the other Party.

11.5.8. **Acknowledgment**. Each Party will acknowledge in any press release, public presentation or publication regarding the collaboration or the Product, the other Party's role in discovering and developing the Product or Discontinued Product, as applicable, that the Product is under license from Isis and otherwise acknowledge the contributions from the other Party, and each Party's stock ticker symbol (e.g., Nasdaq: ISIS; NYSE: AZN). Isis may include the Product (and identify AstraZeneca as its partner for the Product) in Isis' drug pipeline.

ARTICLE 12.
MISCELLANEOUS

12.1. Dispute Resolution.

12.1.1. Resolution by Senior Representatives. The Parties will seek to settle amicably any and all disputes, controversies or claims arising out of or in connection with this Agreement. Any dispute between the Parties, including any a failure to reach consensus on a matter within the JSC's decision-making authority will be promptly presented to the Executive Vice President of AstraZeneca's Innovative Medicines and Early Development (IMED) Biotech Unit and the Chief Operating Officer of Isis (the "***Senior Representatives***"), or their respective designees, for resolution. Such Senior Representatives, or their respective designees, will meet in-person or by teleconference as soon as reasonably possible thereafter, and use their good faith efforts to mutually agree upon the resolution of the dispute, controversy or claim.

12.1.2. Request for Arbitration. If after negotiating in good faith pursuant to Section 12.1.1, the Parties fail after good faith discussions undertaken within reasonable promptness, to reach an amicable agreement within 90 days, then either Party may upon written notice to the other submit to binding arbitration pursuant to Section 12.1.4(a) below; provided that any dispute within the JSC's decision-making authority whether or not resolved by the Senior Representatives will not be subject to arbitration. No statements made by either Party during such discussions will be used by the other Party or admissible in arbitration or any other subsequent proceeding for resolving the dispute.

12.1.3. Expert Determination for [***] Development Candidate.

(a) If the JSC fails to designate a [***] Development Candidate but Isis believes that a Lead Compound from the [***] Program satisfies the [***] Success Criteria such that AstraZeneca is not entitled to the benefit of the [***] described in Section 6.6.1 and such dispute (the "[***] ***Dispute***") is not resolved by the Senior Representatives in accordance with Section 12.1.1, either Party may initiate an expedited dispute resolution by Expert (as defined below) to resolve the matter by serving written notice thereof on the other Party (a "***Referral Notice***").

(b) Within [***] following any Referral Notice, the Parties will engage the services of an independent scientist with no less than 10 years' experience in drug discovery (the "***Expert***"), *provided that* if the Parties are unable to agree on who will be appointed as expert within such period, either Party may request the International Chamber of Commerce ("***ICC***") to appoint the Expert.

(c) The Expert will be directed to review the Lead Candidate Data Package provided to the JSC and to determine, within [***] of being provided such package, whether any Lead Compound from the [***] Program satisfies the [***] Success Criteria.

(d) The Expert will act as an expert and not as an arbitrator and the decision of the Expert shall be final and binding on both Parties. Any legal dispute regarding the scope, legal effect or validity of the determination shall be subject to the arbitration procedures set out in Section 12.1.4.

(e) Each Party shall bear its own counsel fees, costs, and disbursements arising out of the [***] Dispute. The costs of any Third Party expert engaged under this Section 12.1.3 will be paid by the Party against whose position the Expert's determination is made.

12.1.4. Arbitration.

(a) Subject to Section 12.2 and Section 12.1.3, any dispute, claim or controversy arising from or related in any way to this Agreement or the interpretation, application, breach, termination or validity thereof, including any claim of inducement of this Agreement by fraud or otherwise, not resolved under the provisions of Section 12.1.1, will be resolved by final and binding arbitration conducted in accordance with the terms of this Section 12.1.4(a). The arbitration will be held in New York, New York, USA according to Rules of Arbitration of the ICC. The arbitration will be conducted by a panel of three arbitrators with significant experience in the pharmaceutical industry, unless otherwise agreed by the Parties, appointed in accordance with applicable ICC rules. Any arbitration herewith will be conducted in the English language to the maximum extent possible. The arbitrators will render a written decision no later than six months following the selection of the arbitrators, including a basis for any damages awarded and a statement of how the damages were calculated. Any award will be promptly paid in U.S. dollars free of any tax, deduction or offset. Each Party agrees to abide by the award rendered in any arbitration conducted pursuant to this Section 12.1.4. With respect to money damages, nothing contained herein will be construed to permit the arbitrator or any court or any other forum to award punitive or exemplary damages, except in the case of breach of ARTICLE 11. By entering into this agreement to arbitrate, the Parties expressly waive any claim for punitive or exemplary damages, except in the case of breach of ARTICLE 11. Each Party will pay its legal fees and costs related to the arbitration (including witness and expert fees). Judgment on the award so rendered will be final and may be entered in any court having jurisdiction thereof.

(b) EACH PARTY HERETO WAIVES ITS RIGHT TO TRIAL OF ANY ISSUE BY JURY. EACH PARTY HERETO WAIVES ANY CLAIM FOR ATTORNEYS' FEES AND COSTS AND PREJUDGMENT INTEREST FROM THE OTHER.

12.1.5. **Court Actions**. Nothing contained in this Agreement will deny either Party the right to seek injunctive or other equitable relief from a court of competent jurisdiction in the context of a *bona fide* emergency or prospective irreparable harm, and such an action may be filed and maintained notwithstanding any ongoing dispute resolution discussions or arbitration proceeding. In addition, either Party may bring an action in any court of competent jurisdiction to resolve disputes pertaining to the validity, construction, scope, enforceability, infringement or other violations of patents or other proprietary or intellectual property rights, and no such claim will be subject to arbitration pursuant to Section 12.1.4.

12.2. **Governing Law; Jurisdiction; Equitable Relief; Losses; Remedies**.

12.2.1. This Agreement will be governed by and construed and enforced in accordance with the laws of the State of New York, USA, without reference to any rules of conflicts of laws. For clarification, any dispute relating to the scope, validity, enforceability or infringement of any Patents will be governed by and construed and enforced in accordance with the patent laws of the applicable jurisdiction.

12.2.2. Each Party acknowledges and agrees that the restrictions set forth in Section 3.1 of this Agreement are reasonable and necessary to protect the legitimate interests of the other Party and that the other Party would not have entered into this Agreement in the absence of such restrictions, and that any breach or threatened breach of any of these provisions will probably result in irreparable injury to the other Party for which there will be no adequate remedy at law. In the event of a breach or threatened breach of any such provision, each Party will be authorized and entitled to obtain from any court of competent jurisdiction equitable relief, whether preliminary or permanent, specific performance and an equitable accounting of all earnings, profits and other benefits arising from such breach, which rights will be cumulative and in addition to any other rights or remedies to which such Party may be entitled in law or equity. Each Party agrees to waive any requirement that the other Party (a) post a bond or other security as a condition for obtaining any such relief, and (b) show irreparable harm, balancing of harms, consideration of the public interest or inadequacy of monetary damages as a remedy. Nothing in this Section 12.2.2 is intended, or should be construed, to limit a Party's rights to equitable relief or any other remedy for a breach of any other provision of this Agreement. Except for (i) the offsets and credits explicitly set forth in Section 6.6, Section 6.8.3(b), Section 6.8.4(b), Section 6.11 and Section 10.3.3(b)(ii), (ii) any amount awarded to be paid by one Party to the other by the panel of arbitrators in a final and binding arbitration proceeding adjudicated under Section 12.1.4(a), and (iii) any offset of undisputed but unpaid amounts under this Agreement, neither Party will have the right to set off any amount it is owed or believes it is owed against payments due or payable to the other Party under this Agreement.

12.2.3. Neither Party will be entitled to recover any Losses relating to any matter arising under one provision of this Agreement to the extent that such Party has already recovered Losses with respect to such matter pursuant to other provisions of this Agreement (including recoveries under Section 9.1 or Section 9.2, and the offsets under Section 6.8.4(b)).

12.2.4. Any provisions of this Agreement that describe a payment as non-refundable shall be without prejudice to either Party's right to bring a claim for breach of this Agreement, misrepresentation or any other claim permissible under Applicable Laws, including seeking recovery of payments made and damages for loss.

12.3. **Assignment and Successors**. Neither this Agreement nor any obligation of a Party hereunder may be assigned by either Party without the consent of the other, which will not be unreasonably withheld, delayed or conditioned, except that each Party may assign this Agreement and the rights, obligations and interests of such Party, in whole or in part (including with respect to a Licensed Program), without the other Party's consent, to any of its Affiliates, to any purchaser of all or substantially all of its assets to which this Agreement or relevant part relates or to any successor corporation resulting from any merger, consolidation, share exchange or other similar transaction; *provided*, if a Party transfers or assigns this Agreement (or any part hereof) to [***] described in this Agreement, then such transferring Party (or such Affiliate) ("***Transferring Party***"), will [***] due that the Transferring Party is obligated to pay to the non-transferring Party ("***Non-Transferring Party***") under ARTICLE 6 for the [***] such that the Non-Transferring Party receives [***]. In addition, Isis may assign or transfer its rights to receive payments under this Agreement (but no liabilities), without AstraZeneca's consent, to an Affiliate or to a Third Party in connection with a payment factoring transaction; *provided, however*, that Isis will provide AstraZeneca advance notice of any such proposed payment factoring transaction giving AstraZeneca a reasonable opportunity to provides comments (which Isis will consider in good faith); [***]. Any purported assignment or transfer made in contravention of this Section 12.3 will be null and void.

To the extent the Non-Transferring Party utilizes a [***] in any year, the Non-Transferring Party will [***] the Transferring Party [***] or [***]. To assist the Transferring Party in determining when [***] pursuant to the foregoing sentence, beginning with the first Annual tax return for the year in which the Transferring Party [***] payment under this Section 12.3, and each year thereafter (including, for clarity, all years in which the Non-Transferring Party [***] or [***]), the Non-Transferring Party will provide the Transferring Party with the Non-Transferring Party s' Annual tax returns (federal and state) and, in years in which the Non-Transferring Party utilizes the [***], supporting documentation for such [***].

12.4. Change of Control Event Involving AstraZeneca.

12.4.1. ***Change of Control Event – Initial Meeting***. AstraZeneca will provide written notice to Isis within [***] following the closing of a Change of Control Event involving AstraZeneca, and such notice will identify the Third Party acquiring company (the "***AstraZeneca-Acquirer***") and the contact information of the person at the AstraZeneca-Acquirer with whom Isis will work to schedule meetings between the AstraZeneca-Acquirer and Isis. Within [***] following the closing of such Change of Control Event, the AstraZeneca-Acquirer will meet with Isis at a mutually agreed date and time at Isis' facilities. Within [***] before the date of such meeting, the AstraZeneca-Acquirer will provide Isis a detailed written plan showing how the AstraZeneca-Acquirer will meet AstraZeneca's obligations under this Agreement.

12.4.2. ***Change of Control Event – Right of First Negotiation***. In the case of a Change of Control Event involving AstraZeneca, if within [***] of such Change of Control Event the AstraZeneca-Acquirer is approached by a Third Party regarding, or elects to offer a Third Party, the opportunity to acquire (by license or otherwise) rights to Develop and Commercialize a Product in [***], then the AstraZeneca-Acquirer will provide written notice to Isis together with any [***] after the date AstraZeneca exercised the applicable Collaboration Program License Right (to the extent not previously provided). Isis will then have [***] to notify the AstraZeneca-Acquirer in writing whether Isis is interested in negotiating with the AstraZeneca-Acquirer to obtain such rights to Develop and Commercialize such Product and, upon such written notice, the AstraZeneca-Acquirer and Isis will negotiate in good faith (including at least [***]) to determine mutually acceptable terms and conditions for conveying such rights to Isis. If Isis does not notify the AstraZeneca-Acquirer within such [***] period that Isis is interested in negotiating with the AstraZeneca-Acquirer to obtain the rights to Develop and Commercialize such Product, or if Isis and the AstraZeneca-Acquirer are unable to reach agreement within [***] after the AstraZeneca-Acquirer's receipt of such notice from Isis, then the AstraZeneca-Acquirer will be free to grant rights to Develop and Commercialize such Product alone or with Third Parties, *provided that* any such grant of rights made by AstraZeneca to a Third Party within [***] of the last offer to Isis shall be on terms [***].

12.4.3. ***Change of Control Event – Effect on Carryover Provisions***. In the case of a Change of Control Event involving AstraZeneca, if, within [***] after the closing of such Change of Control Event, Isis delivers written notice to AstraZeneca that Isis would like to activate the provisions of this Section 12.4.3 (an "***Activation Notice***"), then the following will apply: (i) AstraZeneca's right under Section 1.10.3(c) to restore and designate a former High Interest Target to this Agreement as a Collaboration Target and AstraZeneca's Carryover Option under Section 1.14.3 will terminate, (ii) any limitations, restrictions or obligations Isis had under Section 1.10.3(c) or related to AstraZeneca's Carryover Option under Section 1.14.3 will terminate, and (iii) any [***] or [***] (as applicable) restriction on AstraZeneca's and its Affiliate's right to Exploit ASOs under Section 1.10.3(b) and Section 1.14.3(c) will terminate.

12.5. Antitrust Filing.

12.5.1. Each Party agrees to prepare and make or cause to be prepared and made appropriate filings under the HSR Act and any other antitrust requirements relating to this Agreement and the transactions contemplated under this Agreement within 10 Business Days after the Execution Date. Each of the Parties agrees to cooperate in the antitrust clearance process, including by furnishing to the other Party such necessary information and reasonable assistance as the other Party may request in connection with its preparation of any filing or submission that is necessary under the HSR Act and other antitrust requirements, and to furnish promptly with the United States Federal Trade Commission ("***FTC***"), the Antitrust Division of the United States Department of Justice ("***DOJ***") and any other antitrust authority, any information reasonably requested by them in connection with such filings. Each Party shall furnish copies (subject to reasonable redactions for privilege or confidentiality concerns) of, and shall otherwise keep the other Party apprised of the status of any communications with, and any inquiries or requests for additional information from, the FTC, DOJ and any other antitrust authority, and shall comply promptly with any such inquiry or request. Each Party shall give the other Party the opportunity to review in advance, and shall consider in good faith the other Party's reasonable comments in connection with any proposed filing or communication with the FTC, DOJ or any other antitrust authority. Each Party shall consult with the other Party, to the extent practicable, in advance of participating in any substantive meeting or discussion with the FTC, the DOJ or any other antitrust authority with respect to any filings, investigation or inquiry and, to the extent permitted by such antitrust authority, give the other Party to the opportunity to attend and participate thereat. Neither Party shall withdraw its filing under the HSR Act or agree to delay the Effective Date without the prior written consent of the other Party. The Parties' rights and obligations hereunder apply only in so far as they relate to the Agreement and to the transactions contemplated under the Agreement.

12.5.2. Each Party shall use commercially reasonable efforts to obtain the expiration or early termination of the HSR Act and any other clearance required under other antitrust requirements relating to the Agreement and the transactions contemplated under the Agreement. Commercially reasonable efforts as used in this Section 12.5.2 will not include proposing, negotiating, committing to and effecting, by consent decree, hold separate order, or otherwise, (a) the sale, divestiture, disposition, licensing or sublicensing of any of a Party's or its Affiliates' assets, properties or businesses, (b) behavioral limitations, conduct restrictions or commitments with respect to such assets, properties or business, or of any of the rights or obligations of a Party under this Agreement, or (c) defending through litigation any claim asserted in court by any party that would restrain, prevent or delay the Effective Date.

(a) Other than the provisions of Section 10.1, ARTICLE 11 and ARTICLE 12 which shall apply as of the Execution Date, the rights and obligations of the Parties under this Agreement will not become effective until the waiting period under the HSR Act has been terminated or expired, or any other timeline required by another antitrust authority and there is no proceeding, order, injunction or judgment relating thereto, pending before any governmental authority in which it is sought to restrain or prohibit the transaction(s) contemplated hereby. Upon the occurrence of the Effective Date, all other provisions of this Agreement shall become effective automatically without the need for further action by the Parties.

12.5.3. Each Party shall be responsible for its fees and costs associated with the preparation and submission of any required notification and report form under the HSR Act (or to any other antitrust authority), and the provision of any supplemental information to the FTC, DOJ or other antitrust authority, including any legal fees incurred by such Party in connection with such Party's obligations pursuant to this Section 12.5.

12.6. **Force Majeure**. No Party will be held responsible to the other Party nor be deemed to be in default under, or in breach of any provision of, this Agreement for failure or delay in performing any obligation of this Agreement when such failure or delay is due to force majeure, and without the fault or negligence of the Party so failing or delaying. For purposes of this Agreement, force majeure means a cause beyond the reasonable control of a Party, which may include acts of God; acts, regulations, or laws of any government; war; terrorism; civil commotion; fire, flood, earthquake, tornado, tsunami, explosion or storm; pandemic; epidemic and failure of public utilities or common carriers. In such event the Party so failing or delaying 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 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 a maximum of 90 days, after which time the Parties will negotiate in good faith any modifications of the terms of this Agreement that may be necessary to arrive at an equitable solution, unless the Party giving such notice has set out a reasonable timeframe and plan to resolve the effects of such force majeure and executes such plan within such timeframe. To the extent possible, each Party will use reasonable efforts to minimize the duration of any force majeure.

12.7. **Notices**. Any notice or request required or permitted to be given under or in connection with this Agreement will be deemed to have been sufficiently given if in writing and personally delivered or sent by facsimile transmission (receipt verified) or internationally recognized overnight express courier service (signature required), prepaid, to the Party for which such notice is intended, at the address set forth for such Party below:

If to Isis, addressed to:	Isis Pharmaceuticals, Inc. 2855 Gazelle Court Carlsbad, CA 92010 Attention: Chief Operating Officer Fax: 760-918-3592
with a copy to:	Isis Pharmaceuticals, Inc. 2855 Gazelle Court Carlsbad, CA 92010 Attention: General Counsel Fax: 760-268-4922
If to AstraZeneca, addressed to:	AstraZeneca AB SE-431 83 Molndal Sweden Attention: Legal Department Fax: +46 31 7763871
with a copy to:	AstraZeneca AB Scientific Partnering and Alliances SE-431 83 Molndal Sweden Attention: Business Development Director, CVMD Fax: +46 31 7763701

or to such other address for such Party as it will have specified by like notice to the other Party; *provided that* notices of a change of address will be effective only upon receipt thereof. If delivered personally or by facsimile transmission, the date of delivery will be deemed to be the date on which such notice or request was given. If sent by internationally recognized overnight express courier service, the date of delivery will be deemed to be the second Business Day after such notice or request was deposited with such service. It is understood and agreed that this Section is not intended to govern the day to day business communications necessary between the parties in performing their duties, in due course, under the terms of this Agreement.

12.8. **Export Clause**. Each Party acknowledges that the laws and regulations of the United States restrict the export and re-export of commodities and technical data of United States origin. Each Party agrees that it will not export or re-export restricted commodities or the technical data of the other Party in any form without the appropriate United States and foreign government licenses.

12.9. **Waiver**. Neither Party may waive or release any of its rights or interests in this Agreement except in writing. The failure of either Party to assert a right hereunder or to insist upon compliance with any term or condition of this Agreement will not constitute a waiver of that right or excuse a similar subsequent failure to perform any such term or condition. No waiver by either Party of any condition or term in any one or more instances will be construed as a continuing waiver or subsequent waiver of such condition or term or of another condition or term.

12.10. **Severability**. If any provision of this Agreement is held to be illegal, invalid or unenforceable by a court of competent jurisdiction, such adjudication will not affect or impair, in whole or in part, the validity, enforceability, or legality of any remaining portions of this Agreement. All remaining portions will remain in full force and effect as if the original Agreement had been executed without the invalidated, unenforceable or illegal part.

12.11. **Entire Agreement; Modifications**. This Agreement (including the attached Appendices, Exhibit and Schedules) sets forth and constitutes the entire agreement and understanding between the Parties with respect to the subject matter hereof, and all prior agreements, understanding, promises and representations, whether written or oral, with respect thereto are superseded hereby. Each Party confirms that it is not relying on any representations or warranties of the other Party except as specifically set forth herein. No amendment, modification, release or discharge will be binding upon the Parties unless in writing and duly executed by authorized representatives of both Parties.

12.12. **Relationship of the Parties**. It is expressly agreed that the Parties will be independent contractors of one another and that the relationship between the Parties will not constitute a partnership, joint venture or agency.

12.13. **Interpretation**. Except as otherwise explicitly specified to the contrary, (a) references to a section, appendix, exhibit or schedule means a section of, or appendix, schedule or exhibit to this Agreement, unless another agreement is specified, (b) the word “including” (in its various forms) means “including without limitation,” (c) the words “will” and “shall” have the same meaning, (d) references to a particular statute or regulation include all rules and regulations thereunder and any predecessor or successor statute, rules or regulation, in each case as amended or otherwise modified from time to time, (e) references to a particular Person include such Person’s successors and assigns to the extent not prohibited by this Agreement, (f) unless otherwise specified, “$” is in reference to United States dollars, (g) the headings contained in this Agreement, in any exhibit or schedule to this Agreement and in the table of contents to this Agreement are for convenience only and will not in any way affect the construction of or be taken into consideration in interpreting this Agreement; and (h) or the context otherwise requires, the word “or” is used in the inclusive sense (and/or).

12.14. **Books and Records**. Any books and records to be maintained under this Agreement by a Party or its Affiliates or Sublicensees will be maintained in accordance with generally accepted accounting principles, or in the case of non-United States sales, other applicable accounting standards, consistently applied.

12.15. **Further Actions**. Each Party will execute, acknowledge and deliver such further instruments, and do all such other acts, as may be necessary or appropriate in order to carry out the expressly stated purposes and the clear intent of this Agreement.

12.16. **Construction of Agreement**. The terms and provisions of this Agreement represent the results of negotiations between the Parties and their representatives, each of which has been represented by counsel of its own choosing, and neither of which has acted under duress or compulsion, whether legal, economic or otherwise. Accordingly, the terms and provisions of this Agreement will be interpreted and construed in accordance with their usual and customary meanings, and each of the Parties hereto hereby waives the application in connection with the interpretation and construction of this Agreement of any rule of law to the effect that ambiguous or conflicting terms or provisions contained in this Agreement will be interpreted or construed against the Party whose attorney prepared the executed draft or any earlier draft of this Agreement.

12.17. **Supremacy**. In the event of any express conflict or inconsistency between this Agreement and any Schedule, Exhibit or Appendix hereto, the terms of this Agreement will apply. The Parties understand and agree that the Schedules and Appendices hereto are not intended to be the final and complete embodiment of any terms or provisions of this Agreement, and are to be updated from time to time during the Agreement Term, as appropriate and in accordance with the provisions of this Agreement.

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

12.19. **Compliance with Laws**. Each Party will, and will ensure that its Affiliates and Sublicensees will, comply with all relevant laws and regulations in exercising its rights and fulfilling its obligations under this Agreement.

[SIGNATURE PAGE FOLLOWS]

* - * - * - *

IN WITNESS WHEREOF, the Parties have caused this Agreement to be executed by their representatives thereunto duly authorized as of the Execution Date.

ASTRAZENECA AB (publ.)

By: /s/ Marcus Schindler

Name: Marcus Schindler

Title: Vice President, Head of CVMD IMED

IN WITNESS WHEREOF, the Parties have caused this Agreement to be executed by their representatives thereunto duly authorized as of the Execution Date.

ISIS PHARMACEUTICALS, INC.

By: /s/ B. Lynne Parshall
Name: B. Lynne Parshall
Title: Chief Operating Officer

List of Appendices, Schedules and Exhibit

APPENDIX 1 – Definitions

APPENDIX 2 – Isis' Lead Candidate Checklist

APPENDIX 3 – Isis In-License Agreements

APPENDIX 4 – Isis Core Technology Patents

APPENDIX 5 – Isis Manufacturing and Analytical Patents

APPENDIX 6 – Isis Product-Specific Patents

APPENDIX 7 – Prior Agreements

SCHEDULE 1.2.1 – Preliminary Core Research Plan

SCHEDULE 1.2.2 – Preliminary Disease Research Plan

SCHEDULE 1.8 – Criteria and Activities to Achieve Target Sanction

SCHEDULE 1.13.1(a) - Draft [***] Drug Discovery Plan

SCHEDULE 1.13.1(b) – Criteria and Activities for Development Candidate Designation

SCHEDULE 1.13.2 – Isis' Development Pipeline as of the Execution Date

SCHEDULE 2.1.1 – JSC Governance

SCHEDULE 2.2 – Alliance Management Activities

SCHEDULE 2.7 – Work Plan Report

SCHEDULE 2.8 – Bioethics Policy

SCHEDULE 5.1.1 – Specific Performance Milestone Events

SCHEDULE 5.5.1 – Isis' Fully Absorbed Cost of Goods Methodology

EXHIBIT 1 – AstraZeneca 5R Framework

APPENDIX 1

DEFINITIONS

For purposes of this Agreement, the following capitalized terms will have the following meanings:

"$" means the lawful currency of the United States.

"***Acceptance of Filing***" means, with respect to an NDA, MAA, JNDA, CNDA or BDRP filed for a Product, (a) in the United States, the receipt of written notice from the FDA in accordance with 21 C.F.R. §314.101(a)(2) that such NDA is officially "*filed*," (b) in the European Union, receipt by AstraZeneca, its Affiliate or Sublicensee of written notice of validation by the EMA of such MAA under the centralized European procedure in accordance with any feedback received from European Regulatory Authorities; *provided that* if the centralized filing procedure is not used, then Acceptance of Filing will be determined upon the validation of such MAA by the applicable Regulatory Authority in a Major Market in the EU, (c) in Japan, receipt by AstraZeneca, its Affiliate or Sublicensee of written notice of acceptance of filing of such JNDA from the Koseisho (i.e., the Japanese Ministry of Health and Welfare, or any successor agency thereto), (c) in China, receipt by AstraZeneca, its Affiliate, or Sublicensee, of written notice of acceptance of filing of such CNDA from the relevant regulatory authority in China (i.e., the China Food and Drug Administration or the provincial-level food and drug regulatory authority, as law and regulation may require, or any successor agencies thereto), and (d) in Brazil, the receipt by AstraZeneca, its Affiliate or Sublicensee of written notice from the Brazilian National Health Surveillance Agency (ANVISA) (or any successor agencies thereto) confirming that the BDRP has been received.

"***Acquiring Party***" has the meaning set forth in Section 3.3.1.

"***Activation Notice***" has the meaning set forth in Section 12.4.3.

"***Additional Core IP***" has the meaning set forth in Section 6.8.3(a).

"***Additional Product-Specific Patents***" has the meaning set forth in Section 6.8.2(b)(1).

"***Affiliate***" of an entity means any corporation, firm, partnership or other entity which directly or indirectly through one or more intermediaries controls, is controlled by or is under common control with a Party to this Agreement at the applicable time during the Term. An entity will be deemed to control another entity if it (i) owns, directly or indirectly, at least 50% of the outstanding voting securities or capital stock (or such lesser percentage which is the maximum allowed to be owned by a foreign corporation in a particular jurisdiction) of such other entity, or has other comparable ownership interest with respect to any entity other than a corporation; or (ii) has the power, whether pursuant to contract, ownership of securities or otherwise, to direct the management and policies of the entity.

"***Agreement***" has the meaning set forth in the Preamble of this Agreement.

"***Agreement Term***" has the meaning set forth in Section 10.1.

"***Alliance Manager"*** has the meaning set forth in Section 2.2.

"***Annual***" or "***Annually***" means the period covering a Calendar Year or occurring once per Calendar Year, as the context requires.

"***Anti-Corruption Laws"*** means the U.S. Foreign Corrupt Practices Act, as amended, the UK Bribery Act 2010, as amended, and any other applicable anti-corruption laws and laws for the prevention of fraud, racketeering, money laundering or terrorism.

"***API***" means the bulk active pharmaceutical ingredient manufactured in accordance with cGMP (unless expressly stated otherwise) for a Product. The quantity of API will be the as-is gross mass of the API after lyophilization (i.e., including such amounts of water, impurities, salt, heavy, metals, etc. within the limits set forth in the API specifications) and before release, retention, stability or characterization samples are removed (if needed).

"***Applicable Law***" or "***Law***" means all applicable laws, statutes, rules, regulations and other pronouncements having the effect of law of any federal, national, multinational, state, provincial, county, city or other political subdivision, agency or other body, domestic or foreign, including any applicable rules, regulations, guidelines, or other requirements of the Regulatory Authorities that may be in effect from time to time.

"***Approval***" means (i) with respect to a Product in the EU, approval from the applicable Regulatory Authority in at least one member state in the EU sufficient for the manufacture, distribution, use, marketing and sale of such Product and either (x) pricing approval in such jurisdiction in accordance with Applicable Laws has been obtained, or (y) the first commercial sale of a Product in the EU has occurred; and (ii) with respect to a Product in any regulatory jurisdiction other than the EU, approval sufficient for the manufacture, distribution, use, marketing and sale of such Product in such jurisdiction in accordance with Applicable Laws.

"***Approval by AstraZeneca's Internal Decision Body to Initiate a Phase 3 Study***" means, with respect to a Product, that the internal governing body within AstraZeneca responsible for authorizing the commencement of a Phase 3 Study, has granted such authorization to commence such a Phase 3 Study.

"***ASO***" means a single-stranded or double-stranded oligonucleotide compound, or analog, variant, mimic, or mimetic thereof, having a sequence that is between six and one hundred nucleotides long and is designed to hybridize to a nucleic acid transcript via the binding, partially or wholly, of such compound to the nucleic acid transcript.

"***AstraZeneca***" has the meaning set forth in the Preamble of this Agreement.

"***AstraZeneca-Acquirer***" has the meaning set forth in Section 12.4.

"***AstraZeneca Background Intellectual Property***" means any Know-How and Patent Rights that: (i) were Controlled by AstraZeneca prior to the Effective Date; and/or (ii) are Controlled by AstraZeneca on or after the Effective Date that were not created or acquired in connection with performance of any Collaboration Plan and/or in connection with the Exploitation of a Product, which Patents and Know-How are necessary to Develop, Manufacture or Commercialize a Product in the Field.

"***AstraZeneca Collaboration Intellectual Property***" means any Know-How and Patent Rights that were discovered, developed, invented or created in connection with the performance of any Collaboration Plan by or on behalf of AstraZeneca, including AstraZeneca's interest in any Jointly-Owned Collaboration Technology.

"***AstraZeneca Conducted Activities***" means, under a Collaboration Plan, any and all Research, pre-clinical and/or clinical activities that are not Isis Conducted Activities.

"***AstraZeneca Field***" means [***].

"***AstraZeneca Full Royalty***" has the meaning set forth in Section 6.7.1.

"***AstraZeneca Indemnitees***" has the meaning set forth in Section 9.2.

"***AstraZeneca Know-How***" means any Know-How owned, used, developed by, or licensed to AstraZeneca or its Affiliates (other than from Isis pursuant to this Agreement), in connection with AstraZeneca's performance of its obligations under this Agreement, in each case to the extent Controlled by AstraZeneca or its Affiliates at any time during the Agreement Term that is necessary to Develop, Manufacture or Commercialize a Product in the Field and such Know-How does not constitute AstraZeneca Background Intellectual Property.

"***AstraZeneca Patents***" means any Patent Rights owned, used, developed by, or licensed to AstraZeneca or its Affiliates (other than from Isis pursuant to this Agreement) that are invented by AstraZeneca or its Affiliates or licensors in connection with AstraZeneca's performance of its obligations under this Agreement, in each case to the extent Controlled by AstraZeneca or its Affiliates at any time during the Agreement Term that is necessary to Develop, Manufacture or Commercialize a Product in the Field and such patents do not constitute AstraZeneca Background Intellectual Property.

"***AstraZeneca Product-Specific Patents***" means all Product-Specific Patents owned, used, created, developed by, or licensed to AstraZeneca or its Affiliates (other than from Isis pursuant to this Agreement) (i) as of the Effective Date, or (ii) arising at any time during the Agreement Term, in each case to the extent (x) Controlled by AstraZeneca or its Affiliates in connection with performance of obligations under this Agreement, and (y) such Product-Specific Patents do not constitute AstraZeneca Background Intellectual Property.

"***AstraZeneca-Prosecuted Patents***" has the meaning set forth in Section 7.2.4(b).

"***AstraZeneca Supported Pass-Through Costs***" means [***].

"***AstraZeneca Technology***" means AstraZeneca's interest in AstraZeneca Collaboration Intellectual Property, AstraZeneca Product-Specific Patents, AstraZeneca Know-How, AstraZeneca Patents, including AstraZeneca Background Intellectual Property, and any trademarks described in Section 4.1.6, owned, used, developed by, or licensed to AstraZeneca or its Affiliates (other than from Isis pursuant to this Agreement) that are necessary or used by AstraZeneca to Develop, Manufacture or Commercialize a Product.

"***Audit***" has the meaning set forth in Section 9.7.6.

"***Audit Report***" has the meaning set forth in Section 6.11.

"***Bankruptcy Code***" has the meaning set forth in Section 10.2.6(b).

"***BDRP***" means a drug registration petition filed with the Brazilian National Health Surveillance Agency (ANVISA) after completion of any necessary Clinical Studies to obtain Approval to market a Product in Brazil.

"***Breaching Party***" means the Party that is believed by the Non-Breaching Party to be in material breach of this Agreement.

"***Business Day***" means any day other than a Saturday or Sunday on which banking institutions in New York, US and London, England are open for business.

"***Calendar Quarter***" means a period of three consecutive calendar months ending on the last day of March, June, September, or December, respectively, and will also include the period beginning on the Effective Date and ending on the last day of the Calendar Quarter in which the Effective Date falls.

"***Calendar Year***" means a year beginning on January 1 (or, with respect to 2015, the Effective Date) and ending on December 31.

"***Candidate Drug***" means a Compound nominated for further development by AstraZeneca in accordance with AstraZeneca's internal processes.

"***Candidate Failure Date***" has the meaning set forth in Section 1.14.3.

"***Cardiovascular Disease***" means [***].

"***Carryover Option***" has the meaning set forth in Section 1.14.3(e)(ii).

"***Carryover Period***" has the meaning set forth in Section 1.14.3(d).

"***CDA***" has the meaning set forth in Section 11.2.

"***cGMP***" means current Good Manufacturing Practices as specified in the United States Code of Federal Regulations, ICH Guideline Q7A, or equivalent laws, rules, or regulations of an applicable Regulatory Authority at the time of manufacture.

"***Change of Control Event***" means any (a) direct or indirect acquisition of all or substantially all of the assets of a Party, (b) direct or indirect acquisition by a Person, or group of Persons acting in concert, of [***]% or more of the voting equity interests of a Party, (c) tender offer or exchange offer that results in any Person, or group of Persons acting in concert, beneficially owning [***]% or more of the voting equity interests of a Party, or (d) merger, consolidation, other business combination or similar transaction involving a Party, pursuant to which any Person owns all or substantially all of the consolidated assets, net revenues or net income of a Party, taken as a whole, or which results in the holders of the voting equity interests of a Party immediately prior to such merger, consolidation, business combination or similar transaction ceasing to hold [***]% or more of the combined voting power of the surviving, purchasing or continuing entity immediately after such merger, consolidation, other business combination or similar transaction, in all cases where such transaction is to be entered into with any Person other than the other Party to this Agreement or its Affiliates.

"***Claims***" has the meaning set forth in Section 9.1.

"***Clinical Study***" or "***Clinical Studies***" means a Phase 1 Study, Phase 2 Study, Phase 2b Study, Phase 3 Study, or such other study in humans that is conducted in accordance with good clinical practices and is designed to generate data in support or maintenance of an NDA, MAA, JNDA or other similar marketing application.

"***CNDA"*** means the Chinese equivalent of an NDA filed with the China Food and Drug Administration or provincial-level food and drug regulatory authority, as law and regulation may require, or any successor agency thereto.

"***CMO***" means a Third Party primarily engaged in providing contract manufacturing or services and is not primarily engaged in drug discovery, development or commercialization of ASOs as pharmaceutical products.

"***Collaboration Plan***" means (i) the Core Research Plan, (ii) the Disease Research Plan, or (iii) any Drug Discovery Plan including the [***] Drug Discovery Plan.

"***Collaboration Program***" means a discovery research program focused on discovering and optimizing at least one ASO designed to bind to the Collaboration Target that is suitable for selection as Development Candidate in accordance with the applicable Drug Discovery Plan.

"***Collaboration Program Exercise Date***" has the meaning set forth in Section 1.16.3.

"***Collaboration Program License Right***" has the meaning set forth in Section 1.16.

"***Collaboration Program License Right Deadline***" has the meaning set forth in Section 1.16.

"***Collaboration Program Term***" has the meaning set forth in Section 1.13.3.

"***Collaboration Target***" means (i) [***], or (ii) any High Interest Targets that are designated under Section 1.10 to be the subject of a Collaboration Program (and thereafter if AstraZeneca exercises its Collaboration Program License Right with respect to such High Interest Target).

"***Commercialize***," "***Commercialization***" or "***Commercializing***" means any and all activities directed to marketing, promoting, detailing, distributing, importing, having imported, exporting, having exported, holding, transporting, selling or offering to sell a Product following receipt of Approval for the Product in the applicable country, including conducting pre-and post-Approval activities, including studies reasonably required to increase the market potential of the Product and studies to provide improved formulation and Product delivery, and launching and promoting the Product in each country.

"***Commercializing Party***" means (a) AstraZeneca, with respect to a Product that is being Developed and Commercialized by or on behalf of AstraZeneca, its Affiliates or Sublicensees hereunder, and (b) Isis, with respect to a Discontinued Product that is being Developed and Commercialized by or on behalf of Isis, its Affiliates or Sublicensees hereunder.

"***Commercially Reasonable Efforts***" with respect to:

(a) AstraZeneca means that level of efforts and resources, at the relevant point in time, commonly used in the pharmaceutical industry for a product of similar commercial potential and in a similar commercial space at a similar stage in its lifecycle, taking into consideration relative safety and efficacy, product profile, the competitiveness of the marketplace, market potential, the relative profitability of the product (including pricing and reimbursement status) and other relevant factors, including technical, legal, scientific and/or medical factors.

(b) Isis means the level of efforts and resources, at the relevant time, that, consistent with Isis' normal practices, Isis would dedicate to an activity when it is seeking to achieve the particular result in a similar timeframe for its own benefit. Without limiting any of the foregoing, Commercially Reasonable Efforts as it applies to Isis' Research or Development of a Product hereunder includes use of Commercially Reasonable Efforts to perform the Isis Conducted Activities under each Collaboration Plan in accordance with the timelines set forth therein.

"***Competitive Infringement***" has the meaning set forth in Section 7.5.1.

"***Competitive ASO***" has the meaning set forth in Section 3.3.

"***Complete***," "***Completed***," or "***Completion***" means[***].

"***Compound***" means any ASO that is designed to bind to a Collaboration Target, where such ASO is discovered by Isis prior to the date on which such Target becomes a High Interest Target (or, with respect to [***], the Effective Date), or in the performance of a Collaboration Plan; and in each case any salt, hydrate, solvate or pro-drug thereof. For clarity, ASOs will be different Compounds if they have different sequences of nucleotides, use different modified nucleotides (including a different backbone, sugar moiety or base modification), or if they employ different Conjugate Technology, such as GalNAc.

"***Confidential Information***" means any confidential or proprietary information or materials, patentable or otherwise, in any form (written, oral, photographic, electronic, magnetic, or otherwise) which is disclosed by the Disclosing Party or otherwise received or accessed by the Receiving Party in the course of performing its obligations or exercising its rights under this Agreement, including trade secrets, Know-How, inventions or discoveries, proprietary information, formulae, processes, techniques and information relating to the past, present and future marketing, financial, and research and development activities of any product or potential product or useful technology of the Disclosing Party or its Affiliates and the pricing thereof. "*Confidential Information*" does not include information that:

(a) was in the lawful knowledge and possession of the Receiving Party or its Affiliates prior to the time it was disclosed to, or learned by, the Receiving Party or its Affiliates, or was otherwise developed independently by the Receiving Party or its Affiliates, as evidenced by written records kept in the ordinary course of business, or other documentary proof of actual use by the Receiving Party or its Affiliates;

(b) was generally available to the public or otherwise part of the public domain at the time of its disclosure to the Receiving Party or its Affiliates;

(c) became generally available to the public or otherwise part of the public domain after its disclosure and other than through any act or omission of the Receiving Party or its Affiliates in breach of this Agreement; or

(d) was disclosed to the Receiving Party or its Affiliates, other than under an obligation of confidentiality, by a Third Party who had no obligation to the Disclosing Party or its Affiliates not to disclose such information to others.

"***Conjugate Technology***" means chemistry designed to enhance targeting and/or uptake of antisense drugs to specific tissues and cells. Conjugate Technology includes N-acetylgalactosamine (GalNAc) ligand conjugates capable of binding to the asialoglycoprotein receptor (ASGP-R) and enhancing the targeting and/or uptake of antisense drugs to the liver.

"***Control***" or "***Controlled***" means possession of the ability to grant a license or sublicense hereunder without violating the terms of any agreement with any Third Party; *provided, however*, that if a Party has a right to grant a license or sublicense, with respect to an item of intellectual property to the other Party only upon payment of compensation (including milestones or royalties) to a Third Party ("***Third Party Compensation***") (other than in the case of a license to AstraZeneca, Isis Supported Pass-Through Costs or AstraZeneca Supported Pass-Through Costs), then the first Party will be deemed to have "*Control*" of the relevant item of intellectual property only if the other Party agrees to bear the cost of such Third Party Compensation. Notwithstanding anything to the contrary under this Agreement, with respect to any Third Party that becomes an Affiliate of a Party after the Effective Date (including a Third Party acquirer), no intellectual property of such Third Party will be included in the licenses granted hereunder by virtue of such Third Party becoming an Affiliate of such Party.

"***Core Research Plan***" has the meaning set forth in Section 1.2.

"***Core Research Program***" has the meaning set forth in Section 1.2.

"***Core Research Term***" has the meaning set forth in Section 1.3.1.

"***Cover***," "***Covered***" or "***Covering***" means, with respect to a patent, that, but for rights granted to a Person under such patent, the act of making, using or selling by such Person would infringe a Valid Claim included in such patent, or in the case of a patent that is a patent application, would infringe a Valid Claim in such patent application if it were to issue as a patent.

"***Develop***," "***Developing***" or "***Development***" means with respect to a Product, any and all discovery, characterization, or preclinical (including IND-Enabling Toxicology Studies), clinical, or regulatory activity with respect to the Product to seek Approval (including the submission of all necessary filings with applicable Regulatory Authorities to support such preclinical and clinical activities and Approval), including human clinical trials conducted after Approval of a Product to seek Approval for additional indications for such Product, including importing, having imported, exporting, having exported, holding and transporting in connection with any activities prior to Approval.

"***Development Candidate***" means, with respect to a Collaboration Program, a Compound that meets the Development Candidate Success Criteria or is otherwise designated by AstraZeneca under Section 1.14.1 (or, with respect to [***], designated by the Expert in accordance with Section 12.1.3).

"***Development Candidate Success Criteria***" means the success criteria for a development candidate for such program as set out in the applicable Drug Discovery Plan. Unless otherwise agreed by the JSC such success criteria will include the items set out in the checklist Isis uses as of the Effective Date when reviewing potential development candidates for approval as attached hereto as Appendix 2.

"***Disclosing Party***" has the meaning set forth in Section 11.1.

"***Discontinued Product***" has the meaning set forth in Section 10.3.1.

"***Disease Research Plan***" has the meaning set forth in Section 1.2.

"***Disease Research Program***" has the meaning set forth in Section 1.2.

"***Disease Research Term***" has the meaning set forth in Section 1.3.2.

[***]

"***DOJ***" means the Antitrust Division of the United States Department of Justice.

"***Drug Discovery Plan***" means any drug discovery plan for a Collaboration Program focused on a particular Collaboration Target as amended from time to time in accordance with this Agreement.

"***Effective Date***" means the date that all necessary authorizations, consents, orders or approval of, or declarations or filings with, or expirations of waiting periods under the HSR Act, as applicable to the consummation of the transactions contemplated by this Agreement, have been received, authorized, permitted or expired.

"***Eligible Target***" has the meaning set forth in Section 1.5.

"***EMA***" means the European Medicines Agency and any successor entity thereto.

"***European Union***" or "***EU***" means each and every country or territory that is officially part of the European Union from time to time.

"***Evaluation Period***" has the meaning set forth in Section 1.16.1.

"***Exclusion Criteria***" has the meaning set forth in Section 1.6.

"***Exclusive Target***" means (i) any Reserved Target, (ii) High Interest Target, or (iii) any Collaboration Target. The term "***Exclusive Targets***" means collectively the Reserved Targets, the High Interest Targets and the Collaboration Targets.

"***Execution Date***" has the meaning set forth in the Preamble of this Agreement.

"***Exploit***" means to Research, Develop, Manufacture and Commercialize and "***Exploiting***" and "***Exploitation***" have corresponding meanings. For purposes of this Agreement, references to the term "*Exploit*" in the context of non-Compounds and non-Products will be read to include the list of activities in the definition of "*Exploit*" (and the relevant supporting defined terms) *mutatis mutandis*.

"***Failed Candidate***" has the meaning set forth in Section 1.14.3(a).

"***FDA***" means the United States Food and Drug Administration and any successor entity thereto.

"***Field***" means (i) with respect to the practice of the Isis Core Technology Patents and the Isis Manufacturing and Analytical Patents, the prophylactic or therapeutic use or form of administration in humans or animals of Product for any indication, (ii) with respect to the practice of the Isis Product-Specific Patents, the prophylactic, therapeutic or diagnostic use or form of administration in humans or animals of a Product for any indication; and (iii) in all other cases, the prophylactic, therapeutic or diagnostic use or form of administration in humans or animals of a product for any indication.

"***First Commercial Sale***" means the first sale of a Product by AstraZeneca, its Affiliate or its Sublicensee to a Third Party in a particular country after Approval of such Product has been obtained in such country.

"***FTC***" means the Antitrust Division of the United States Department of Justice.

"***FTE***" means the efforts of one or more employees of Isis equivalent to the efforts of one full-time Isis employee for one year, or in the case of less than a full-time dedicated person, a full-time equivalent person-year based upon a total of one thousand seven hundred and ten (1710) hours per year of work on the development program.

"***FTE Rate***" means [***].

"***Fully Absorbed Cost of Goods***" means the costs incurred by Isis as determined using the methodology set forth in SCHEDULE 5.5.1 fairly applied and as employed on a consistent basis throughout Isis' operations.

"***Government Official***" means any Person employed by or acting on behalf of a government, government-controlled entity or public international organization; any political party, party official or candidate; any Person who holds or performs the duties of an appointment, office or position created by custom or convention; and any Person who hold himself out to be the authorized intermediary of any of the foregoing.

"***High Interest Target***" has the meaning set forth in Section 1.7.1(a).

"***High Interest Target List***" has the meaning set forth in Section 1.7.1(a).

"***HSR Act***" means the United States Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended from time to time.

"***ICC***" has the meaning set forth in Section 12.1.3(b).

"***IND***" means an Investigational New Drug Application (as defined in the Food, Drug and Cosmetic Act, as amended) filed with the FDA or its foreign counterparts.

"***IND-Enabling Toxicology Studies***" means the pharmacokinetic and toxicology studies required to meet the requirements for filing an IND, including API manufacturing to support such activities.

"***Indemnification Claim Notice***" has the meaning set forth in Section 9.3.

"***Indemnified Party***" has the meaning set forth in Section 9.3.

"***Indication***" means [***].

"***Indirect Taxes***" means value added taxes, sales taxes, consumption taxes and other similar taxes required by law to be disclosed on the invoice.

"***Initiation***" or "***Initiate***" means, with respect to any Clinical Study, dosing of the first human subject in such Clinical Study.

"***Integrated Product Plan***" or "***IPP***" has the meaning set forth in Section 5.1.2.

"***IP Managers***" has the meaning set forth in Section 7.1.5(a).

"***Isis***" has the meaning set forth in the Preamble of this Agreement.

"***Isis Background Intellectual Property***" means any Know-How and Patent Rights that: (i) were Controlled by Isis prior to the Effective Date; and/or (ii) are Controlled by Isis on or after the Effective Date that were not created or acquired in connection with performance of any Collaboration Plan and/or in connection with the Exploitation of a Product, in each case which Patents and Know-How are necessary to practice Isis Collaboration Intellectual Property.

"***Isis Collaboration Intellectual Property***" means any Know-How and Patent Rights that were discovered, developed, invented or created in connection with the performance of any Collaboration Plan by or on behalf of Isis, including Isis' interest in any Jointly-Owned Collaboration Technology.

"***Isis Conducted Activities***" means the Research and Development activities for which Isis is designated as responsible under any Collaboration Plan.

"***Isis Core Technology Patents***" means all Patent Rights owned, used, developed by, or licensed to Isis or its Affiliates (other than from AstraZeneca pursuant to this Agreement), in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term, claiming subject matter generally applicable to ASOs, other than Isis Product-Specific Patents or Isis Manufacturing and Analytical Patents. A list of Isis Core Technology Patents as of the Effective Date is set forth on Appendix 4 attached hereto.

"***Isis Field***" means [***].

"***Isis In-License Agreements***" means any agreement listed in Appendix 3 as may be updated in accordance with Section 6.8.5 or otherwise with AstraZeneca's written consent.

"***Isis Indemnitees***" has the meaning set forth in Section 9.1.

"***Isis Internal ASO Safety Database***" has the meaning set forth in Section 5.4.

"***Isis Know-How***" means any Know-How, including Isis' interest in any Jointly-Owned Collaboration Know-How, owned, used, developed by, or licensed to Isis or its Affiliates (other than from AstraZeneca pursuant to this Agreement), in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term that is necessary or useful to Develop, Manufacture or Commercialize a Product in the Field. Isis Know-How does not include the Isis Manufacturing and Analytical Know-How.

"***Isis Manufacturing and Analytical Know-How***" means Know-How, including Isis' interest in any Jointly-Owned Collaboration Know-How, that relates to the synthesis or analysis of a Product regardless of sequence or chemical modification, owned, used, developed by, or licensed to Isis or its Affiliates (other than from AstraZeneca pursuant to this Agreement), in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term. Isis Manufacturing and Analytical Know-How does not include the Isis Know-How.

"***Isis Manufacturing and Analytical Patents***" means Patent Rights, including Isis' interest in any Jointly-Owned Collaboration Patents, that claim methods and materials used in the synthesis or analysis of a Product regardless of sequence or chemical modification, owned, used, developed by, or licensed to Isis or its Affiliates (other than from AstraZeneca pursuant to this Agreement), in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term. A list of Isis Manufacturing and Analytical Patents as of the Effective Date is set forth on Appendix 5 attached hereto. Isis Manufacturing and Analytical Patents do not include the Isis Product-Specific Patents or the Isis Core Technology Patents.

"***Isis Product-Specific Patents***" means all Product-Specific Patents, in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term. A list of Isis Product-Specific Patents as of the Effective Date is set forth on Appendix 6 attached hereto.

"***Isis Supported Pass-Through Costs***" means [***].

"***Japan NDA***" or "***JNDA***" means the Japanese equivalent of an NDA filed with the Koseisho (i.e., the Japanese Ministry of Health and Welfare, or any successor agency thereto).

"***Jointly-Owned Collaboration Know-How***" means Know-How discovered, developed, invented or created jointly in the performance of a Collaboration Plan by or on behalf of both Parties or their respective Affiliates or Third Parties acting on their behalf that is necessary or useful to Develop, Manufacture or Commercialize a Product in the Field.

"***Jointly-Owned Collaboration Patents***" means any Patent Rights that claim or cover Jointly-Owned Collaboration Know-How.

"***Jointly-Owned Collaboration Technology***" means Jointly-Owned Collaboration Know-How and Jointly-Owned Collaboration Patents.

"***Kidney Disease***" means [***].

"***Know-How***" means inventions, technical information, know-how and materials, including technology, data, compositions, formulas, biological materials, assays, reagents, constructs, compounds, discoveries, procedures, processes, practices, protocols, methods, techniques, results of experimentation or testing, knowledge, trade secrets, skill and experience, in each case whether or not patentable or copyrightable, and in each case that are not Covered by an issued Patent Right.

"***Knowledge***" means the good faith, actual understanding of the facts and information by a Party's or any of its Affiliate's executive officers and their attorneys employed in their Legal Department and Patent Department as of the Effective Date or a Bring-Down Date (as applicable); *provided that*, with respect to information regarding the status of Patent Rights or other intellectual property rights, "*Knowledge*" means the good faith, actual understanding of the facts and information by a Party's or any of its Affiliate's executive officers and their attorneys employed in their Legal Department and Patent Department as of the Effective Date or a Bring-Down Date (as applicable) after performing a diligent investigation with respect to such facts and information as is customary in the conduct of its business with respect to such Patent Rights or other intellectual property rights (and not, for clarity, a diligent investigation solely in connection with this Agreement).

"***Lead Candidate***" means, in the case of a Collaboration Program, the Compound identified by Isis as being the lead candidate for such program.

"***Lead Candidate Data Package***" means, with respect to a Collaboration Program, [***].

"***Lead Compounds***" has the meaning set forth in Section 1.14.1.

"***Licensed CMO***" has the meaning set forth in Section 4.1.2(a)(ii).

"***Licensed Know-How***" means Isis Manufacturing and Analytical Know-How, and Isis Know-How. For clarity, at the Execution Date Licensed Know-How does not include any Know-How covering formulation technology or delivery devices unless such Know-How is included in the Jointly-Owned Collaboration Know-How.

"***Licensed Patents***" means the Isis Product-Specific Patents, Isis Core Technology Patents, Isis Manufacturing and Analytical Patents and Isis' interest in Jointly-Owned Collaboration Patents. For clarity, at the Execution Date Licensed Patents do not include any Patent Rights claiming formulation technology or delivery devices unless such Patent Rights are included in the Jointly-Owned Collaboration Patents.

"***Licensed Program***" means a Collaboration Program following exercise of the applicable Collaboration Program License Right for so long as the license under Section 4.1.1 for such program is effective.

"***Licensed Technology***" means any and all Licensed Patents, Licensed Know-How, and any trademarks described in Section 4.1.6, to the extent necessary or useful to Research, Develop, Manufacture or Commercialize a Product in the Field.

"***Losses***" has the meaning set forth in Section 9.1.

"***MAA***" means a marketing authorization application filed with the EMA after completion of Clinical Studies to obtain Approval for a Product under the centralized European filing procedure or, if the centralized EMA filing procedure is not used, filed using the applicable procedures with the applicable Regulatory Authority in any European Union country.

"***MAA Approval***" means the grant of a marketing authorization by the European Commission for a Product in the European Union.

"***Major Market***" means any of the following countries: [***].

"***Manufacture***" or "***Manufactured***" or "***Manufacturing***" means any activity involved in or relating to the manufacturing, quality control testing (including in-process, release and stability testing), releasing or packaging, importing and keeping, for pre-clinical and clinical purposes, of API or a Product in finished form.

"***Material Anti-Corruption Law Violation"*** means a violation of an Anti-Corruption Law relating to the subject matter of this Agreement which would if it were publicly known, in the reasonable view of AstraZeneca, have a material adverse effect on Isis or on the reputation of AstraZeneca because of its relationship with Isis.

"***Metabolic Disorder***" means [***].

"***Minimum Third Party Payments***" means [***].

"***MSA***" has the meaning set forth in Section 5.5.2.

"***NDA***" means a New Drug Application filed with the FDA after completion of Clinical Studies to obtain Approval for a Product in the United States.

"***Net Sales***" means the gross invoiced amount on sales of Products by or on behalf of AstraZeneca, its Affiliates, and its Sublicensees to Third Parties (which Third Parties will include Distributors) after deduction of the following amounts, to the extent taken:

(a) normal and customary trade, quantity or prompt settlement discounts (including initial launch stocking discounts, chargebacks and allowances) actually allowed;

(b) amounts repaid or credited by reason of rejection, returns or recalls of goods, rebates or *bona fide* price reductions determined by AstraZeneca, its Affiliates or its Sublicensees in good faith;

(c) rebates and similar payments made with respect to sales paid for by any governmental or Regulatory Authority such as, by way of illustration and not in limitation of the Parties' rights hereunder, Federal or state Medicaid, Medicare or similar state program in the United States or equivalent governmental program in any other country;

(d) any invoiced amounts which are not collected by AstraZeneca, its Affiliates or its Sublicensees, including bad debts;

(e) excise taxes, value added taxes, sales taxes, consumption taxes and other similar taxes (excluding any income, franchise or withholding taxes), customs duties, customs levies and import fees imposed on the sale, importation, use or distribution of the Products, including fees paid pursuant to Section 9008 of the Patient Protection and Affordable Care Act that AstraZeneca, its Affiliates or its or their Sublicensees, as applicable, allocable to sales of such Products in accordance with AstraZeneca's, its Affiliates' or its or their Sublicensees' standard policies and procedures consistently applied across its products, as applicable;

(f) the portion of administrative fees paid during the relevant time period to group purchasing organizations or pharmaceutical benefit managers relating to such Products;

(g) service fees payable under any wholesaler agreement, distribution services agreement, inventory management agreement or other similar agreement;

(h) any other similar and customary deductions (including co-pay cards) that are consistent with the United States generally accepted accounting principles or, in the case of non-United States sales, other applicable accounting standards;

(i) an allowance for transportation costs, distribution expenses, special packaging and related insurance charges equal to [***] ([***]) of the amount arrived at after application of the deductions under clauses (a) to (h) above; and

(j) the actual cost paid by AstraZeneca, its Affiliates or Sublicensees for each unit of a Device.

Net Sales (including any deductions) will be calculated using AstraZeneca's internal audited systems used to report such sales as adjusted for any of the items above not taken into account in such systems, and in each case which are in accordance with generally accepted accounting principles, fairly applied and as employed on a consistent basis throughout AstraZeneca's operations. Deductions pursuant to subsection (d) above will be taken in the Calendar Quarter in which such sales are no longer recorded as a receivable. As used above, the term *"Device"* means any device approved by a Regulatory Authority for use with a Product that is necessary to administer the Product to a patient (i.e. without such device the Product cannot be delivered in accordance with the Approval).

If a Product is sold as part of a Combination Product (as defined below), the Net Sales from such Product, for the purposes of determining royalty payments, will be determined by multiplying the Net Sales (as determined without reference to this paragraph) of the Combination Product by the fraction A/(A+B), where A is the standard sales price of the ready-for-sale form of the Product, containing the same amount of Compound as the sole active ingredient as the Combination Product in question, in the given country when sold separately in finished form; and B is the standard sales price of the ready-for-sale form of the product containing the same amount of the other therapeutically active ingredient(s) that is contained in the Combination Product in question, in the given country, each during the applicable royalty period or, if sales of all compounds did not occur in such period, then in the most recent royalty reporting period. In the event, however, that if, in a specific country either or both of the Compound and the other therapeutically active ingredient in such Combination Product are not sold separately in such country, a market price for such Product and such other active ingredient will be negotiated by the Parties in good faith for the purposes of performing the calculation above to determine royalty payments on the Net Sales from such Combination Product. As used above, the term ***"Combination Product"*** means a Product that includes at least one additional therapeutically active ingredient (whether coformulated or copackaged) and is not a Compound.

"***New Third Party Compound Technology***" has the meaning set forth in Section 1.13.2.

[***]

"***Non-Breaching Party***" means the Party that believes the Breaching Party is in material breach of this Agreement.

"***Non-Transferring Party***" has the meaning set forth in Section 12.3.

"***Other Leads***" has the meaning set forth in Section 1.14.1.

"***Party***" or "***Parties***" means AstraZeneca and Isis individually or collectively.

"***Party Representatives***" has the meaning set forth in Section 9.7.1.

"***Patent Costs***" means the reasonable fees and expenses paid to outside legal counsel, and filing, maintenance and other reasonable out-of-pocket expenses paid to Third Parties, incurred in connection with the Prosecution and Maintenance of Patent Rights.

"***Patent Rights***" means (a) patents, patent applications and similar government-issued rights protecting inventions in any country or jurisdiction however denominated, (b) all priority applications, divisionals, continuations, substitutions, continuations-in-part of and similar applications claiming priority to any of the foregoing, and (c) all patents and similar government-issued rights protecting inventions issuing on any of the foregoing applications, together with all registrations, reissues, renewals, re-examinations, confirmations, supplementary protection certificates, and extensions of any of (a), (b) or (c).

"[***]" means the gene, [***].

"[***] ***Carryover Option***" means a Carryover Option exercised with respect to [***].

"[***] ***CD Milestone***" has the meaning set forth in Section 6.3.

"[***] ***Compound***" means any ASO that is designed to bind to [***], where such ASO is (i) discovered by Isis prior to the Effective Date, or (ii) discovered by Isis in the performance of the [***] Program. For clarity, ASOs will be different Compounds if they have different sequences of nucleotides, use different modified nucleotides (including a different backbone, sugar moiety or base), or if they employ different Conjugate Technology, such as GalNAc.

"[***] ***Drug Discovery Plan***" means the drug discovery plan for the [***] Program (a draft of which is attached hereto as SCHEDULE 1.13.1(a)) to be adopted by the JSC and thereafter as updated by the JSC from time to time in accordance with this Agreement.

"[***] ***Program***" means the Research and/or Development program for [***] Products under this Agreement.

"[***] ***Product***" means each [***] Compound and any product containing such [***] Compound as an active pharmaceutical ingredient (including any salt, hydrate, solvate or pro-drug thereof).

"[***] ***Program***" means the drug discovery program for [***] Products under this Agreement.

"[***] ***Success Criteria***" means the Development Candidate Success Criteria for the [***] Program as set out in the [***] Drug Discovery Plan.

"***Permitted Licenses***" means (1) licenses granted by Isis before or after the Effective Date to any Third Party under the Isis Core Technology Patents, the Isis Manufacturing and Analytical Patents, or the Isis Manufacturing and Analytical Know-How (but not under the Isis Product-Specific Patents) to (a) use oligonucleotides (or supply oligonucleotides to end users) solely to conduct pre-clinical research, or (b) enable such Third Party to manufacture or formulate oligonucleotides as a contract manufacturer, where (i) such Third Party is primarily engaged in providing contract manufacturing or services and is not primarily engaged in drug discovery, development or commercialization of therapeutics; and (ii) Isis does not assist such Third Party to identify, discover or make a Product; and (2) material transfer agreements with academic collaborators or non-profit institutions in connection with the Isis Conducted Activities approved by AstraZeneca, such approval not to be unreasonably withheld or delayed.

"***Person***" means any corporation, limited or general partnership, limited liability company, joint venture, trust, unincorporated association, governmental body, authority, bureau or agency, any other entity or body, or an individual.

"***Phase 1 Study***" means the first clinical study conducted in humans. "*Phase 1 Study*" includes any clinical study designated under an IPP as a "*Phase 1 Study", "Phase 1(a) Study",* "*Phase 1 Trial*", or "*Phase 1a Trial*".

"***Phase 2 Study***" means the first clinical study where the protocol anticipates that a patient participating in the study will be administered Product for more than eight weeks. For clarity, the continuation of treatment of patients for more than eight weeks in an open label arm of a Phase 1(b) Study will not result in that study being deemed to be a Phase 2 Study. "*Phase 2 Study*" includes any clinical study designated under an IPP as a "*Phase 2 Study,*" "*Phase 2a Study*," *Phase 2b Study*," "*Phase 2 Trial*," *Phase 2a Trial*" or "*Phase 2b Trial*".

"***Phase 2b Study***" means a further Phase 2 Study for a Product for the same Indication that is intended to identify the definite dose range for efficacy at the primary endpoint for that Indication.

"***Phase 3 Study***" means a clinical study in humans performed to gain evidence of statistical significance of the efficacy of a Product in a target patient population, and to obtain expanded evidence of safety for such Product that is needed to evaluate the overall benefit-risk relationship of such Product and provide an adequate basis for obtaining Regulatory Approval, including physician labeling, as described in 21 C.F.R. 312.21(c), or its equivalent outside the United States. "*Phase 3 Study*" includes any clinical study designated under an IPP as a "*Phase 3 Study,*" "*Phase 3 Trial*," "*Pivotal Study*" or "*Registration Study*."

"***Pre-Clinical Studies***" means *in vitro* and *in vivo* studies of one or more Compounds, not in humans, including those studies conducted in whole animals and other test systems, designed to determine the toxicity, bioavailability, and pharmacokinetics of the Product and whether the Product has a desired effect.

"***Primary Diseases***" has the meaning set forth in the Recitals. "*Primary Diseases*" does not include any neurology diseases or ocular diseases associated with a Primary Disease (e.g., diabetic retinopathy).

"***Prior Agreements***" means the agreements listed on APPENDIX 7 attached hereto.

"***Proceeding***" means an action, suit or proceeding.

"***Product***" means (i) each Compound and any product containing such Compound as an active pharmaceutical ingredient (including any salt, hydrate, solvate or pro-drug thereof), or (ii) a [***] Product.

"***Product-Specific Patents***" means Patent Rights Controlled by a Party or any of its Affiliates on or after the Effective Date claiming: (i) the specific composition of matter of a Product, or (ii) methods of using such a Product as a prophylactic, therapeutic or diagnostic.

"***Prosecution and Maintenance***" or "***Prosecute and Maintain***" means, with regard to a Patent Right, the preparing, filing, prosecuting and maintenance of such Patent Right, as well as handling re-examinations, reissues, and requests for patent term extensions with respect to such Patent Right, together with the conduct of interferences, the defense of oppositions and other similar proceedings with respect to the particular Patent Right. For clarification, "*Prosecution and Maintenance*" or "*Prosecute and Maintain*" will not include any other enforcement actions taken with respect to a Patent Right.

"***Receiving Party***" has the meaning set forth in Section 11.1.

"***Regulatory Authority***" means any governmental authority, including the FDA, EMA or Koseisho (i.e., the Japanese Ministry of Health and Welfare, or any successor agency thereto), that has responsibility for regulating or otherwise exercising authority with respect to the Development, Manufacture, marketing, sale or other Commercialization of a Product in any country.

"***Regulatory Documentation***" means any regulatory submissions, notifications, registrations, approvals and/or other filings and correspondence made to or with a Regulatory Authority in any country or jurisdiction, and any other records required by Applicable Law to be maintained that may be necessary or useful to Develop, manufacture, market, sell or otherwise Commercialize a Product in the Field.

"***Release Notice***" means a written notice delivered by AstraZeneca to Isis within [***] after the Target Failure Date or Candidate Failure Date (as applicable), pursuant to which AstraZeneca releases Isis from any obligation to restore a former High Interest Target or a former Collaboration Target (together with ASOs designed to bind to such former High Interest Target or former Collaboration Target) to the Collaboration pursuant to Sections 1.10.3(c) or 1.14.3(e).

"***Relevant Authority***" means any court or government body, whether national, supra-national, federal, state, local, foreign or provincial, including any political subdivision thereof, including any department, commission, board, bureau, agency, or other regulatory or administrative governmental authority or instrumentality, and further including any quasi-governmental Person or entity exercising the functions of any of these.

"***Research***" means conducting research activities with Compounds, including pre-clinical research and lead optimization, *but specifically excluding* Development and Commercialization. When used as a verb, "*Researching*" means to engage in Research.

"***Research Collaboration***" means the conduct of the Disease Research Program, the Core Research Program and the Collaboration Programs in accordance with this Agreement.

"***Reserved Target***" has the meaning set forth in Section 1.7.

"***Reserved Target List***" has the meaning set forth in Section 1.7.

"***RMC***" means Isis' Research Management Committee, or any successor committee.

"***Royalty Period***" has the meaning set forth in Section 6.7.2(a).

"***Senior Representatives***" has meaning set forth in Section 12.1.1.

"***Service Provider***" means the Third Party(ies) conducting the original and revised studies under a Collaboration Plan.

"***Specific Performance Milestone Events***" has the meaning set forth in Section 5.1.1.

"***Sublicensee***" means a Third Party to whom a Party or its Affiliates or Sublicensees has granted a sublicense or license under any Licensed Technology (in the case of AstraZeneca) or AstraZeneca Technology (in the case of Isis), as the case may be, licensed to such Party in accordance with the terms of this Agreement.

"***Target***" means any (i) pre-mRNA or mRNA of a gene target, and/or (ii) non-coding RNA.

"***Target Failure Date***" has the meaning set forth in Section 1.10.3.

"***Target Sanction***" means [***].

"***Target Sanction Data Package***" means, with respect to a High Interest Target, [***].

"***Terminated Program***" has the meaning set forth in Section 10.3.1.

"***Terminated Target***" has the meaning set forth in Section 10.3.1.

"***Third Party***" means a Person or entity other than the Parties or their respective Affiliates.

"***Third Party Claims***" has the meaning set forth in Section 9.1.

"***Third Party Obligations***" means any financial and non-financial encumbrances, obligations, restrictions, or limitations imposed by an agreement between a Party and a Third Party that relate to a Product or an Exclusive Target, including field or territory restrictions, covenants, milestone payments, diligence obligations, sublicense revenue, royalties, or other payments.

"***Transferring Party***" has the meaning set forth in Section 12.3.

[***]

"***United States***" or "***U.S.***" means the fifty states of the United States of America and all of its territories and possessions and the District of Columbia.

"***Valid Claim***" means a claim (i) of any issued, unexpired United States or foreign Patent Right, which will not, in the country of issuance, have been donated to the public, disclaimed, nor held invalid or unenforceable by a court of competent jurisdiction in an unappealed or unappealable decision, or (ii) of any United States or foreign patent application within a Patent Right, which will not, in the country in question, have been cancelled, withdrawn, abandoned nor been pending for more than seven years, not including in calculating such seven-year period of time in which such application is in interference or opposition or similar proceedings or time in which a decision of an examiner is being appealed. Notwithstanding the foregoing, on a country-by-country basis, a patent application pending for more than seven years will not be considered to have any Valid Claim for purposes of this Agreement unless and until a patent meeting the criteria set forth in clause (i) above with respect to such application issues.

"***Work Plan Reports***" has the meaning set forth in Section 2.7.

APPENDIX 2
Isis' Lead Candidate Checklist

[***]

APPENDIX 3

Isis In-License Agreements

[***]

APPENDIX 4

Isis Core Technology Patents

[***]

APPENDIX 5

Isis Manufacturing and Analytical Patents

[***]

APPENDIX 6

Isis Product-Specific Patents

(RELEVANT TO [***])

[***]

APPENDIX 7

Prior Agreements

[***]

SCHEDULE 1.2.1

Preliminary Core Research Plan

[***]

SCHEDULE 1.2.2

Outline for Preliminary Disease Research Plan

[***]

SCHEDULE 1.8

Criteria and Activities to Achieve Target Sanction

[***]

SCHEDULE 1.13.1(a)

Draft [***] Drug Discovery Plan

[***]

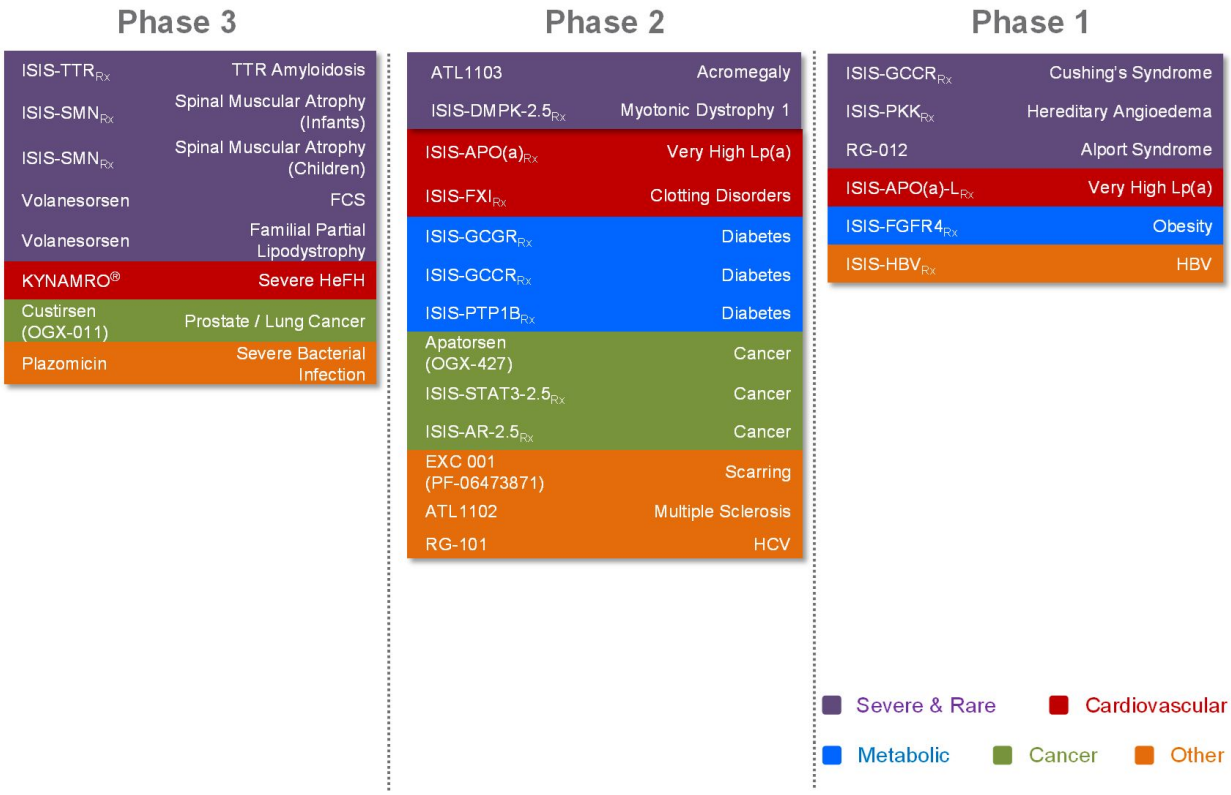
SCHEDULE 1.13.1(b)

Criteria and Activities for Development Candidate Designation

[***]

SCHEDULE 1.13.2

Isis' Development Pipeline as of the Execution Date



SCHEDULE 2.1.1

JSC GOVERNANCE

(a) The JSC will determine the JSC operating procedures, including frequency of meetings (at least quarterly), location of meetings, and responsibilities for agendas and minutes. The JSC will codify these operating procedures in the written minutes of the first meeting.

(a) The JSC may hold meetings in person or by audio or video conference as determined by the JSC; but at least two meetings per year will be in person (one held at Isis' facilities, and the other held at AstraZeneca's facilities outside of the U.S.). Alliance Managers will attend JSC meetings as participating non-members. In addition, upon prior approval of the other Party, each Party may invite its employees or consultants to attend JSC meetings, including any subject matter expert(s) with valuable knowledge of the relevant Exclusive Target.

(b) The co-chairs will be responsible for ensuring that activities occur as set forth in this Agreement, including ensuring that JSC meetings occur, JSC recommendations are properly reflected in the minutes, and any dispute is given prompt attention and resolved in accordance with Section 1.13.1, Section 2.1.3, Section 7.1.5 and Section 12.1, as applicable.

(c) The JSC members from the same Party will collectively have one vote. The JSC will strive to make recommendations with approval of both Isis members and AstraZeneca members, and record such recommendations in the minutes of the applicable JSC meeting.

(d) The JSC may form subcommittees and working groups as it determines in order to carry out its activities under this Agreement, all of which will dissolve when the JSC dissolves.

SCHEDULE 2.2

Alliance Management Activities

Each Alliance Manager will be the primary point of contact for the Parties regarding their collaboration under this Agreement and will be responsible for:

(a) promoting the overall health of the relationship between the Parties;

(b) developing a mutually agreed alliance launch plan covering any activities and systems that the Parties need to implement within the first [***] after the Effective Date to support the Collaboration Plans;

(c) organizing each JSC meeting, including agendas, drafting minutes, and publishing final minutes;

(d) supporting the co-chairs of the JSC with organization of meetings, information exchange, meeting minutes, and facilitating dispute resolution as necessary;

(e) preparing status and progress reports on the above as determined necessary by the JSC and ensuring that reports are produced and maintained and are of sufficient quality;

(f) assisting the JSC with completing Work Plan Reports under Section 2.7 and ensuring that such reports are provided to AstraZeneca;

(g) ensuring compliance in maintaining the Isis Internal ASO Safety Database as outlined in Section 5.4;

(h) ensuring proper approval of publications prior to submission as required in Section 11.5.5; and

(i) review material transfer agreements and keeping records of the creation and supply of materials.

SCHEDULE 2.7

WORK PLAN REPORT

[***]

SCHEDULE 2.8

AstraZeneca Bioethics Policy

The AstraZeneca Bioethics Policy is applicable to everyone involved in R&D activities including any third party who acts on our behalf.

The AstraZeneca Bioethics Policy defines the principles, behaviours and ethical standards governing our research and development worldwide. While many topics are covered by existing national laws and regulations, this policy sets out the commitment beyond ordinary legal compliance of AstraZeneca and third parties acting on AstraZeneca's behalf.

Further information on Using Animals in Research Studies at AstraZeneca is available on our web site (http://www.astrazeneca.com/Responsibility/Research-ethics/Animal-research)

AstraZeneca considers the responsible use of animals to be ethically appropriate in biomedical research and product safety testing, where suitable alternatives are not available. The following principles apply to all animal studies conducted by AstraZeneca and third parties who conduct animal studies on our behalf and to the breeding and supplying of animals for use in such studies:

- A humane approach must be adopted in the care and treatment of all animals, and the greatest consideration is given to their health and welfare, consistent with meeting the necessary scientific objectives. AstraZeneca is committed to the principles of the 3R: Replacement, Reduction and Refinement.

- All animal studies must be carefully considered and justified to ensure that the study is scientifically necessary; there is no practicable alternative to the use of animals (Replacement); only the minimum number of an appropriate species of animal will be used to achieve the scientific objectives (Reduction); and that the study is designed and undertaken to minimise pain and distress to the animals involved (Refinement).

- AstraZeneca is committed to sharing of knowledge of good practices and 3Rs achievements both throughout the AstraZeneca group of companies and the wider scientific community.

- We must ensure that our own facilities and animal welfare programmes, as well as those of third parties who conduct animal studies on our behalf, comply with our policies. All animal studies must be undertaken in compliance with all relevant local and national laws and regulations, and with the principles of the "Guide for the Care and Use of Laboratory Animals" 8th Edition, Institute for Laboratory Animal Research. Wherever possible, our preference is to work with third parties accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International (AAALAC International).

- AstraZeneca does not conduct or resource work using wild-caught non-human primates or great ape species. In the rare case where there is no credible alternative model to develop a treatment for serious disease, exceptions may be considered. The decision to progress requires rigorous secondary ethical and scientific review to challenge the need for the study, followed by AstraZeneca Board-level approval.

SCHEDULE 5.1.1

Specific Performance Milestone Events

[To be added after Collaboration Program License Right Exercise]

SCHEDULE 5.5.1

Isis' Fully Absorbed Cost of Goods Methodology
Cost Estimate of API Cost per Kilogram
(OOO's)

[***]

Exhibit 1

AstraZeneca 5R Framework

[***]

Exhibit 10.7

Certain identified information in this exhibit, marked by [***], has been excluded because it is both (i) not material, and (ii) the type that the registrant treats as private or confidential.

AMENDMENT NO. 1

This Amendment No. 1 (the "Amendment") to the Strategic Collaboration Agreement dated July 31st, 2015 (the "Agreement"), is made by and between

(1) ASTRAZENECA AB, a company incorporated in Sweden under no. 556011-7482 with its registered office at SE-151 85 Södertälje, Sweden ("AstraZeneca") and

(2) IONIS PHARMACEUTICALS, INC., a Delaware corporation, (formally known as Isis Pharmaceuticals, Inc.) having its principal place of business at 2855 Gazelle Court, Carlsbad, California 92010 ("Ionis"),

and is made effective as of October 18th, 2018 (the "Amendment Effective Date").

Recitals

WHEREAS, the Parties desire to further amend and restate certain terms and conditions of the Agreement.

Agreement

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

1. **Definitions**

Any capitalized term not separately defined in this Amendment shall have the meaning ascribed to it in the Agreement.

2. **Modifications**

Section 5.1.2. of the Agreement is hereby deleted in its entirety and replaced by the following:

"5.1.2. **Integrated Product Plans**. For each Licensed Program, AstraZeneca will prepare a global integrated Product plan or a comparable document consistent with AstraZeneca's then current internal practices for AstraZeneca's internal programs outlining key aspects of the Development of the Product being Developed from such Program through all Approvals as well as, as Development proceeds and when such information is available, key aspects of worldwide regulatory strategy, pricing and market access strategy, market launch, and Commercialization (each plan or other such document, an "Integrated Product Plan" or "IPP"). On a Product-by-Product basis, AstraZeneca will prepare each IPP no later than [***] for the relevant Product, and the IPP will contain high level information consistent with AstraZeneca's development and commercialization plans for its similar products at similar stages of development and commercialization in the same AstraZeneca franchise, including without limitation a status update, timelines, goals, and the criteria AstraZeneca will use to make internal decisions, but excluding information that AstraZeneca is required not to share even under confidentiality pursuant to restrictions imposed by any Third Party. Once AstraZeneca has prepared an IPP, AstraZeneca will update it consistent with AstraZeneca's standard practice (including if the IPP is updated and presented to an AstraZeneca internal committee) but at least Annually and will provide such updates to Ionis. AstraZeneca and Ionis will meet (through the JSC or as the Parties may otherwise agree) on a yearly basis to discuss the draft of the IPP and AstraZeneca will consider, in good faith, any proposals and comments made by Ionis or incorporation in the IPP. AstraZeneca and Ionis will [***], to discuss the status of execution of the IPP. Additionally, subject to AstraZeneca's confidentiality obligations to any Third Party, AstraZeneca may provide more frequent updates in the case of extraordinary material events (e.g. approvals, regulatory feedback, etc.) as deemed appropriate by AstraZeneca. For the avoidance of doubt, information provided by AstraZeneca to Ionis pursuant to this Section 5.1.2 shall be treated by Ionis as AstraZeneca's Confidential Information subject to the provisions in Article 11."

3. **Amendment Effective Date**

This Amendment shall become effective on the Amendment Effective Date.

4. **Entire Agreement**

This Amendment, together with the Agreement, constitutes the entire agreement between the Parties with respect to the subject matter of the Agreement. The Agreement together with this Amendment supersedes all prior agreements, whether written or oral, with respect to the subject matter of the Agreement, as amended. Each Party confirms that it is not relying on any representations, warranties, or covenants of the Party except as specifically set out in the Agreement as amended. Nothing in this Amendment is intended to limit or exclude any liability or fraud. The Parties hereby agree that subject to the modifications specifically stated in this Amendment, all other terms and conditions of the Agreement shall remain in full force and effect.

5. **Execution**

THIS AMENDMENT IS EXECUTED by the authorized representatives of the parties as of the date first written above.

ASTRAZENECA AB (publ.)	**IONIS PHARMACEUTICALS, INC.**
Signature: */s/*Regina Fritsche Danielseon	Signature: /s/Brett Monia
Name: Regina Fritsche Danielson	Name: Brett Monia
Title: VP and Head of IMED CVRM	Title: Chief Operating Officer

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: July 30, 2025

/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: July 30, 2025

/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 June 30, 2025, 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: July 30, 2025

/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.