UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, DC 20549

Form 10-Q

(Mark One)

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

For the Quarterly Period Ended June 30, 2010

OR

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

For the transition period from to

Commission file number 0-19125

Isis 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.)

1896 Rutherford Road, Carlsbad, CA 92008
(Address of principal executive offices, including zip code)

760-931-9200
(Registrant's telephone number, including area code)

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

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

Common Stock, $.001 Par Value

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 x No o

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

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

Large accelerated filer x	Accelerated filer o
Non-accelerated filer o (Do not check if a smaller reporting company)	Smaller reporting company o

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 o No x

The number of shares of voting common stock outstanding as of August 2, 2010 was 99,176,854.

ISIS PHARMACEUTICALS, INC.
FORM 10-Q

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TRADEMARKS

Isis Pharmaceuticals® is a registered trademark of Isis Pharmaceuticals, Inc.
Regulus Therapeutics™ is a trademark of Regulus Therapeutics Inc.
Ibis T5000™ is a trademark of Ibis Biosciences, Inc.
Vitravene™ is a trademark of Novartis AG.

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

	June 30, 2010 (Unaudited)	December 31, 2009
ASSETS		
Current assets:		
Cash and cash equivalents	$ 46,038	$ 105,255
Short-term investments	475,990	469,057
Contracts receivable	5,040	10,899
Inventories	2,794	2,768
Other current assets	7,023	8,147
Total current assets	536,885	596,126
Property, plant and equipment, net	36,071	27,338
Licenses, net	13,454	14,542

Patents, net	16,152	15,909
Deposits and other assets	3,789	3,269
Total assets	$ 606,351	$ 657,184
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 5,355	$ 4,696
Accrued compensation	4,312	7,135
Income taxes payable	—	7,323
Accrued liabilities	13,302	12,339
Current portion of long-term obligations	4,977	4,270
Current portion of deferred contract revenue	77,268	75,681
Total current liabilities	105,214	111,444
$2^{5}/_{8}$% convertible subordinated notes	128,907	125,100
Long-term obligations, less current portion	5,620	11,478
Long-term financing obligation	10,147	—
Investment in Regulus Therapeutics Inc.	4,070	—
Long-term deferred contract revenue	90,164	107,097
Total liabilities	344,122	355,119
Stockholders' equity:		
Common stock, $0.001 par value; 200,000,000 shares authorized, 99,113,712 and 98,850,934 shares issued and outstanding at June 30, 2010 and December 31, 2009, respectively	99	99
Additional paid-in capital	991,436	985,620
Accumulated other comprehensive income	941	2,153
Accumulated deficit	(730,247)	(696,150)
Total Isis Pharmaceuticals, Inc. stockholders' equity	262,229	291,722
Noncontrolling interest in Regulus Therapeutics Inc.	—	10,343
Total stockholders' equity	262,229	302,065
Total liabilities and stockholders' equity	$ 606,351	$ 657,184

See accompanying notes.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2010	2009 (1)	2010	2009 (1)
Revenue:				
Research and development revenue under collaborative agreements	$ 21,143	$ 30,768	$ 49,699	$ 60,453
Licensing and royalty revenue	2,360	224	3,730	2,115
Total revenue	23,503	30,992	53,429	62,568
Expenses:				
Research and development	39,124	32,146	71,111	60,688
General and administrative	3,051	3,673	5,869	7,350
Total operating expenses	42,175	35,819	76,980	68,038
Loss from operations	(18,672)	(4,827)	(23,551)	(5,470)
Other income (expense):				
Equity in net loss of Regulus Therapeutics Inc.	(3,942)	—	(5,428)	—
Investment income	859	1,678	1,814	3,812
Interest expense	(3,263)	(3,155)	(6,500)	(6,236)
Gain (loss) on investments, net	(136)	2,612	(1,146)	2,671
Loss from continuing operations, before income tax benefit (expense)	(25,154)	(3,692)	(34,811)	(5,223)
Income tax benefit (expense)	—	11	—	(149)
Net loss from continuing operations	(25,154)	(3,681)	(34,811)	(5,372)
Discontinued operations:				
Loss from discontinued operations	—	—	—	(29)
Gain on sale of Ibis Biosciences, Inc., net of tax	—	94	—	187,119

Net income from discontinued operations, net of tax	—	94	—	187,090
Net income (loss)	(25,154)	(3,587)	(34,811)	181,718
Net loss attributable to noncontrolling interest in Regulus Therapeutics Inc.	—	857	—	1,770
Net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (25,154)	$ (2,730)	$ (34,811)	$ 183,488
Basic and diluted net income (loss) per share:				
Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (0.25)	$ (0.03)	$ (0.35)	$ (0.03)
Net income from discontinued operations	—	—	—	1.91
Basic and diluted net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (0.25)	$ (0.03)	$ (0.35)	$ 1.88
Shares used in computing basic and diluted net income (loss) per share	99,091	98,116	99,052	97,820

(1) During the preparation of the year end 2009 annual tax provision, we determined that certain tax items had been attributed to discontinued operations that are appropriately associated with continuing operations. As a result, we revised the tax provisions reflected in each of the first three quarters during 2009 to reflect the correction of this allocation. The historical condensed consolidated statements of operations for the three and six months ended June 30, 2009 reflect the revised tax provisions.

See accompanying notes.

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

	Six Months Ended June 30,	
	2010	2009(1)
Net cash used in operating activities	$ (16,661)	$ (44,824)
Investing activities:		
Purchases of short-term investments	(326,163)	(406,873)
Proceeds from the sale of short-term investments	302,273	258,424
Purchases of property, plant and equipment	(11,894)	(10,215)
Proceeds from land sold to BioMed	10,147	—
Reduction of cash due to deconsolidation of Regulus Therapeutics Inc. upon adoption of a new accounting standard	(16,228)	—
Acquisition of licenses and other assets	(2,455)	(1,481)
Purchases of strategic investments	(658)	(349)
Proceeds from sale of strategic investments	—	2,848
Net cash used in investing activities	(44,978)	(157,646)
Financing activities:		
Net proceeds from issuance of equity	1,282	7,627
Excess tax benefits on share-based compensation	—	108
Proceeds from equipment financing arrangement	3,083	2,705
Principal payments on debt obligations	(1,943)	(1,166)
Proceeds from sale of Ibis Biosciences, Inc. to Abbott Molecular Inc.	—	175,000
Proceeds from Alnylam's capital contribution to Regulus Therapeutics Inc.	—	10,000
Net cash provided by financing activities	2,422	194,274
Net decrease in cash and cash equivalents	(59,217)	(8,196)
Cash and cash equivalents at beginning of period	105,255	223,985
Cash and cash equivalents at end of period	$ 46,038	$ 215,789
Supplemental disclosures of cash flow information:		
Interest paid	$ 2,413	$ 2,396
Income taxes paid	$ 7,700	$ 6,805
Supplemental disclosures of non-cash investing activities:		
Amounts accrued for capital and patent expenditures	$ 831	$ 914

(1) During the preparation of the year end 2009 annual tax provision, we determined that certain tax items had been attributed to discontinued operations that are appropriately associated with continuing operations. As a result, we revised the tax provisions reflected in each of the first three quarters during 2009 to reflect the correction of this allocation. The historical condensed consolidated statement of cash flows for the six months ended June 30, 2009 reflects the revised tax provisions.

See accompanying notes.

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ISIS PHARMACEUTICALS, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
June 30, 2010
(Unaudited)

1. Basis of Presentation

The unaudited interim condensed consolidated financial statements for the three and six month periods ended June 30, 2010 and 2009 have been prepared on the same basis as the audited financial statements for the year ended December 31, 2009. The financial statements include all normal recurring adjustments, which we consider necessary for a fair presentation of the financial position at such dates and the operating results and cash flows for those periods. Results for the interim periods are not necessarily indicative of the results for the entire year. For more complete financial information, these financial statements, and notes thereto, should be read in conjunction with the audited financial statements for the year ended December 31, 2009 included in our Annual Report on Form 10-K filed with the Securities and Exchange Commission ("SEC").

The condensed consolidated financial statements include the accounts of Isis Pharmaceuticals, Inc. ("we", "us" or "our") and our wholly owned subsidiaries, Isis USA Ltd. and Symphony GenIsis, Inc. In addition to our wholly owned subsidiaries, our condensed consolidated financial statements include our equity investment in Regulus Therapeutics Inc., an entity we identified as a variable interest entity. Beginning in the first quarter of 2010, as a result of adopting a new accounting standard for identifying which enterprise has the power to direct activities of a variable interest entity, we concluded that we are no longer the primary beneficiary of Regulus. As such we have presented our share of Regulus' operating results on a separate line in our condensed consolidated statement of operations called "Equity in net loss of Regulus Therapeutics Inc." On our condensed consolidated balance sheet, we have presented our investment in Regulus on a separate line in the non-current liabilities section called "Investment in Regulus Therapeutics Inc." Prior to the adoption of the new accounting standard, we were the primary beneficiary of Regulus and as such we consolidated Regulus' financial results on a line-by-line basis. We have not reclassified amounts in the prior period financial statements to conform to the current period presentation. As a result of completing the sale of Ibis Biosciences, Inc. to Abbott Molecular Inc., or AMI, in January 2009, we presented Ibis' financial position and results of operations separately as discontinued operations in our condensed consolidated financial statements. All significant intercompany balances and transactions have been eliminated in consolidation.

2. Significant Accounting Policies

Revenue Recognition

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

Research and development revenue under collaborative agreements

We often enter into collaborations under which we receive non-refundable upfront payments for prior or future expenditures. We recognize revenue related to upfront payments ratably over our period of performance relating to the term of the contractual arrangements. Occasionally, we are required to estimate our period of performance when the agreements we enter into do not clearly define such information. The revenue we recognize could be materially different if different estimates prevail. To date, we have not had to make material adjustments to our estimates. We have made estimates of our continuing obligations on several agreements. Our collaborative agreements typically include a research and/or development project plan that includes the activities the agreement requires each party to perform during the collaboration and the party responsible for performing them. We estimate the period of time over which we will complete the activities for which we are responsible and use that period of time as our period of performance for purposes of revenue recognition and amortize revenue over such period. When our collaborators have asked us to continue performing work in a collaboration beyond the initial period of performance, we have extended our amortization period to correspond to the new extended period of performance. In no case have adjustments to performance periods and related adjustments to revenue amortization periods had a material impact on our revenue.

Our collaborations often include contractual milestones. When we achieve these milestones, we are entitled to payment, according to the underlying agreements. We generally recognize revenue related to milestone payments upon completion of the milestone's substantive performance requirement, as long as we are reasonably assured of collecting the resulting receivable, the amounts are not refundable and we have no future performance obligations related to the achievement of the milestone.

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We often enter into revenue arrangements that contain multiple deliverables. In these cases, we recognize revenue from each element of the arrangement as long as we are able to determine a separate fair value for each element, we have completed our obligation to deliver or perform on that element and we are reasonably assured of collecting the resulting receivable.

As part of our Genzyme strategic alliance, in February 2008 Genzyme Corporation made a $150 million equity investment in us by purchasing five million shares of our common stock at $30 per share. The price Genzyme paid for our common stock represented a significant premium over the fair value of our stock. Using a Black-Scholes option valuation model, we determined that the value of the premium was $100 million, which represented value Genzyme gave to us to help fund the companies' research collaboration, which began in January 2008. We accounted for this premium as deferred revenue and are amortizing it along with the $175 million licensing fee that we received in June 2008 ratably into revenue until June 2012, which represents the end of our performance obligation based on the current research and development plan.

Licensing and royalty revenue

We often enter into agreements to license our proprietary patent rights on an exclusive or non-exclusive basis in exchange for license fees and/or royalties. We generally recognize as revenue immediately those licensing fees and royalties for which we have no significant future performance obligations and are reasonably assured of collecting the resulting receivable.

Short-term investments

We consider all liquid investments with maturities of 90 days or less when purchased to be cash equivalents. Our short-term investments have initial maturities of greater than 90 days from date of purchase. We classify our short-term investments as "available-for-sale" and carry them at fair market value based upon prices for identical or similar items on the last day of the fiscal period. We record unrealized gains and losses as a separate component of stockholders' equity and include net realized gains and losses in gain (loss) on investments in the condensed consolidated statement of operations. We use the specific identification method to determine the cost of securities sold.

We have equity investments in privately- and publicly-held biotechnology companies. We hold ownership interests of less than 20 percent in each of the respective companies except Regulus, our majority owned subsidiary, which we began accounting for using the equity method in the first quarter of 2010. Prior to 2010, we consolidated Regulus' financial results on a line-by-line basis. In determining if and when a decrease in market value below our cost in our equity positions is temporary or other-than-temporary, we examine historical trends in the stock price, the financial condition of the company, near term prospects of the company and our current need for cash. We record unrealized gains and losses related to temporary declines in the publicly-held companies as a separate component of stockholders' equity and account for securities in the privately-held companies, except for Regulus, under the cost method of accounting because we own less than 20 percent and do not have significant influence in their operations. When we determine that a decline in value in either a public or private investment is other-than-temporary, we recognize an impairment loss in the period in which the other-than-temporary decline occurs. During the first six months of 2010, we recognized a $1.1 million loss on investments primarily consisting of an $880,000 non-cash loss related to the other-than-temporary impairment of our equity investment in Antisense Therapeutics Limited and $349,000 of valuation allowances we recorded related to the investments we made in Excaliard Pharmaceuticals, Inc. and Achaogen, Inc. Because realization of our Excaliard and Achaogen investments is uncertain we recorded a full valuation allowance. During the first six months of 2009, we recognized a $2.7 million gain on investments primarily consisting of a $2.5 million gain when we sold all of the common stock of OncoGenex Pharmaceuticals Inc. that we owned. We determined that there were no other-than-temporary declines in value of our investments during the first six months of 2009.

Inventory valuation

We capitalize the costs of raw materials that we purchase for use in producing our drugs because until we use these raw materials they have alternative future uses. We include in inventory raw material costs for drugs that we manufacture for our partners under contractual terms and that we use primarily in our clinical development activities and drug products. We can use each of our raw materials in multiple products and, as a result, each raw material has future economic value independent of the development status of any single drug. For example, if one of our drugs failed, we could use the raw materials allocated for that drug to manufacture our other drugs. We expense these costs when we deliver the drugs to our partners, or as we provide these drugs for our own clinical trials. We reflect our inventory on the balance sheet at the lower of cost or market value under the first-in, first-out method. We review inventory periodically and reduce the carrying value of items we consider to be slow moving or obsolete to their estimated net realizable value. We consider several factors in estimating the net realizable value, including shelf life of raw materials, alternative uses for our drugs and clinical trial materials and historical write-offs. We did not record any inventory write-offs during the first six months of 2010 and 2009. Total inventory, which consisted of raw materials, was $2.8 million as of June 30, 2010 and December 31, 2009.

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Patents

We capitalize costs consisting principally of outside legal costs and filing fees related to obtaining patents. We review our capitalized patent costs regularly to ensure that they include costs for patent applications that have future value. We evaluate costs related to patents that we are not actively pursuing and write off any of these costs. We amortize patent costs over their estimated useful lives of ten years, beginning with the date the United States Patent and Trademark Office issues the patent. For the first six months of 2010 and 2009, we recorded a non-cash charge of $385,000 and $351,000, respectively, which we included in research and development expenses, related to the write-down of our patent costs to their estimated net realizable values.

Long-lived assets

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

Equity method of accounting

On January 1, 2010, we adopted an accounting standard, which replaced the quantitative-based risks and rewards calculation for determining which enterprise, if any, has a controlling financial interest in a variable interest entity. The new approach focuses on identifying which enterprise has the power to direct the activities of a variable interest entity that most significantly impacts the variable interest entity's economic performance and (1) the obligation to absorb losses of the variable interest entity or (2) the right to receive benefits from the variable interest entity. As a result of adopting this new accounting standard, we were required to change the way we account for our variable interest in Regulus. Since we and Alnylam Pharmaceuticals, Inc. share the ability to impact Regulus' economic performance, we are no longer the primary beneficiary of Regulus. We adopted the new standard on a prospective basis; therefore, beginning in the first quarter of 2010, we deconsolidated Regulus from our condensed consolidated financial statements and began to account for

our ownership interest in Regulus using the equity method of accounting. This means that we no longer include Regulus' revenue and operating expenses in our operating results. Instead we include our share of Regulus' operating results on a separate line in our condensed consolidated statement of operations called "Equity in net loss of Regulus Therapeutics Inc." On our condensed consolidated balance sheet, we present our investment in Regulus on a separate line in the non-current liabilities section called "Investment in Regulus Therapeutics Inc." We have not reclassified amounts in the prior period financial statements to conform to the current period presentation. For additional information, see Note 3, *Investment in Regulus Therapeutics Inc.*

Use of estimates

The preparation of condensed consolidated financial statements in conformity with accounting principles generally accepted in the United States requires management to make estimates and assumptions that affect the amounts reported in the condensed consolidated financial statements and accompanying notes. Actual results could differ from those estimates. Historically, our estimates have been accurate as we have not experienced any material differences between our estimates and our actual results.

Basic and diluted net income (loss) per share

We compute basic net income (loss) per share by dividing the net income (loss) by the weighted-average number of common shares outstanding during the period. As we incurred a loss from continuing operations for the three and six months ended June 30, 2010 and 2009, we did not include the following diluted common equivalent shares in the computation of diluted net loss from continuing operations per share because the effect would have been anti-dilutive:

- $2^5/_8$% convertible subordinated notes;
- GlaxoSmithKline convertible promissory notes;
- Dilutive stock options; and
- Warrants issued to Symphony GenIsis Holdings LLC

Consolidation of variable interest entities

We identify entities as variable interest entities either: (1) that do not have sufficient equity investment at risk to permit the entity to finance its activities without additional subordinated financial support, or (2) in which the equity investors lack an essential characteristic of a controlling financial interest. As of June 30, 2010, we had collaborative arrangements with eight entities that we consider to be variable interest entities. We are not the primary beneficiary for any of these entities. For the six months ended June 30, 2009, our condensed consolidated financial statements included one variable interest entity, Regulus, for which we were the primary beneficiary. As a result of adopting the new accounting standard related to our investment in Regulus in the first quarter of 2010, we deconsolidated Regulus because we are no longer the primary beneficiary of Regulus. See Note 3, *Investment in Regulus Therapeutics Inc.*, for additional details.

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Comprehensive income (loss)

We report, in addition to net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders, comprehensive income (loss) and its components as follow (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2010	2009	2010	2009
Comprehensive income (loss):				
Unrealized holding gains (losses)	$ (437)	$ 3,499	$ (286)	$ 2,990
Reclassification adjustment for realized gains (loss) included in net income (loss)	—	1,648	(925)	1,648
Net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders	(25,154)	(2,730)	(34,811)	183,488
Comprehensive income (loss)	$ (25,591)	$ 2,417	$ (36,022)	$ 188,126

Convertible debt

We account for our $2^5/_8$% convertible notes by separating the liability and equity components of the instruments in a manner that reflects our nonconvertible debt borrowing rate when we recognize interest expense in subsequent periods. As a result, we assigned a value to the debt component of our $2^5/_8$% convertible notes equal to the estimated fair value of a similar debt instrument without the conversion feature, which resulted in us recording the debt at a discount. We are amortizing the resulting debt discount over the life of the debt as additional non-cash interest expense. At June 30, 2010, the principal and accrued interest payable on our $2^5/_8$% convertible notes was $162.5 million and $1.6 million, respectively, and the fair value using quoted market prices was $154.1 million. At December 31, 2009, the principal and accrued interest payable on the notes was $162.5 million and $1.6 million, respectively, and the fair value using quoted market prices was $165.8 million.

Stock-based compensation expense

We account for our stock-based compensation expense related to employee stock options and employee stock purchases by estimating the fair value of each employee stock option grant and the employee stock purchase plan ("ESPP") purchase rights on the date of grant using the Black-Scholes model. The expected term of stock options granted represents the period of time that they are expected to be outstanding. We estimated the expected term of options granted based on historical exercise patterns.

For the six months ended June 30, 2010 and 2009, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	Six Months Ended June 30,	
	2010	2009
Risk-free interest rate	2.8%	1.8%
Dividend yield	0.0%	0.0%
Volatility	55.7%	56.9%
Expected Life	5.1 years	4.9 years

ESPP:

	Six Months Ended June 30,	
	2010	2009
Risk-free interest rate	0.2%	0.3%
Dividend yield	0.0%	0.0%
Volatility	54.8%	70.4%
Expected Life	6 months	6 months

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Stock-based compensation expense (in thousands, except per share data) was allocated as follows:

	Three Months Ended June 30,		Six Months Ended June 30,	
	2010	2009	2010	2009
Research and development	$ 2,611	$ 2,879	$ 5,436	$ 5,138
General and administrative	521	686	1,052	1,130
Non-cash compensation expense related to stock options included in continuing operations	3,132	3,565	6,488	6,268
Non-cash compensation expense related to stock options included in equity in net loss of Regulus Therapeutics Inc.	139	—	301	—
Non-cash compensation benefit related to stock options included in discontinued operations	—	—	—	(1,558)
Total	$ 3,271	$ 3,565	$ 6,789	$ 4,710
Basic and diluted stock-based compensation expense, per share:				
Net loss per share included in continuing operations	$ (0.03)	$ (0.04)	$ (0.07)	$ (0.06)
Net loss per share related to stock options included in equity in net loss of Regulus Therapeutics Inc.	—	—	—	—
Net income per share included in discontinued operations	—	—	—	0.01
Total	$ (0.03)	$ (0.04)	$ (0.07)	$ (0.05)

As part of our Regulus joint venture, both we and Alnylam issued our own company's stock options to members of Regulus' Board of Directors, Scientific Advisory Board and employees of Regulus. In January 2009 as part of Regulus' conversion to a C-Corporation both we and Alnylam modified our own company's stock options issued to Regulus' employees, members of Regulus' Board of Directors and Scientific Advisory Board to stop vesting in these stock awards before the awards were fully vested. Additionally, in February 2009, Regulus issued options to purchase its own common stock to Regulus' employees, members of Regulus' Board of Directors and members of Regulus' Scientific Advisory Board.

As of June 30, 2010, total unrecognized compensation cost related to non-vested stock-based compensation plans was $13.6 million. We will adjust total unrecognized compensation cost for future changes in estimated forfeitures. We expect to recognize this cost over a weighted average period of 1.4 years.

Impact of recently issued accounting standards

In October 2009, the FASB issued a new accounting standard for revenue arrangements with multiple deliverables. This new standard requires companies to separate multiple-deliverable arrangements and at inception allocate arrangement consideration using a selling price hierarchy. The new standard also requires additional disclosures about multiple-deliverable arrangements. This guidance is effective prospectively for revenue arrangements entered into or materially modified in fiscal years beginning on or after June 15, 2010 and is effective for our fiscal year 2011. We do not expect this new standard to have a material impact on our financial statements.

In March 2010, the FASB issued a new accounting standard that establishes a revenue recognition method for milestone payments in research and development agreements. Under the new standard, entities can make an accounting policy election to recognize a payment that is contingent upon the achievement of a substantive milestone in its entirety in the period in which the milestone is achieved. We have historically applied a revenue recognition method for milestone payments that is consistent with this new standard. Therefore when we adopt this new standard in 2011, the only change required is to provide additional information about the substantive nature of the milestones in our research and development agreements.

3. Investment in Regulus Therapeutics Inc.

In September 2007, we and Alnylam established Regulus as a company focused on the discovery, development, and commercialization of microRNA-based therapeutics. Regulus combines the strengths and assets of our and Alnylam's technologies, know-how, and intellectual property relating to microRNA-based therapeutics.

We and Alnylam each granted Regulus exclusive licenses to our respective intellectual property for microRNA therapeutic applications, as well as certain early fundamental patents in the microRNA field, including the "Tuschl III", "Sarnow" and "Esau" patent series. Alnylam made an initial investment of $10 million in Regulus to balance venture ownership. We own 51 percent of Regulus and Alnylam owns the remaining 49 percent. Regulus operates as an independent company with a separate board of directors, scientific advisory board and management team. We and Alnylam retain rights to develop and commercialize on pre-negotiated terms microRNA therapeutic products that Regulus decides not to develop either itself or with a partner.

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We and Alnylam provide Regulus research and development and general and administrative services under the terms of a services agreement.

In January 2009, Regulus completed a legal reorganization from a limited liability company to a C-Corporation. In March 2009, Regulus raised $20 million in a Series A preferred equity financing, in which we and Alnylam were the sole and equal investors.

Regulus Collaborations

sanofi-aventis

In June 2010, Regulus entered into a global, strategic alliance with sanofi-aventis to discover, develop, and commercialize microRNA therapeutics. The alliance includes $750 million of potential milestone payments in addition to a $25 million upfront fee, a $10 million future equity investment and annual research support for three years with the option to extend two additional years. In addition, Regulus is eligible to receive royalties on microRNA therapeutic products commercialized by sanofi-aventis. Sanofi-aventis also received an option for a broader technology alliance that provides Regulus certain rights to participate in development and commercialization of resulting products. If exercised, this three-year option is worth up to an additional $50 million to Regulus. We and Alnylam are each eligible to receive 7.5% of the upfront payment and all potential milestone payments, in addition to royalties on product sales. As a result, in July 2010 we received a payment of $1.9 million from Regulus.

GlaxoSmithKline

In April 2008, Regulus entered into a strategic alliance with GlaxoSmithKline, or GSK, to discover, develop and commercialize novel microRNA-targeted therapeutics to treat inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease. The alliance utilizes Regulus' expertise and intellectual property position in the discovery and development of microRNA-targeted therapeutics and provides GSK with an option to license drug candidates directed at four different microRNA targets with relevance in inflammatory disease. Regulus will be responsible for the discovery and development of the microRNA antagonists through completion of clinical proof of concept, unless GSK chooses to exercise its option earlier. After exercise of the option, GSK will have an exclusive license to drugs Regulus develops under each program for the relevant microRNA target for further development and commercialization on a worldwide basis. Regulus will have the right to further develop and commercialize any microRNA therapeutics which GSK chooses not to develop or commercialize.

In 2008, Regulus received $20 million in upfront payments from GSK, including a $15 million option fee and a $5 million note. The note plus interest will convert into Regulus stock in the future if Regulus achieves a minimum level of financing with institutional investors. In addition, we and Alnylam are guarantors of the note, and if the note does not convert or if Regulus does not repay the note in cash by April 2011, we, Alnylam and Regulus may elect to repay the note plus interest with shares of each company's common stock or cash. Regulus is eligible to receive from GSK up to $144.5 million in development, regulatory and sales milestone payments for each of the four microRNA-targeted drugs discovered and developed as part of the alliance. In May 2009, Regulus received a $500,000 discovery milestone payment from its collaboration with GSK for demonstrating a pharmacological effect in immune cells by specific microRNA inhibition. In addition, Regulus would receive from GSK tiered royalties up to double digits on worldwide sales of drugs resulting from the alliance.

In February 2010, Regulus announced the establishment of a new worldwide strategic alliance with GSK to develop and commercialize microRNA therapeutics targeting microRNA 122, or miR-122, for the treatment of hepatitis C virus, or HCV, infection. The new HCV alliance expands the ongoing GSK-Regulus immuno-inflammatory disease alliance formed in 2008. Under the terms of this HCV collaboration, Regulus received $8 million from GSK, including a $3 million license fee and a second $5 million note (guaranteed by Isis and Alnylam) that will convert into Regulus stock in the future if Regulus achieves a minimum level of financing with institutional investors. In addition, Regulus is eligible to receive several near-term significant payments associated with the advancement of an HCV drug, plus additional milestone payments with the potential to earn more than $150 million in miR-122-related combined payments and double-digit royalties consistent with the existing immuno-inflammatory diseases alliance terms established in April 2008. Because GSK has selected Regulus' miR-122 for the new collaboration, the number of immuno-inflammatory programs GSK has an option to license under the 2008 immuno-inflammatory alliance has been reduced from four to three.

As part of the HCV collaboration, Regulus granted GSK a limited license to develop and commercialize the miR-122 antagonist SPC 3649, if GSK acquires rights to this compound. Regulus will receive development and regulatory milestones as well as royalties if GSK develops and commercializes SPC 3649.

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Equity method of accounting

On January 1, 2010, as a result of adopting the new accounting standard for identifying which enterprise has the power to direct activities of a variable interest entity, we prospectively changed the way we account for our variable interest in Regulus. Since we and Alnylam share the ability to impact Regulus' economic performance, we are no longer the primary beneficiary of Regulus. Beginning in the first quarter of 2010, we deconsolidated Regulus from our condensed consolidated financial statements and began to account for our ownership interest in Regulus using the equity method of accounting. Below is a table summarizing the accounting impact to our balance sheet as of January 1, 2010 as a result of adopting the equity method of accounting (in thousands):

	As Originally Reported	As Adjusted	Effect of Change
Total Assets	$ 657,184	$ 626,006	$ (31,178)
Total Liabilities	$ (355,121)	$ (335,524)	$ 19,597
Total Stockholders' Equity	$ (302,063)	$ (290,482)	$ 11,581

Under the equity method of accounting, we are required to suspend losses if our share of Regulus' net loss exceeds the amount of funding we were required to provide. Since we and Alnylam are guarantors of both of the convertible notes that Regulus issued to GSK, we continued to recognize losses in excess of our net investment in Regulus up to the $5 million we guaranteed. If we had been applying the equity method from inception, we would have suspended recognizing our share of Regulus' losses in 2008 because it would have exceeded the amount we guaranteed under the first GSK convertible note. When we made the $10 million investment in March 2009 we would have recognized all of the suspended losses.

4. Discontinued Operations

In January 2009, AMI completed its acquisition of Ibis for a total purchase price of $215 million. Since we sold Ibis to AMI and Ibis met the criteria for a component of an entity, we reflect Ibis as a discontinued operation. Accordingly, we have presented the operating results of Ibis in our condensed consolidated statements of operations as discontinued operations. Net income from discontinued operations for the first six months of 2009 primarily consisted of the $202.5 million gain related to the sale of Ibis to AMI less $15.4 million of income tax expense. The components of discontinued operations for the six months ended June 30, 2009 are as follows (in thousands):

Revenue	$ —
Total operating expenses	35
Loss from operations	(35)
Loss attributed to noncontrolling interest in Ibis Biosciences, Inc.	6
Loss from discontinued operations	(29)
Gain on sale of Ibis Biosciences, Inc., net of tax	187,119
Net income from discontinued operations, net of tax	$ 187,090

We do not have any remaining assets and liabilities from discontinued operations in our accompanying condensed consolidated balance sheets at June 30, 2010 and December 31, 2009. We have not separately classified cash flows from discontinued operations in our condensed consolidated statement of cash flows.

5. Investments

As of June 30, 2010, our excess cash was primarily invested in commercial paper and debt instruments with strong credit ratings of financial institutions, corporations, U.S. government agencies and the U.S. Treasury. We have established guidelines relative to diversification and maturities that maintain safety and liquidity. We periodically review and modify these guidelines to maximize trends in yields and interest rates without compromising safety and liquidity.

The following table summarizes the contract maturity of the available-for-sale securities we held as of June 30, 2010:

One year or less	71%
After one year but within five years	29%
Total	100%

At June 30, 2010, we had an ownership interest of less than 20% in each of five private companies and two public companies with which we conduct business. The companies are Santaris Pharma A/S, Achaogen, Atlantic Pharmaceuticals Limited, Altair Therapeutics Inc. and Excaliard, which are privately-held and ATL and iCo Therapeutics Inc., which are publicly-traded. We account for securities in the privately-held companies under the cost method of accounting. During the first six months of 2010, we recognized a $1.1 million loss on investments primarily consisting of an $880,000 non-cash loss related to the other-than-temporary impairment of our equity investment in ATL and $349,000 of valuation allowances we recorded related to the investments we made in Excaliard and Achaogen. Because realization of our Excaliard and Achaogen investments is uncertain we recorded a full valuation allowance.

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Beginning in the first quarter of 2010, we deconsolidated Regulus from our condensed consolidated financial statements and began to account for our ownership interest in Regulus using the equity method of accounting. As a result, our short-term investments balance at June 30, 2010 did not include Regulus' short-term investments, compared to $14.5 million at December 31, 2009. The following is a summary of our investments (in thousands):

June 30, 2010	Amortized Cost	Unrealized Gains	Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Short-term investments:					
Corporate debt securities	$ 135,289	$ 218	$ (146)	$ —	$ 135,361
Debt securities issued by U.S. government agencies	139,089	104	(1)	—	139,192
Debt securities issued by the U.S. Treasury	65,134	63	(2)	—	65,195
Debt securities issued by states of the United States and political subdivisions of the states	275	—	(5)	—	270
Total securities with a maturity of one year or less	339,787	385	(154)	—	340,018
Corporate debt securities	44,951	63	(129)	—	44,885
Debt securities issued by U.S. government agencies	91,055	35	(3)	—	91,087
Total securities with a maturity of more than one year	136,006	98	(132)	—	135,972
Subtotal	$ 475,793	$ 483	$ (286)	$ —	$ 475,990

Equity securities:					
Current portion (included in Other current assets)	$ 1,538	$ 1,548	$ —	$ (880)	$ 2,206
Long-term portion (included in Deposits and other assets)	625	—	—	—	625
Subtotal	$ 2,163	$ 1,548	$ —	$ (880)	$ 2,831
	$ 477,956	$ 2,031	$ (286)	$ (880)	$ 478,821

December 31, 2009	Amortized Cost	Unrealized Gains	Unrealized Losses	Estimated Fair Value
Short-term investments:				
Corporate debt securities	$ 102,598	$ 174	$ (34)	$ 102,738
Debt securities issued by U.S. government agencies	151,008	178	(17)	151,169
Debt securities issued by the U.S. Treasury	32,027	42	(10)	32,059
Debt securities issued by states of the United States and political subdivisions of the states	275	—	—	275
Total securities with a maturity of one year or less	285,908	394	(61)	286,241
Corporate debt securities	41,388	262	(103)	41,547
Debt securities issued by U.S. government agencies	110,313	65	(218)	110,160
Debt securities issued by U.S. Treasury	31,136	2	(29)	31,109
Total securities with a maturity of more than one year	182,837	329	(350)	182,816
Subtotal	$ 468,745	$ 723	$ (411)	$ 469,057
Equity securities:				
Current portion (included in Other current assets)	$ 1,229	$ 2,645	$ —	$ 3,874
Long-term portion (included in Deposits and other assets)	625	—	—	625
Subtotal	$ 1,854	$ 2,645	$ —	$ 4,499
	$ 470,599	$ 3,368	$ (411)	$ 473,556

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Investments we consider to be temporarily impaired at June 30, 2010 are as follows (in thousands):

	Number of Investments	Less than 12 months of temporary impairment: Estimated Fair Value	Less than 12 months of temporary impairment: Unrealized Losses	More than 12 months of temporary impairment: Estimated Fair Value	More than 12 months of temporary impairment: Unrealized Losses	Total temporary impairment: Estimated Fair Value	Total temporary impairment: Unrealized Losses
Corporate debt securities	66	$ 104,220	$ (272)	$ 4,510	$ (3)	$ 108,730	$ (275)
Debt securities issued by U.S. government agencies	10	23,725	(4)	—	—	23,725	(4)
Debt securities issued by the U.S. Treasury	1	9,990	(2)	—	—	9,990	(2)
Debt securities issued by states of the United States and political subdivisions of the states	1	270	(5)	—	—	270	(5)
Total temporarily impaired securities	78	$ 138,205	$ (283)	$ 4,510	$ (3)	$ 142,715	$ (286)

We believe that the decline in value of these securities is temporary and primarily related to the change in market interest rates since purchase. We believe it is more likely than not that we will be able to hold these securities to maturity. Therefore we anticipate full recovery of their amortized cost basis at maturity.

6. Fair Value Measurements

We use a three-tier fair value hierarchy to prioritize the inputs used in our fair value measurements. These tiers include: Level 1, defined as observable inputs such as quoted prices in active markets, which includes our money market funds and treasury securities classified as available-for-sale securities and equity securities in publicly-held biotechnology companies; Level 2, defined as inputs other than quoted prices in active markets that are either directly or indirectly observable, which includes our fixed income securities and commercial paper classified as available-for-sale securities; and Level 3, defined as unobservable inputs in which little or no market data exists, therefore requiring an entity to develop its own assumptions. To estimate the fair value of securities classified as Level 2, we utilize the services of various fixed income pricing providers that use an industry standard valuation model, which is based on a market approach. The significant inputs for the valuation model include reported trades, broker/dealer quotes, benchmark securities and bids.

Below is a table of the assets that we measure at fair value on a recurring basis. For the following major security types, we break down the inputs used to measure fair value at June 30, 2010 (in thousands):

	Total	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 41,860	$ 28,315	$ 13,545	$ —
Corporate debt securities (2)	180,247	—	180,247	—
Debt securities issued by U.S. government agencies (2)	230,278	—	230,278	—
Debt securities issued by the U.S. Treasury (2)	65,195	65,195	—	—
Debt securities issued by states of the United States and political subdivisions of the states (2)	270	—	270	—
Equity securities (3)	2,207	2,207		—
Total	$ 520,057	$ 95,717	$ 424,340	$ —

(1) Included in cash and cash equivalents on our condensed consolidated balance sheet.

(2) Included in short-term investments on our condensed consolidated balance sheet.

(3) Included in other current assets on our condensed consolidated balance sheet.

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7. Long-Term Obligations

Equipment Financing Arrangement

In October 2008, we entered into a loan agreement related to an equipment financing and in September 2009, we amended the loan agreement to increase the aggregate maximum amount of principal we can draw under the agreement. Under the loan agreement, we and Regulus could borrow up to $19.4 million in principal to finance the purchase of equipment until the end of the draw down period, which ended in July 2010. The $19.4 million does not include the $600,000 Ibis borrowed in October 2008 that was fully repaid in the first quarter of 2009. Each draw down under the loan agreement has a term of three years, with principal and interest payable monthly. We calculate interest on amounts we borrow under the loan agreement based upon the three year interest rate swap at the time we make each draw down plus 4 percent. We are using the equipment purchased under the loan agreement as collateral. In June 2010, we drew down an additional $3.1 million in principal under the loan agreement. As of June 30, 2010, we have drawn down $15.1 million in principal under this loan agreement at a weighted average interest rate of 6.47 percent. The carrying balance under this loan agreement at June 30, 2010 and December 31, 2009 was $10.2 million and $10.0 million, respectively.

8. Lease Agreements

We currently occupy approximately 138,500 square feet of laboratory and office space, including a 28,704 square foot facility, which houses our manufacturing suites for our drug development business built to meet Good Manufacturing Practices. We are located in four buildings in Carlsbad, California. We lease all of these buildings under lease agreements. The leases on the three buildings we primarily use for laboratory and office space for our drug development business expire at the end of 2011.

On March 30, 2010 we entered a new lease agreement with an affiliate of BioMed Realty, L.P. Under the lease, BioMed will construct a new 176,000 square foot research facility in Carlsbad, California. Upon completion of construction, we will lease the new facility and consolidate the majority of our operations in the new facility. The lease has an initial term of 20 years with an option to extend the lease for up to four five-year periods.

Our rent under the new lease is based on a percentage of the total construction costs spent by BioMed to acquire the land and build the new facility. We will begin paying rent on January 1, 2012. Once the new facility is complete, we will be responsible for the costs associated with owning and maintaining the facility. Since our rent is based on a percentage of total construction costs spent by BioMed to acquire the land and build the new facility, and the facility is not yet built, it is difficult for us to calculate our future payment obligations under the lease. However, as of June 30, 2010, we estimate that the maximum potential future payments we may be required to make over the 20 year term of the lease are $172 million.

Under the lease we have an option to purchase the facility at the end of the fifth, sixth, seventh, eighth, ninth, fifteenth and twentieth year of the lease. The purchase price for the purchase options ending on the fifth through ninth year will be set based on the total construction costs spent by BioMed to acquire the land and build the new facility less rent payments made through the purchase date. The purchase price for the purchase options ending on the fifteenth and twentieth year will be based on fair market value at those times.

In conjunction with the new lease agreement with BioMed, we purchased a parcel of land for $10.1 million and subsequently sold it to BioMed, who will construct the new facility on it. Since we have the option to purchase the facility, including the land, we have continuing involvement in the land which requires us to account for the purchase and sale of the land as a financing transaction. As such, our fixed assets at June 30, 2010 included the land. Additionally, we have recorded a corresponding amount in our non-current liabilities as a long-term financing obligation. Since land is not a depreciable asset, the value of the land and financing obligation we recorded will not change until we exercise our purchase option or the lease is terminated.

We also lease from BioMed an approximately 28,700 square foot facility that houses our manufacturing suites for our drug development business. On March 30, 2010 we amended the lease to extend the term through December 31, 2031, subject to four five-year options to extend the lease, and to obtain an option to purchase the manufacturing facility on similar terms as the purchase options described above.

9. Income Taxes

At December 31, 2009, our balance sheet included an income taxes payable of $7.3 million. As of June 30, 2010 our balance sheet included an income tax receivable of $517,000. This change relates to $7.7 million of income tax payments made to various taxing authorities during the first quarter of 2010 for our 2009 estimated tax liability. The income tax receivable represents the potential amount that could be refunded to us when we file our state and federal income tax returns later this year.

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10. Collaborative Arrangements and Licensing Agreements

The information discussed below represents significant partnerships we entered into during 2010. There are no other material changes from the information provided in Note 7—*Collaborative Arrangements and Licensing Agreements* of the Consolidated Financial Statements section, included in our

Traditional Pharmaceutical Alliances and Licensing

GlaxoSmithKline

In March 2010, we entered into a new strategic alliance with GSK that will apply our antisense drug discovery platform to seek out and develop new therapeutics against targets for rare and serious disease, including infectious diseases and some conditions causing blindness.

Under the terms of the agreement, which covers up to six programs, we received an upfront $35 million payment from GSK, which we began amortizing into revenue in the second quarter of 2010 over the five year period of our performance based on the research plan included in the agreement. For the three and six months ended June 30, 2010, we recognized revenue of $1.8 million and our balance sheet included deferred revenue of $33.3 million relating to the $35 million upfront payment. We are also eligible to receive on average up to $20 million in milestone payments per program up to Phase 2 proof-of-concept. GSK has the option to license drugs from these programs at Phase 2 proof-of-concept, and will be responsible for all further development and commercialization. We will be eligible to receive license fees and milestone payments, totaling up to nearly $1.5 billion, in the event all six programs are successfully developed for one or more indications and commercialized through to pre-agreed sales targets. In addition, we will receive up to double-digit royalties on sales from any product that GSK successfully commercializes.

11. Segment Information and Concentration of Business Risk

Segment information

We currently report our financial results in two segments, Drug Discovery and Development and Regulus. Segment loss from operations includes revenue less research and development expenses and general and administrative expenses attributable to each segment. See the Business Segments discussion within the "Management's Discussion and Analysis of Financial Condition and Results of Operations" in Item 2 below for additional information on the segments.

Our Drug Discovery and Development segment generates revenue from collaborations with corporate partners and from licensing proprietary patent rights. Revenue from collaborations with corporate partners may consist of upfront payments, funding for research and development activities, milestone payments and royalties or profit sharing payments. This segment's proprietary technology to discover and characterize novel antisense inhibitors has enabled our scientists to modify the properties of our antisense drugs for optimal use with particular targets and thus, to produce a broad proprietary portfolio of drugs applicable to many disease targets.

Our Regulus segment generates revenue from research grants and collaborations with corporate partners such as its strategic alliances with GSK and sanofi-aventis.

The following is information for revenue, loss from operations and total assets by segment (in thousands):

	Isis Drug Discovery and Development	Regulus
Three Months Ended June 30, 2010		
Revenue:		
Research and development	$ 21,143	$ 809
Licensing and royalty	2,360	—
Total segment revenue	$ 23,503	$ 809
Loss from operations	$ (18,672)	$ (7,876)

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	Drug Discovery and Development	Regulus	Consolidated Total
Three Months Ended June 30, 2009			
Revenue:			
Research and development	$ 29,643	$ 1,125	$ 30,768
Licensing and royalty	224	—	224
Total segment revenue	$ 29,867	$ 1,125	$ 30,992
Loss from operations	$ (3,127)	$ (1,700)	$ (4,827)

	Isis Drug Discovery and Development	Regulus
Six Months Ended June 30, 2010		
Revenue:		
Research and development	$ 49,699	$ 1,495
Licensing and royalty	3,730	—
Total segment revenue	$ 53,429	$ 1,495
Loss from operations	$ (23,551)	$ (10,944)
Total assets as of June 30, 2010	$ 606,351	$ 34,445

	Drug Discovery and Development	Regulus	Consolidated Total
Six Months Ended June 30, 2009			
Revenue:			
Research and development	$ 58,690	$ 1,763	$ 60,453

Licensing and royalty	2,115	—	2,115
Total segment revenue	$ 60,805	$ 1,763	$ 62,568
Loss from operations	$ (1,906)	$ (3,564)	$ (5,470)
Total assets as of December 31, 2009	$ 634,820	$ 22,364	$ 657,184

As a result of adopting the new accounting standard related to our investment in Regulus, we deconsolidated Regulus from our condensed consolidated financial statements and began to account for ownership interest in Regulus using the equity method of accounting. Therefore in the first quarter of 2010 we began presenting our net share of Regulus' operating results on a separate line in our statement of operations called "Equity in net loss of Regulus Therapeutics Inc."

Concentrations of business risk

We have historically funded our operations from collaborations with corporate partners and a relatively small number of partners have accounted for a significant percentage of our revenue. Revenue from significant partners, which is defined as 10% or more of our total revenue, was as follows:

	Three Months Ended June 30,		Six Months Ended June 30,	
	2010	2009	2010	2009
Partner A	71%	54%	62%	53%
Partner B	4%	7%	20%	7%
Partner C	0%	22%	0%	22%

Contract receivables from one significant partner comprised approximately 83% of contract receivables at June 30, 2010. Contract receivables from one significant partner comprised approximately 92% of contract receivables at December 31, 2009.

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

Forward-Looking Statements

In addition to historical information contained in this Report on Form 10-Q, this Report includes forward-looking statements regarding our business, the therapeutic and commercial potential of our technologies and products in development, and the financial position of Isis Pharmaceuticals, Inc. and Regulus Therapeutics, our majority-owned subsidiary. Any statement describing our goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward looking statements. Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning our programs are described in additional detail in our Annual Report on Form 10-K for the year ended December 31, 2009, which is on file with the U.S. Securities and Exchange Commission, and those identified within this Item entitled "Risk Factors" beginning on page 28 of this Report.

Overview

We are the leading company in antisense technology, exploiting a novel drug discovery platform we created to generate a broad pipeline of first-in-class drugs. Antisense technology is a direct route from genomics to drugs. With our highly efficient and prolific drug discovery platform we can expand our drug pipeline and our partners' pipelines with antisense drugs that address significant unmet medical needs. Our business strategy is to do what we do best—to discover unique antisense drugs and develop these drugs to key value inflection points. In this way, our organization remains small and focused. We discover new drugs, outlicense our drugs to partners and build a broad base of license fees, milestone payments and royalty income. We maximize the value of the drugs we discover by putting them in the hands of quality partners with late-stage development and commercialization expertise. For example, we partner our drugs with leading pharmaceutical companies with late-stage development, commercialization and marketing expertise, such as Bristol-Myers Squibb, Genzyme, GSK and Eli Lilly and Company. Additionally, we have created a consortium of smaller companies that can broadly exploit the technology with their expertise in specific disease areas. We call these smaller companies our satellite companies. In addition to our cutting edge antisense programs, we maintain technology leadership beyond our core areas of focus through collaborations with Alnylam and Regulus, a company we established and jointly own focused on microRNA therapeutics. We also exploit our inventions with other therapeutic opportunities through collaborations with Achaogen and Archemix Corp. Beyond human therapeutics, we benefit from the commercialization of products of our inventions by other companies that are better positioned to maximize the commercial potential of these inventions, such as Ibis, a subsidiary of ours that we sold in early 2009 to AMI. All of these aspects fit into our unique business model and create continued shareholder value.

We protect our proprietary RNA-based technologies and products through our substantial patent estate. We remain one of the most prolific patent holders in the United States, ranked as having one of the highest ratios of issued patents per employee with approximately 1,600 issued patents. With our ongoing research and development, our patent portfolio continues to grow. The patents not only protect our key assets—our technology and our drugs—they also form the basis for lucrative licensing and partnering arrangements. To date, we have generated more than $395 million from our intellectual property sale and licensing program that helps support our internal drug discovery and development programs.

The clinical success of mipomersen, the lead drug in our cardiovascular franchise, is a clear example of the power of our RNA-based technology. Our clinical experience with mipomersen demonstrates that antisense drugs work in man. We and Genzyme have completed the four Phase 3 studies planned to support the initial regulatory filings for mipomersen. Across all four studies, treatment with mipomersen produced promising results in patients who have persistently high LDL-C levels despite being treated on maximally tolerated lipid-lowering therapy. These data are consistent with our observations of

mipomersen in earlier clinical studies and support the profile of the drug as a novel treatment to reduce LDL-C in patients with high cholesterol, and at high cardiovascular risk and who cannot reduce their LDL-C sufficiently with currently available lipid-lowering therapies.

With mipomersen we have additional evidence, as we have shown with other antisense drugs, that we can predict the activity of our drugs in man from the preclinical successes we observe in animals. We believe mipomersen's success has validated our technology platform and increased the value of our drugs.

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Since 2007, our partnerships, including our strategic alliance with GSK, have generated an aggregate of more than $815 million in payments from licensing fees, equity purchase payments and milestone payments. In addition, for our partnered drugs we have the potential to earn more than $3.2 billion in future milestone payments. We also will share in the future commercial success of our inventions and drugs resulting from these partnerships through earn out, profit sharing, and/or royalty arrangements. Our strong financial position is a result of the persistent execution of our business strategy and our inventive and focused research and development capabilities.

Business Segments

We currently focus our business on two principal segments:

Drug Discovery and Development Within our primary business segment, we are exploiting a novel drug discovery platform we created to generate a broad pipeline of first-in-class drugs for us and our partners. With our proprietary drug discovery platform we can rapidly identify drugs, providing a wealth of potential targets to treat a broad range of diseases. We focus our efforts in therapeutic areas where our drugs will work best, efficiently screening many targets in parallel and carefully selecting the best drugs. This efficiency combined with our rational approach to selecting disease targets enables us to build a large and diverse portfolio of drugs designed to treat a variety of health conditions including cardiovascular, metabolic, inflammatory, ocular and neurodegenerative diseases, and cancer. We currently have 23 drugs in development. Our partners are licensed to develop, with our support, 12 of these 23 drugs, which substantially reduces our development costs.

Regulus Therapeutics Inc. In September 2007, we and Alnylam established Regulus as a company focused on the discovery, development and commercialization of microRNA therapeutics. Regulus is addressing therapeutic opportunities that arise from alterations in microRNA expression. Since microRNAs may act as master regulators, affecting the expression of multiple genes in a disease pathway, microRNA therapeutics define a new platform for drug discovery and development and microRNAs may also prove to be an attractive new diagnostic tool for disease characterization.

Beginning in the first quarter of 2010, as a result of adopting a new accounting standard, we no longer included Regulus' revenue and operating expenses in our operating results and no longer included Regulus' cash in our cash balance. See Note 2, *Significant Accounting Policies*, and Note 3, *Investment in Regulus Therapeutics Inc.*, in the Notes to the condensed consolidated financial statements for a more detailed explanation of this change.

Recent Events

Drug Development Highlights

- Mipomersen is being developed by us and Genzyme for patients with high cardiovascular risk who cannot adequately control their cholesterol levels with current therapies and who need new treatment options. We and Genzyme reported positive data from two Phase 3 studies evaluating mipomersen in patients with severe hypercholesterolemia and patients with high-cholesterol at high risk for coronary heart disease.
  - In a Phase 3 study evaluating mipomersen in patients with severe hypercholesterolemia, we and Genzyme reported that the study met its primary endpoint with a 36 percent reduction in LDL-C compared with a 13 percent increase in placebo.
  - In a Phase 3 study evaluating mipomersen in patients with high-cholesterol at high risk for developing coronary heart disease, we and Genzyme reported that the study met its primary endpoint with a 37 percent reduction in LDL-C compared with a 5 percent decrease in placebo.
  - In both studies all secondary endpoints were met.
  - In both studies, frequently observed adverse events were injection site reactions, flu-like symptoms and elevations in liver transaminases, as seen in previous studies.
- We reported new data from seven programs in our metabolic disease franchise at the American Diabetes Association's Scientific Sessions.
  - We reported the full data from a positive Phase 2 study evaluating ISIS 113715 in patients with type 2 diabetes whose glucose levels were uncontrolled despite being treated with maximum doses of sulfonylureas.
  - We reported the full data from a positive Phase 1 study evaluating ISIS-GCGR$_{Rx}$ in patients who were given a glucagon challenge that doubled both plasma glucagon and glucose levels.
  - We presented new data from our obesity drug discovery program to a number of metabolic targets in a variety of animal models showing that antisense inhibition provided therapeutic benefit including reductions in fat mass and body weight and improved glucose metabolism.
- We added a new development candidate, ISIS-GSK1$_{Rx}$, to our pipeline that was selected as part of our collaboration with GSK to develop therapeutic drugs to treat rare and infectious diseases for which we earned a $5 million milestone payment.
- Achaogen initiated a Phase 2 study on ACHN-490, for which we earned a $2 million milestone payment.
- Excaliard reported positive Phase 2 data demonstrating that treatment with EXC 001 reduced scarring in patients following elective abdominal surgery.
- iCo received approval to initiate a Phase 2 study on iCo-007 in patients with diabetic macular edema.
- OncoGenex and Teva initiated a Phase 3 study on OGX-011 in patients with prostate cancer.
- OncoGenex reported positive Phase 1 data on OGX-427 at the American Society of Clinical Oncology.

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Corporate Highlights

- We formed a new strategic alliance worth up to nearly $1.5 billion with GSK to develop antisense drugs to treat rare and infectious diseases. Including the recently earned $5 million milestone payment that GSK will pay to us in the third quarter, we will have received $40 million of the potential $155 million in pre-licensing payments.

- Regulus formed a new alliance with sanofi-aventis worth potentially over $750 million to develop and commercialize microRNA therapeutics, including Regulus' leading fibrosis program targeting microRNA-21.
- We received $1.9 million from Regulus, representing 7.5 percent of the $25 million upfront payment Regulus received from sanofi-aventis.
- We and BMS extended our collaboration by two years and will continue to develop a follow-on drug to BMS-PCSK9$_{Rx}$ for franchise extension.

Critical Accounting Policies

We prepare our condensed consolidated financial statements in conformity with accounting principles generally accepted in the United States of America. As such, we are required to 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 discusses the development, selection and disclosure of such estimates with our audit committee of our board of directors. There are specific risks associated with these critical accounting policies and we caution that future events rarely develop exactly as expected, and that best estimates routinely require adjustment.

Historically, our estimates have been accurate as we have not experienced any material differences between our estimates and our actual results. The significant accounting policies, which we believe are the most critical to aid in fully understanding and evaluating our reported financial results, require the following:

- Assessment of the propriety of revenue recognition and associated deferred revenue;
- Determination of the proper valuation of investments in marketable securities and other equity investments;
- Estimations to assess the recoverability of long-lived assets, including property and equipment, intellectual property and licensed technology;
- Determination of the proper valuation of inventory;
- Determination of the appropriate cost estimates for unbilled preclinical studies and clinical development activities;
- Estimation of our net deferred income tax asset valuation allowance;
- Determination of when we are the primary beneficiary for entities that we identify as variable interest entities;
- Determination of the fair value of convertible debt without the conversion feature; and
- Estimations to determine the fair value of stock-based compensation, including the expected life of the option, the expected stock price volatility over the term of the expected life and estimated forfeitures.

Except as set forth below, there have been no material changes to our critical accounting policies and estimates from the information provided in Item 7, "Management's Discussion and Analysis of Financial Condition and Results of Operations", included in our Annual Report on Form 10-K for the year ended December 31, 2009.

Consolidation of variable interest entities

On January 1, 2010, we adopted an accounting standard, which replaced the quantitative-based risks and rewards calculation for determining which enterprise, if any, has a controlling financial interest in a variable interest entity. The new approach focuses on identifying which enterprise has the power to direct the activities of a variable interest entity that most significantly impacts the variable interest entity's economic performance and (1) the obligation to absorb losses of the variable interest entity or (2) the right to receive benefits from the variable interest entity. As a result of adopting this new accounting standard, we were required to change the way we account for our variable interest in Regulus. Since we and Alnylam Pharmaceuticals, Inc. share the ability to impact Regulus' economic performance, we are no longer the primary beneficiary of Regulus. We adopted the new standard on a prospective basis, therefore beginning in the first quarter of 2010, we deconsolidated Regulus from our condensed consolidated financial statements and began to account for our ownership interest in Regulus using the equity method of accounting. This means that we no longer include Regulus' revenue and operating expenses in our operating results. Instead we include our share of Regulus' operating results on a separate line in our condensed consolidated statement of operations called "Equity in net loss of Regulus Therapeutics Inc." On our condensed consolidated balance sheet, we present our investment in Regulus on a separate line in the non-current liabilities section called "Investment in Regulus Therapeutics Inc." We have not reclassified amounts in the prior period financial statements to conform to the current period presentation. For additional information, see Note 3, *Investment in Regulus Therapeutics Inc.*

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Results of Operations

As a result of adopting the new accounting standard related to our investment in Regulus, we have presented our net share of Regulus' operating results on a separate line in our statements of operations called "Equity in net loss of Regulus Therapeutics Inc." for the three and six months ended June 30, 2010, compared to the line-by-line consolidation for the same periods in 2009. We have not reclassified amounts in the prior period financial statements to conform to the current period presentation. We discuss Regulus' operating results in a separate section below.

As a result of selling Ibis to AMI, Ibis' financial results are considered discontinued operations. Accordingly, we have presented the operating results of Ibis for 2009 in our financial statements separately as discontinued operations.

Revenue

Total revenue for the three and six months ended June 30, 2010 was $23.5 million and $53.4 million, respectively, compared to $31.0 million and $62.6 million for the same periods in 2009. Our revenue fluctuates based on the nature and timing of payments under agreements with our partners, including license fees, milestone-related payments and other payments. For example, in the first quarter of 2010 we recognized as revenue a $6 million milestone

payment we received from BMS for initiating Phase 1 studies on BMS-PCSK9$_{Rx}$. And, in the second quarter of 2010, we began recognizing revenue from the $35 million upfront payment we received from GSK. Additionally, we earned $1.9 million from Regulus related to its recent strategic alliance with sanofi-aventis. Although we recognized new revenue from GSK, BMS and Regulus in the first half of 2010, our revenue compared to the first half of 2009 decreased slightly, primarily because the amortization of the upfront fees from our Ortho-McNeil-Janssen Pharmaceuticals, Inc., or OMJP, and BMS collaborations ended in the third quarter of 2009 and April 2010, respectively. Revenue for the first half of 2010 also decreased by $1.8 million because we are no longer including Regulus' revenue in our 2010 revenue.

Recently, we earned a $5 million milestone payment from GSK when we identified a drug development candidate to move forward in development under our GSK partnership. Because we achieved the milestone in July, we will recognize revenue from the milestone payment in the third quarter of 2010.

Collaborations with Alnylam, GSK and Genzyme include ongoing research and development activities. Therefore, we will continue to recognize significant amounts of revenue from these collaborations in the future from the amortization of the upfront fees we received.

Drug Discovery & Development

Research and Development Revenue Under Collaborative Agreements

Research and development revenue under collaborative agreements for the three and six months ended June 30, 2010 was $21.1 million and $49.7 million, respectively, compared to $30.8 million and $60.5 million for the same periods in 2009. The decrease in the first half of 2010 compared to the first half of 2009 was primarily due to the decrease in revenue from our collaboration with OMJP that we describe above offset by the revenue we recorded for the $6 million milestone payment we received from BMS and the $1.8 million amortization of the upfront payment from GSK. Research and development revenue also decreased by $1.8 million because we are no longer including Regulus' revenue in our 2010 revenue.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties for the three and six months ended June 30, 2010 was $2.4 million and $3.7 million, respectively, compared to $224,000 and $2.1 million for the same periods in 2009. The increase primarily relates to the $1.9 million sublicensing revenue we earned from Regulus in the second quarter of 2010 when Regulus entered into a strategic alliance with sanofi-aventis.

Operating Expenses

Operating expenses for the three and six months ended June 30, 2010 were $42.2 million and $77.0 million, respectively, compared to $35.8 million and $68.0 million for the same periods in 2009. The higher expenses in 2010 were primarily due to an increase in costs associated with advancing mipomersen toward its initial regulatory filings planned for the first half of next year offset in part by a $5.3 million decrease because we are no longer including Regulus' operating expenses in our 2010 operating expenses.

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

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Research and Development Expenses

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

The following table sets forth information on research and development costs (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2010	2009	2010	2009
Research and development expenses	$ 36,513	$ 29,267	$ 65,675	$ 55,550
Non-cash compensation expense related to stock options	2,611	2,879	5,436	5,138
Total research and development expenses	$ 39,124	$ 32,146	$ 71,111	$ 60,688

For the three and six months ended June 30, 2010, we incurred total research and development expenses of $36.5 million and $65.7 million, respectively, compared to $29.3 million and $55.6 million for the same periods in 2009. The higher expenses in 2010 were primarily due to an increase in costs associated with advancing mipomersen toward its initial regulatory filings planned for the first half of next year offset in part by a $4.4 million decrease because we are no longer including Regulus' research and development expenses in our 2010 operating expenses. All amounts discussed exclude non-cash compensation expense related to stock options.

Drug Discovery & Development

Antisense Drug Discovery

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

As we continue to advance our antisense technology, we are investing in our antisense drug discovery programs to expand our and our partners' drug pipeline. We anticipate that our existing relationships and collaborations, as well as prospective new partners, will continue to help fund our research

programs, as well as contribute to the advancement of the science by funding core antisense technology research.

Our antisense drug discovery expenses were as follows (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2010	2009	2010	2009
Antisense drug discovery	$ 8,293	$ 6,009	$ 16,039	$ 11,398
Non-cash compensation expense related to stock options	778	812	1,581	1,510
Total antisense drug discovery	$ 9,071	$ 6,821	$ 17,620	$ 12,908

Antisense drug discovery costs for the three and six months ended June 30, 2010 were $8.3 million and $16.0 million, respectively, compared to $6.0 million and $11.4 million for the same periods in 2009, all amounts exclude non-cash compensation expense related to stock options. The higher expenses in 2010 were primarily due to increased activity levels related to our planned investment to expand our pipeline by adding three to five new drugs this year and additional spending to implement an improved chemistry platform for our drugs, called Generation 2.5, that should increase the potency, expand the available routes of administration and enhance the commercial potential of our drugs. These activities resulted in an increase in personnel, laboratory supplies and research services provided by third parties in 2010.

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Antisense Drug Development

The following table sets forth research and development expenses for our major antisense drug development projects (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2010	2009	2010	2009
Mipomersen	$ 9,356	$ 5,532	$ 15,859	$ 10,289
Other antisense development projects	7,298	3,814	11,163	8,278
Development overhead costs	1,344	1,151	2,759	2,447
Non-cash compensation expense related to stock options	776	939	1,681	1,768
Total antisense drug development	$ 18,774	$ 11,436	$ 31,462	$ 22,782

Antisense drug development expenditures were $18.0 million and $29.8 million for the three and six months ended June 30, 2010, compared to $10.5 million and $21.0 million for the same periods in 2009, all amounts exclude non-cash compensation expense related to stock options. We attribute the increase to the broad Phase 3 program for mipomersen and an increase in other antisense development projects due to the expansion of our drug pipeline.

We may conduct multiple clinical trials on a drug candidate, including multiple clinical trials for the various indications we may be studying. Furthermore, as we obtain results from trials we may elect to discontinue clinical trials for certain drug candidates in certain indications in order to focus our resources on more promising drug candidates or indications. Our Phase 1 and Phase 2 programs are clinical research programs that fuel our Phase 3 pipeline. When our products are in Phase 1 or Phase 2 clinical trials, they are in a dynamic state where we continually adjust the development strategy for each product. Although we may characterize a product as “in Phase 1” or “in Phase 2,” it does not mean that we are conducting a single, well-defined study with dedicated resources. Instead, we allocate our internal resources on a shared basis across numerous products based on each product’s particular needs at that time. This means we are constantly shifting resources among products. Therefore, what we spend on each product during a particular period is usually a function of what is required to keep the products progressing in clinical development, not what products we think are most important. For example, the number of people required to start a new study is large, the number of people required to keep a study going is modest and the number of people required to finish a study is large. However, such fluctuations are not indicative of a shift in our emphasis from one product to another and cannot be used to accurately predict future costs for each product. And, because we always have numerous products in preclinical and early stage clinical research, the fluctuations in expenses from product to product, in large part, offset one another. If we partner a drug, it may affect the size of a trial, its timing, its total cost and the timing of the related cost. Our partners are developing, with our support, 12 of our 23 drug candidates, which substantially reduces our development costs. As part of our collaboration with Genzyme, we are over time transitioning the development responsibility to Genzyme and Genzyme will be responsible for the commercialization of mipomersen. We are contributing up to the first $125 million in funding for the development costs of mipomersen. Thereafter we and Genzyme will share development costs equally. Our initial development funding commitment and the shared funding will end when the program is profitable.

Manufacturing and Operations

Expenditures in our manufacturing and operations function consist primarily of personnel costs, specialized chemicals for oligonucleotide manufacturing, laboratory supplies and outside services. This function is responsible for providing drug supplies to antisense drug discovery and antisense drug development, including the analytical testing to satisfy good laboratory and good manufacturing practices requirements.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2010	2009	2010	2009
Manufacturing and operations	$ 4,636	$ 3,806	$ 8,770	$ 6,611
Non-cash compensation expense related to stock options	400	374	803	699
Total manufacturing and operations	$ 5,036	$ 4,180	$ 9,573	$ 7,310

Manufacturing and operations expenses for the three and six months ended June 30, 2010 were $4.6 million and $8.8 million, respectively, compared to $3.8 million and $6.6 million for the same periods in 2009, all amounts exclude non-cash compensation expense related to stock options. The increase in expenses was primarily a result of an increase in personnel costs and services provided by third parties to support our expanded clinical development programs including our broad Phase 3 program for mipomersen and depreciation expense related to the upgrades made to our manufacturing facility.

R&D Support

In our research and development 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 costs.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2010	2009	2010	2009
Personnel costs	$ 1,962	$ 1,930	$ 3,946	3,898
Occupancy	1,464	1,705	3,008	3,327
Depreciation and amortization	1,506	2,410	2,745	3,631
Insurance	254	233	481	457
Other	400	748	905	1,421
Non-cash compensation expense related to stock options	657	795	1,370	1,515
Total R&D support costs	$ 6,243	$ 7,821	$ 12,455	$ 14,249

R&D support costs for the three and six months ended June 30, 2010 were $5.6 million and $11.1 million, respectively, compared to $7.0 million and $12.7 million for the same periods in 2009, all amounts exclude non-cash compensation expense related to stock options. The decrease primarily relates to the decrease in patent amortization costs and Regulus' R&D support costs of $620,000 for the six months ended June 30, 2009 which we are no longer including in our 2010 operating expenses.

General and Administrative Expenses

General and administrative expenses include corporate costs required to support our company, our employees and our stockholders. These costs include personnel and outside costs in the areas of legal, human resources, investor relations, and finance. Additionally, we include in general and administrative expenses such costs as rent, repair and maintenance of buildings and equipment, depreciation, utilities, information technology and procurement costs that we need to support the corporate functions listed above.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2010	2009	2010	2009
General and administrative expenses	$ 2,530	$ 2,987	$ 4,817	$ 6,220
Non-cash compensation expense related to stock options	521	686	1,052	1,130
Total general and administrative expenses	$ 3,051	$ 3,673	$ 5,869	$ 7,350

General and administrative expenses for the three and six months ended June 30, 2010 were $2.5 million and $4.8 million, respectively, compared to $3.0 million and $6.2 million for the same periods in 2009. The decrease primarily relates to Regulus' general and administrative expenses of $1.1 million for the six months ended June 30, 2009 which we are no longer including in our 2010 operating expenses. All amounts discussed exclude non-cash compensation expense related to stock options.

Equity in Net Loss of Regulus Therapeutics Inc.

Beginning in the first quarter of 2010, as a result of adopting a new accounting standard, we no longer include Regulus' revenue and operating expenses in our operating results. Instead we are presenting our share of Regulus' operating results on a separate line in our condensed consolidated statement of operations called "Equity in net loss of Regulus Therapeutics Inc." Prior to the adoption of the new accounting standard, we consolidated Regulus' financial results on a line-by-line basis. See Note 2, *Significant Accounting Policies*, and Note 3, *Investment in Regulus Therapeutics Inc.*, in the Notes to the condensed consolidated financial statements for a more detailed explanation of this change.

Our equity in net loss of Regulus for the three and six months ended June 30, 2010 was $3.9 million and $5.4 million, respectively. Under the new standard, we had the option to adopt it on a retrospective or prospective basis. We chose to adopt it prospectively therefore we did not adjust our prior period results. If we had retrospectively adopted the new standard, the equity in net loss of Regulus for the three and six months ended June 30, 2009 would have been $817,000 and $3.6 million, respectively, which would have represented our share of Regulus' loss in the three and six months ended June 30, 2009 plus $1.7 million in losses for the first six months of 2009 which would have been previously suspended. Under the equity method of accounting, we are required to suspend losses if our share of Regulus' net loss exceeds the amount of funding we were required to provide. In the second half of 2010, we anticipate that our share of Regulus' net loss will exceed the $5 million guarantee we provided on the $10 million of convertible notes Regulus issued to GSK. At the time that our share of Regulus' net loss exceeds $5 million we will suspend recording our portion of their loss. When we made the $10 million investment in

March 2009, we would have recognized all of the suspended losses. The increase in our equity in net loss of Regulus primarily represents the increase in Regulus' operating expenses in 2010. We discuss expenses related to Regulus in a separate section below.

Investment Income

Investment income for the three and six months ended June 30, 2010 totaled $859,000 and $1.8 million, respectively, compared to $1.7 million and $3.8 million for the same periods in 2009. The decrease in investment income was primarily due to a lower average return on our investments resulting from the current market conditions and a lower average cash balance.

Interest Expense

Interest expense for the three and six months ended June 30, 2010 was $3.3 million and $6.5 million and was slightly higher compared to $3.2 million and $6.2 million for the same periods in 2009.

Gain (Loss) on Investments, Net

Loss on investments for the three and six months ended June 30, 2010 was $136,000 and $1.1 million, respectively, compared to a gain on investment of $2.6 million and $2.7 million for the same periods in 2009. The net loss on investments for the first six months of 2010 consists of an $880,000 non-cash loss related to the other-than-temporary impairment of our equity investment in ATL and $349,000 of valuation allowances we recorded related to the investments we made in Excaliard and Achaogen. Because realization of our Excaliard and Achaogen investments is uncertain we recorded a full valuation allowance. The gain on investments for the first six months of 2009 primarily represents a $2.5 million gain when we sold all of the common stock of OncoGenex that we owned.

Income Tax Expense

Even though we finished the first half of 2009 with a net loss from continuing operations, we had taxable income, which is primarily a result of the significant upfront payments that we received from our strategic alliance with Genzyme in 2008 and the gain we recognized on the sale of Ibis to AMI in early 2009. We recorded income tax expense of $149,000 for the first six months of 2009 as part of our financial results from continuing operations.

Net Loss from Continuing Operations attributable to Isis Pharmaceuticals, Inc. Common Stockholders

The following table sets forth computations for our net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2010	2009	2010	2009
Net loss from continuing operations, including income tax benefit (expense) and equity in net loss of Regulus Therapeutics Inc.	$ (25,154)	$ (3,681)	$ (34,811)	$ (5,372)
Net loss attributable to noncontrolling interest in Regulus Therapeutics Inc.	—	857	—	1,770
Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (25,154)	$ (2,824)	$ (34,811)	$ (3,602)

Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders for the three and six months ended June 30, 2010 was $25.2 million and $34.8 million, respectively, compared to $2.8 million and $3.6 million for the same periods in 2009. The increase in our net loss from continuing operations for the first half of 2010 compared to 2009 was primarily due to the following:

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- $18.1 million increase in our net operating loss described above;
- $7.2 million increase in net loss relating to the accounting treatment for Regulus;
- $2.0 million decrease in investment income due to a lower average return on investments resulting from the current market conditions and a lower average cash balance; and
- $2.5 million gain in 2009 from the sale of OncoGenex common stock that we owned, offset in part by $880,000 in a non-cash loss related to the impairment of our equity investment in ATL.

Net Income from Discontinued Operations

Since we sold Ibis to AMI in the first quarter of 2009 and Ibis met the criteria for a component of an entity, we reflected Ibis as a discontinued operation on our financial statements. Accordingly, we have presented the operating results of Ibis in our condensed consolidated statements of operations as discontinued operations. Net income from discontinued operations, net of tax, for the three and six months ended June 30, 2009 was $94,000 and $187.1 million, respectively, and primarily consisted of the $202.5 million gain less $15.4 million of income taxes.

Net Income (Loss) and Net Income (Loss) Per Share attributable to Isis Pharmaceuticals, Inc. Common Stockholders

Net loss attributable to Isis Pharmaceuticals, Inc. common stockholders for the three and six months ended June 30, 2010 was $25.2 million and $34.8 million, respectively, compared to a net loss of $2.7 million for the three months ended June 30, 2009 and net income of $183.5 million for the six months ended June 30, 2009. Basic and diluted net loss per share for the three and six months ended June 30, 2010 was $0.25 per share and $0.35 per share, respectively, compared to basic and diluted net loss of $0.03 per share for the three months ended June 30, 2009 and net income per share of $1.88 for the six months ended June 30, 2009. Net income and net income per share for the first half of 2009 primarily consisted of the $187.1 million gain, net of tax, which we recognized when we sold Ibis to AMI in the first quarter of 2009.

Regulus Therapeutics Segment

Regulus' revenue for the three and six months ended June 30, 2010 was $809,000 and $1.5 million, respectively, compared to $1.1 million and $1.8 million for the same periods in 2009. Although Regulus is amortizing the $3 million upfront license fee it received from GSK for its HCV alliance targeting miR-122 and the $25 million upfront payment it received from sanofi-aventis, revenue was higher in 2009 primarily due to the $500,000 discovery milestone payment that Regulus earned from its collaboration with GSK.

The following table sets forth information on Regulus' operating expenses (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2010	2009	2010	2009
Research and development expenses	$ 7,504	$ 2,256	$ 10,297	$ 4,411
General and administrative expenses	1,042	480	1,841	1,137
Non-cash compensation expense/(benefit) related to stock options	139	89	301	(221)
Total Regulus' operating expenses	$ 8,685	$ 2,825	$ 12,439	$ 5,327

Operating expenses for Regulus were $8.5 million and $12.1 million for the three and six months ended June 30, 2010, compared to $2.7 million and $5.5 million for the same periods in 2009, all amounts exclude non-cash compensation expense related to stock options. The increase primarily relates to the $3.8 million of sublicense fees owed to Isis and Alnylam from its strategic alliance with sanofi-aventis, Regulus' continued efforts to build its team to support its internal microRNA programs and the efforts associated with its GSK collaboration. With the strategic alliances with GSK and sanofi-aventis, we anticipate that Regulus' expenses will increase going forward as Regulus advances its research and development activities.

Liquidity and Capital Resources

We have financed our operations with revenue primarily from research and development under collaborative agreements. Additionally, we have earned licensing and royalty revenue from the sale or licensing of our intellectual property. We have also financed our operations through the sale of our equity securities and the issuance of long-term debt. From our inception through June 30, 2010, we have earned approximately $872.1 million in revenue from contract research and development and the sale and licensing of our intellectual property. From the time we were founded through June 30, 2010, we have raised net proceeds of approximately $817.4 million from the sale of our equity securities and we have borrowed approximately $565.3 million under long-term debt arrangements to finance a portion of our operations.

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As of June 30, 2010, we had cash, cash equivalents and short-term investments of $522.0 million and stockholders' equity of $262.2 million. In comparison, we had cash, cash equivalents and short-term investments of $574.3 million and stockholders' equity of $302.1 million at December 31, 2009. At June 30, 2010, we had consolidated working capital of $431.7 million, compared to $484.7 million at December 31, 2009. The decrease in cash and working capital primarily relates to cash used in the first six months of 2010 for our operations, including a $7.7 million payment that we made for 2009 income taxes. Our cash and working capital also decreased because we are no longer including Regulus' cash, which was $30.7 million at December 31, 2009, in our cash balance. So far in 2010, we have received more than $55 million from our corporate partnerships, including $35 million from GSK.

As of June 30, 2010, our debt and other obligations totaled $139.5 million, compared to $140.8 million at December 31, 2009. The decrease primarily relates to the $5.3 million convertible promissory note and the $949,000 equipment financing arrangement on the books of Regulus as of December 31, 2009 which we are no longer consolidating in our 2010 balance sheet and $1.9 million of principal payments we made on our equipment financing arrangement, offset by $3.1 million of additional draw downs on our equipment financing arrangement and $3.8 million of non-cash amortization of the debt discount we recorded in the first six months of 2010 related to our $2^5/_8$ percent convertible notes. We will continue to use equipment lease financing as long as the terms remain commercially attractive.

The following table summarizes our contractual obligations as of June 30, 2010. The table provides a breakdown of when obligations become due. We provide a more detailed description of the major components of our debt in the paragraphs following the table:

	Payments Due by Period (in millions)				
Contractual Obligations (selected balances described below)	Total	Less than 1 year	1-3 years	3-5 years	After 5 years
$2^5/_8$ percent Convertible Subordinated Notes (principal and interest payable)	$ 179.6	$ 4.3	$ 8.5	$ 166.8	$ —
Equipment Financing Arrangements (principal and interest payable)	$ 11.0	$ 5.5	$ 5.4	$ 0.1	$ —
Other Obligations (principal and interest payable)	$ 1.6	$ 0.1	$ 0.1	$ 0.1	$ 1.3
Operating Leases	$ 31.7	$ 3.3	$ 3.5	$ 2.3	$ 22.5
Total	$ 223.8	$ 13.2	$ 17.5	$ 169.3	$ 23.8

Our contractual obligations consist primarily of our publicly traded convertible debt. In addition, we also have equipment financing arrangements and other obligations.

In January 2007, we completed a $162.5 million convertible debt offering, which raised proceeds of approximately $157.1 million, net of $5.4 million in issuance costs. We included the issuance costs in our balance sheet and are amortizing these costs to interest expense over the life of the debt. The $162.5 million convertible subordinated notes mature in 2027 and bear interest at $2^5/_8$ percent, which is payable semi-annually. The $2^5/_8$ percent notes are convertible, at the option of the note holders, into approximately 11.1 million shares of our common stock at a conversion price of $14.63 per share. We will be able to redeem these notes at a redemption price equal to 100.75 percent of the principal amount between February 15, 2012 and February 14, 2013; 100.375 percent of the principal amount between February 15, 2013 and February 14, 2014; and 100 percent of the principal amount thereafter. Holders of the

2 5/8 percent notes may also require us to repurchase the 2 5/8 percent notes on February 15, 2014, February 15, 2017 and February 15, 2022, and upon the occurrence of certain defined conditions, at 100 percent of the principal amount of the 2 5/8 percent notes being repurchased plus unpaid interest.

In October 2008, we entered into a loan agreement related to an equipment financing and in September 2009, we amended the loan agreement to increase the aggregate maximum amount of principal we can draw under the agreement. Under the loan agreement, we and Regulus could borrow up to $19.4 million in principal to finance the purchase of equipment until the end of the draw down period, which ended in July 2010. The $19.4 million does not include the $600,000 Ibis borrowed in October 2008 that was fully repaid in the first quarter of 2009. Each draw down under the loan agreement has a term of three years, with principal and interest payable monthly. We calculate interest on amounts we borrow under the loan agreement based upon the three year interest rate swap at the time we make each draw down plus 4 percent. We are using the equipment purchased under the loan agreement as collateral. In June 2010, we drew down an additional $3.1 million in principal under the loan agreement. As of June 30, 2010, we have drawn down $15.1 million in principal under this loan agreement at a weighted average interest rate of 6.47 percent. The carrying balance under this loan agreement at June 30, 2010 and December 31, 2009 was $10.2 million and $10.0 million, respectively.

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We currently occupy approximately 138,500 square feet of laboratory and office space, including a 28,704 square foot facility, which houses our manufacturing suites for our drug development business built to meet Good Manufacturing Practices. We are located in four buildings in Carlsbad, California. We lease all of these buildings under lease agreements. The leases on the three buildings we primarily use for laboratory and office space for our drug development business expire at the end of 2011.

On March 30, 2010 we entered a new lease agreement with an affiliate of BioMed Realty, L.P. Under the lease, BioMed will construct a new 176,000 square foot research facility in Carlsbad, California. Upon completion of construction, we will lease the new facility and consolidate the majority of our operations in the new facility. The lease has an initial term of 20 years with an option to extend the lease for up to four five-year periods.

Our rent under the new lease is based on a percentage of the total construction costs spent by BioMed to acquire the land and build the new facility. We will begin paying rent on January 1, 2012. Once the new facility is complete, we will be responsible for the costs associated with owning and maintaining the facility. Since our rent is based on a percentage of total construction costs spent by BioMed to acquire the land and build the new facility, and the facility is not yet built, it is difficult for us to calculate our future payment obligations under the lease. However, as of June 30, 2010, we estimate that the maximum potential future payments we may be required to make over the 20 year term of the lease are $172 million.

We also lease from BioMed an approximately 28,700 square foot facility that houses our manufacturing suites for our drug development business. On March 30, 2010 we amended the lease to extend the term through December 31, 2031, subject to four five-year options to extend the lease, and to obtain an option to purchase the manufacturing facility on similar terms as the purchase options described above.

In addition to contractual obligations, we had outstanding purchase orders as of June 30, 2010 for the purchase of services, capital equipment and materials as part of our normal course of business.

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

RISK FACTORS

Investing in our securities involves a high degree of risk. You should consider carefully the following information about the risks described below, together with the other information contained in this report and in our other public filings in evaluating our business. If any of the following risks actually occur, our business could be materially harmed, and our financial condition and results of operations could be materially and adversely affected. As a result, the trading price of our securities could decline, and you might lose all or part of your investment. We have marked with an asterisk those risk factors that reflect substantive changes from the risk factors included in our Annual Report on Form 10-K for the year ended December 31, 2009.

Risks Associated with our Drug Discovery and Development Business

If we or our partners fail to obtain regulatory approval for our drugs, we will not be able to sell them.

We and our partners must conduct time-consuming, extensive and costly clinical trials to show the safety and efficacy of each of our drugs, including mipomersen and ISIS 113715, before a drug can be approved for sale. We must conduct these trials in compliance with FDA regulations and with comparable regulations in other countries. If the FDA or another regulatory agency believes that we or our partners have not sufficiently demonstrated the safety or efficacy of our drugs, including mipomersen and ISIS 113715, it will not approve them or will require additional studies, which can be time consuming and expensive and which will delay commercialization of a drug. We and our partners may not be able to obtain necessary regulatory approvals on a timely basis, if at all, for any of our drugs, including mipomersen and ISIS 113715. Failure to receive these approvals or delays in these approvals could prevent or delay commercial introduction of a product, including mipomersen and ISIS 113715, and, as a result, could negatively impact our ability to generate revenue from product sales. In addition, following approval of a drug, we and our partners must comply with comprehensive government regulations regarding how we manufacture, market and distribute drug products. If we fail to comply with these regulations, regulators could force us to withdraw a drug from the market or impose other penalties or requirements that also could have a negative impact on our financial results.

We have only introduced one commercial drug product, Vitravene. We cannot guarantee that any of our other drugs, including mipomersen and ISIS 113715, will be safe and effective, will be approved for commercialization or that our partners or we can successfully commercialize these drugs.

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

Drug discovery and development has inherent risks and the historical failure rate for drugs is high. Antisense technology in particular is relatively new and unproven. If we cannot demonstrate that our drugs, including mipomersen and ISIS 113715, are safe and effective drugs for human use, we may need to abandon one or more of our drug development programs.

In the past, we have invested in clinical studies of drugs that have not met the primary clinical end points in their Phase 3 studies. In March 2003, we reported the results of a Phase 3 clinical trial of Affinitak in patients with late-stage NSCLC and in October 2004, we reported the results of a second similar Phase 3 clinical trial. In each case, Affinitak failed to demonstrate improved survival sufficient to support a new drug application filing. In December 2004, we reported the results of our Phase 3 clinical trials of alicaforsen in patients with active Crohn's disease, in which alicaforsen did not demonstrate statistically significant induction of clinical remissions compared to placebo. Similar results could occur with the clinical trials for our other drugs, including mipomersen and ISIS 113715. If any of our drugs in clinical studies, including mipomersen and ISIS 113715, do not show sufficient efficacy in patients with the targeted indication, it could negatively impact our development and commercialization goals for these and other drugs and our stock price could decline.

Even if our drugs are successful in preclinical and early human clinical studies, these results do not guarantee the drugs will be successful in late-stage clinical trials.

Successful results in preclinical or early human clinical trials, including the Phase 2 results for mipomersen and ISIS 113715, may not predict the results of late-stage clinical trials. There are a number of factors that could cause a clinical trial to fail or be delayed, including:

- the clinical trial 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 trial due to adverse side effects of a drug on subjects or patients in the trial;
- we may decide, or regulators may require us, to conduct additional preclinical testing or clinical trials;
- enrollment in our clinical trials may be slower than we anticipate;
- the cost of our clinical trials may be greater than we anticipate; and
- the supply or quality of our drugs or other materials necessary to conduct our clinical trials may be insufficient, inadequate or delayed.

Any failure or delay in one of our clinical trials, including our Phase 2 or Phase 3 development programs for mipomersen and ISIS 113715, could reduce the commercial viability of our drugs, including mipomersen and ISIS 113715.

If the market does not accept our products, we are not likely to generate revenues or become consistently profitable.

Our success will depend upon the medical community, patients and third-party payors accepting our products as medically useful, cost-effective and safe. Even if approved for commercialization, doctors may not use our products to treat patients. We currently have one commercially approved drug product, Vitravene, a treatment for CMV, retinitis in AIDS patients, which addresses a small market. Our partners and we may not successfully commercialize additional products.

The degree of market acceptance for any of our products depends upon a number of factors, including:

- the receipt and scope of regulatory approvals;
- the establishment and demonstration in the medical and patient community of the efficacy and safety of our drugs and their potential advantages over competing products;

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- the cost and effectiveness of our drugs compared to other available therapies;
- the patient convenience of the dosing regimen for our drugs; and
- reimbursement policies of government and third-party payors.

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

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

If we successfully commercialize any of our drugs, we would be required to establish large-scale commercial manufacturing capabilities either on our own or through a third party manufacturer. In addition, as our drug development pipeline increases and matures, we will have a greater need for clinical trial and commercial manufacturing capacity. We have limited experience manufacturing pharmaceutical products of the chemical class represented by our drugs, called oligonucleotides, on a commercial scale for the systemic administration of a drug. There are a small number of suppliers for certain capital equipment and raw materials that we use to manufacture our drugs, and some of these suppliers will need to increase their scale of production to meet our

projected needs for commercial manufacturing. Further, we must continue to improve our manufacturing processes to allow us to reduce our product costs. We may not be able to manufacture at a cost or in quantities necessary to make commercially successful products.

Also, manufacturers, including us, must adhere to the FDA's current Good Manufacturing Practices regulations, which the FDA enforces through its facilities inspection program. We and our contract manufacturers may not be able to comply or maintain compliance with Good Manufacturing Practices regulations. Non-compliance could significantly delay or prevent our receipt of marketing approval for potential products, including mipomersen and ISIS 113715, or result in FDA enforcement action after approval that could limit the commercial success of our potential products, including mipomersen and ISIS 113715.

If our drug discovery and development business fails to compete effectively, our drugs will not contribute significant revenues.

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

- priced lower than our drugs;
- safer than our drugs;
- more effective than our drugs; or
- more convenient to use than our drugs.

These competitive developments could make our products obsolete or non-competitive.

Certain of our partners are pursuing other technologies or developing other drugs either on their own or in collaboration with others, including our competitors, to develop treatments for the same diseases targeted by our own collaborative programs. Competition may negatively impact a partner's focus on and commitment to our drugs and, as a result, could delay or otherwise negatively affect the commercialization of our drugs.

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 trials of new pharmaceutical products and in obtaining FDA and other regulatory approvals of products for use in health care. Accordingly, our competitors may succeed in obtaining regulatory approval for products earlier than we do. We will also compete with respect to marketing and sales capabilities, areas in which we have limited or no experience.

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Disagreements between Alnylam and us regarding the development of our microRNA technology may cause significant delays and other impediments in the development of this technology, which could negatively affect the value of the technology and our investment in Regulus.

Regulus is a jointly owned company that we and Alnylam established to focus on the discovery, development, and commercialization of microRNA. As part of this joint venture, we exclusively licensed to Regulus our intellectual property rights covering microRNA. Regulus is operated as an independent company and governed by a board of directors. We and Alnylam can elect an equal number of directors to serve on the Regulus Board. Regulus researches and develops microRNA projects and programs pursuant to an operating plan that its board approves. Any disagreements between Alnylam and us regarding a development decision or any other decision submitted to Regulus' board may cause significant delays in the development and commercialization of our microRNA technology and could negatively affect the value of our investment in Regulus.

We depend on third parties in the conduct of our clinical trials for our drugs 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 in the conduct of our clinical trials for our drugs and expect to continue to do so in the future. For example, Medpace is the primary clinical research organization for clinical trials for mipomersen. We rely heavily on these parties for successful execution of our clinical trials, but do not control many aspects of their activities. For example, the investigators are not our employees. However, we are responsible for ensuring that these third parties conduct each of our clinical trials in accordance with the general investigational plan and protocols for the trial. Third parties may not complete activities on schedule, or may not conduct our clinical trials in accordance with regulatory requirements or our stated protocols. The failure of these third parties to carry out their obligations or a termination of our relationship with these third parties could delay or prevent the development, approval and commercialization of our drugs, including mipomersen.

Risks Associated with our Businesses as a Whole

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

Because product 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, 2010, we had an accumulated deficit of approximately $730.2 million and stockholders' equity of approximately $262.2 million. Most of the losses resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations. Most of our revenue has come from collaborative arrangements, with additional revenue from research grants and the sale or licensing of our patents as well as interest income. We currently have only one product, Vitravene, approved for commercial use. This product has limited sales potential, and Novartis, our exclusive distribution partner for this product, no longer markets it. We expect to incur additional operating losses over the next several years, and these losses may increase if we cannot increase or sustain revenue. We may not successfully develop any additional products or services, or achieve or sustain future profitability.

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

To date, corporate partnering has played a key role in our strategy to fund our development programs and to add key development resources. We plan to continue to rely on additional collaborative arrangements to develop and commercialize our products, including ISIS 113715. However, we may not be able to negotiate additional attractive collaborative arrangements.

Our corporate partners are developing and/or funding, many of the drugs in our development pipeline, including Altair, ATL, Atlantic Pharmaceuticals, Bristol-Myers Squibb, iCo, Eli Lilly and Company, OncoGenex, and Teva. In addition, we have a major strategic alliance with Genzyme in which Genzyme will develop and commercialize mipomersen. If any of these pharmaceutical companies stop funding and/or developing these products, our business could suffer and we may not have, or be willing to dedicate, the resources available to develop these products on our own.

Our collaborators can terminate their relationships with us under certain circumstances, some of which are outside of our control. For example, in November 2004 based on the disappointing results of the Phase 3 clinical trials, Eli Lilly and Company discontinued its investment in Affinitak.

In addition, the disappointing results of the two Affinitak clinical trials, our Phase 3 clinical trials of alicaforsen in patients with active Crohn's disease, or any future clinical trials could impair our ability to attract new collaborative partners. If we cannot continue to secure additional collaborative partners, our revenues could decrease and the development of our drugs could suffer.

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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 product development programs.

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

- conduct clinical trials;
- seek and obtain regulatory approvals; and
- manufacture, market and sell existing and future products.

Once we have secured a collaborative arrangement to further develop and commercialize one of our development programs, such as our collaborations with Genzyme and Bristol-Myers Squibb, these collaborations may not continue or result in commercialized drugs, or may not progress as quickly as we anticipated.

For example, a collaborator such as Genzyme or Bristol-Myers Squibb, could determine that it is in its financial interest to:

- pursue alternative technologies or develop alternative products that may be competitive with the product 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 drugs than it does for its own drugs under development.

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 drugs.

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

For planning purposes, we estimate and may disclose the timing of a variety of clinical, regulatory and other milestones, such as when we anticipate a certain drug will enter the clinic, when we anticipate completing a clinical trial, or when we anticipate filing an application for marketing approval. We base our estimates on present facts and a variety of assumptions. Many underlying assumptions are outside of our control. If we do not achieve milestones in accordance with our or investors' expectations, the price of our securities would likely decrease.

For example, in April 2008 the FDA provided guidance regarding approval requirements for mipomersen. The FDA indicated that reduction of LDL-C is an acceptable surrogate endpoint for accelerated approval of mipomersen for use in patients with homozygous familial hypercholesterolemia, or hoFH. The FDA will require data from two preclinical studies for carcinogenicity to be included in the hoFH filing, which is now anticipated to take place in the first half of 2011. The FDA also indicated that for broader indications in high risk, high cholesterol patients an outcome study would be required for approval. This FDA guidance caused us to revise our development plans and timelines and, as a result, to accelerate our planned outcome trial.

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

Our success depends to a significant degree upon our ability to continue to develop and secure intellectual property rights to proprietary products and services. However, we may not receive issued patents on any of our pending patent applications in the United States or in other countries. In addition, the scope of any of our issued patents may not be sufficiently broad to provide us with a competitive advantage. Furthermore, our issued patents or patents licensed to us may be successfully challenged, invalidated or circumvented so that our patent rights would not create an effective competitive barrier or revenue source.

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

It is possible that in the future we may have to defend our intellectual property rights. In the event of an intellectual property dispute, we may be forced to litigate to defend our rights or assert them against others. Disputes could involve arbitration, litigation or proceedings declared by the United States Patent and Trademark Office or the International Trade Commission or foreign patent authorities. Intellectual property litigation can be extremely expensive, and this expense, as well as the consequences should we not prevail, could seriously harm our business.

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For example, in December 2006, the European Patent Office, or EPO, Technical Board of Appeal reinstated with amended claims our Patent EP0618925 which claims a class of antisense compounds, any of which is designed to have a sequence of phosphorothioate-linked nucleotides having two regions of chemically modified RNA flanking a region of DNA. Prior to its reinstatement, this patent was originally opposed by several parties and revoked by an EPO Opposition Division in December of 2003. We intend to fully exercise our rights under this patent by pursuing licensing arrangements, but if licensing efforts are unsuccessful we may choose to assert our rights through litigation.

If a third party claims that our products 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 applications held by others that relate to our business. This is especially true since patent applications in the United States are filed confidentially for the first 18 months. Moreover, the validity and breadth of biotechnology patents involve complex legal and factual questions for which important legal issues remain unresolved.

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

All of our drugs are undergoing clinical trials or are in the early stages of research and development. All of our drugs under development will require significant additional research, development, preclinical and/or clinical testing, regulatory approval and a commitment of significant additional resources prior to their commercialization. As of June 30, 2010, we had cash, cash equivalents and short-term investments equal to $522.0 million. If we do not meet our goals to commercialize our products, or to license our drugs and proprietary technologies, we will need additional funding in the future. Our future capital requirements will depend on many factors, such as the following:

- 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 trials;
- the time and costs involved in obtaining regulatory approvals;
- competing technological and market developments, including the introduction by others of new therapies that address our markets; and
- the profile and launch timing of our drugs.

If we need additional funds, we may need to raise them through public or private financing. Additional financing may not be available at all or on acceptable terms. If we raise additional funds by issuing equity securities, the shares of existing stockholders will be diluted and their price, as well as the price of our other securities, may decline. If adequate funds are not available or not available on acceptable terms, we may have to cut back on one or more of our research, drug discovery or development programs. For example, in January 2005 we decided to terminate the development of two lower priority drugs, ISIS 14803 and ISIS 104838. 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, drugs or products.

The loss of key personnel, or the inability to attract and retain highly skilled personnel, could make it more difficult to run our business and reduce our likelihood of success.

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

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

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our securities. During the 12 months preceding June 30, 2010, the market price of our common stock ranged from $8.46 to $18.81 per share. On August 2, 2010, the closing price of our common stock on The Nasdaq Global Select Market was $9.99. Many factors can affect the market price of our securities, including, for example, fluctuations in our operating results, announcements of collaborations, clinical trial results, technological innovations or new products being developed by us or our competitors, governmental regulation, regulatory approval, developments in patent or other proprietary rights, public concern regarding the safety of our drugs and general market conditions.

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. These materials and various wastes resulting from

their use are stored at our facilities in Carlsbad, California pending ultimate use and disposal. We cannot completely eliminate the risk of contamination, which could cause:

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

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

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

We manufacture our research and clinical supplies in a separate manufacturing facility located in Carlsbad, California. The facilities and the equipment we use to research, develop and manufacture our drugs would be costly to replace and could require substantial lead time to repair or replace. Our facilities may be harmed by natural or man-made disasters, including, without limitation, earthquakes, floods, fires and acts of terrorism, and in the event they are affected by a disaster, our development and commercialization efforts would be delayed. Although we possess insurance for damage to our property and the disruption of our business from casualties, this insurance may not be sufficient to cover all of our potential losses and may not continue to be available to us on acceptable terms, or at all.

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

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

Our certificate of incorporation also requires that any action required or permitted to be taken by our stockholders must be taken at a duly called annual or special meeting of stockholders and may not be taken by written consent. In addition, only our board of directors, chairman of the board or chief executive officer can call special meetings of our stockholders. We also have implemented 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. These provisions, as well as Delaware law and other of our agreements, may discourage certain types of transactions in

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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. 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 subordinated 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 addition, our collaboration agreement with Genzyme regarding mipomersen provides that if we are acquired, Genzyme may elect to purchase all of our rights to receive payments under the mipomersen collaboration agreement for a purchase price to be mutually agree to by us and Genzyme, or, if we cannot agree, a fair market value price determined by an independent investment banking firm. This provision may make it more difficult or complicated for us to enter into an acquisition agreement with a potential acquirer.

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 registered for resale 4.25 million shares of our common stock issuable upon the exercise of the warrant we originally issued to Symphony GenIsis Holdings. In addition, we have registered for resale our $2^{5}/_{8}$ percent convertible subordinated notes, including the approximately 11.1 million shares issuable upon conversion of the notes. The addition of any of these shares into the public market may have an adverse effect on the price of our securities.

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

Each year we are required to evaluate our internal controls systems in order to allow management to report on and our Independent Registered Public Accounting Firm to attest to, our internal controls as required by Section 404 of the Sarbanes-Oxley Act. As a result, we will incur additional expenses and will suffer a diversion of management's time. 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.

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

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

ITEM 3. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

We are exposed to changes in interest rates primarily from our long-term debt arrangements and, secondarily, investments in certain short-term investments. We invest our excess cash in highly liquid short-term investments that are typically held 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.

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ITEM 4. CONTROLS AND PROCEDURES

As of the end of the period covered by this Quarterly Report on Form 10-Q, we carried out an evaluation, under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, 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. Based on this evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective as of June 30, 2010. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to June 30, 2010.

An evaluation was also performed under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, of any change in our internal control over financial reporting that occurred during our last fiscal quarter and that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting. That evaluation did not identify any change in our internal control over financial reporting that occurred during our latest fiscal quarter and that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

We maintain disclosure controls and procedures that are designed to ensure that information required to be disclosed 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. In designing and evaluating the disclosure controls and procedures, management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable and not absolute assurance of achieving the desired control objectives.

PART II — OTHER INFORMATION

ITEM 1. LEGAL PROCEEDINGS

On February 11, 2008, we notified Bruker Daltonics, Ibis' manufacturing and commercialization partner for the T5000 System, that we were initiating the formal dispute resolution process under Ibis' agreement with them. We asserted that Bruker's performance of its manufacturing, commercialization and product service obligations are unsatisfactory and fail to meet their obligations under this agreement. Executive level negotiations and formal mediation efforts failed to achieve resolution of this dispute. On May 22, 2008, Bruker filed a complaint against Isis Pharmaceuticals, Inc. and Ibis Biosciences, Inc. in Superior Court of Middlesex County, Massachusetts alleging monetary damages due to breach of contract by us and Ibis. We and Ibis filed an Answer, Affirmative Defenses and Counterclaim on July 14, 2008, alleging breach of contract by Bruker. Discovery remains in its early stage. As such, we have no basis on which to predict or record a loss related to this claim as of June 30, 2010. We will continue to represent and defend Ibis Biosciences in this matter.

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

Not applicable

ITEM 3. DEFAULT UPON SENIOR SECURITIES

Not applicable

ITEM 4. (REMOVED AND RESERVED)

Not applicable

ITEM 5. OTHER INFORMATION

Not applicable

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ITEM 6. EXHIBITS

a. Exhibits

Exhibit Number	Description of Document
10.1	Collaboration and License Agreement dated June 17, 2010 between sanofi-aventis and Regulus Therapeutics Inc. *Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.*
10.2	Non-Exclusive Technology Alliance and Option Agreement dated June 17, 2010 between sanofi-aventis and Regulus Therapeutics Inc. *Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.*
10.3	Amendment Number One to the Amended and Restated License and Collaboration Agreement dated June 10, 2010 among the Registrant, Alnylam Pharmaceuticals, Inc. and Regulus Therapeutics Inc. *Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.*
10.4	Amendment Number One to the Founding Investor Rights Agreement dated June 7, 2010 among the Registrant, Alnylam Pharmaceuticals, Inc. and Regulus Therapeutics Inc.
31.1	Certification by Chief Executive Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2	Certification by Chief Financial Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
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 Isis Pharmaceuticals, Inc. Quarterly Report on Form 10-Q for the quarter ended June 30, 2010, formatted in Extensive Business Reporting Language (XBRL): (i) condensed consolidated balance sheets, (ii) condensed consolidated statements of operations, (iii) condensed consolidated statements of cash flows, and (iv) notes to condensed consolidated financial statements (tagged as blocks of text).

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Isis Pharmaceuticals, Inc.

(Registrant)

SIGNATURES

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

Signatures	Title	Date
/s/ Stanley T. Crooke Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board, President, and Chief Executive Officer (Principal executive officer)	August 9, 2010
/s/ B. Lynne Parshall B. Lynne Parshall, J.D.	Director, Executive Vice President, Chief Financial Officer and Secretary (Principal financial and accounting officer)	August 9, 2010

CONFIDENTIAL TREATMENT REQUESTED UNDER 17 C.F.R. §§ 200.80(B)4, AND 240.24B-2

COLLABORATION AND LICENSE AGREEMENT

between

REGULUS THERAPEUTICS INC.

And

SANOFI-AVENTIS

COLLABORATION AND LICENSE AGREEMENT

THIS COLLABORATION AND LICENSE AGREEMENT (the ***"Agreement"***) is made and entered into this June 17, 2010 (the ***"Effective Date"***), by and between **SANOFI-AVENTIS**, a French Corporation (***"Sanofi"***) having a place of business at 174, avenue de France, 75013, Paris, France, registered in the Paris Trade and Company Register under no. 395 030 844, and **REGULUS THERAPEUTICS INC.**, a Delaware Corporation (***"Regulus"***) having a place of business at 1896 Rutherford Road, Carlsbad, California 92008. Sanofi and Regulus each may be referred to herein individually as a ***"Party,"*** or collectively as the ***"Parties."***

WHEREAS, Regulus possesses certain patent rights, know-how and technology with respect to therapeutic microRNA Compounds;

WHEREAS, Regulus and Sanofi each desire to collaborate (the ***"Collaboration"***) to conduct a Research Program to identify one or more Licensed Compounds for a limited number of Collaboration Targets for Sanofi to advance into human clinical trials and ultimately Commercialize as Products; and

WHEREAS, Sanofi will have exclusive rights to Licensed Compounds and Products arising from the Research Program and (unless otherwise specified in the R&D Plan) will be solely responsible for the clinical development and Commercialization of Products worldwide, in each case on the terms set forth in this Agreement.

NOW, THEREFORE, in consideration of the foregoing and the mutual covenants herein contained, the Parties do hereby agree as follows.

ARTICLE 1

DEFINITIONS

The terms used in this Agreement with initial letters capitalized, whether used in the singular or the plural, will have the meaning set forth in **APPENDIX 1**, or if not listed in **APPENDIX 1**, the meaning designated in places throughout the Agreement.

ARTICLE 2

GRANT OF RIGHTS; EXCLUSIVITY

Section 2.1 License Grants to Sanofi. Subject to the terms and conditions of this Agreement, Regulus hereby grants to Sanofi a worldwide, royalty-bearing, exclusive license, with the right to grant sublicenses as set forth in Section 2.2 below, under the Regulus Know-How and Regulus Patents to Research, Develop, make, have made, use, gain Approval, Commercialize, sell, offer for sale, have sold, export and import Licensed Compounds and Products in the Product Field.

Section 2.2 Sublicenses. The licenses granted to Sanofi under Section 2.1 are sublicensable only in connection with a sublicense of a Licensed Compound or Product to any

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Affiliate of Sanofi or to any Third Party, in each case to Research Develop, make, have made, use, gain Approval, Commercialize, sell, offer for sale, have sold, export and import Licensed Compound or Product in the Product Field in accordance with the terms of this Agreement.

Section 2.3 Exclusivity.

2.3.1 During the [***] Research Term, and at any time thereafter during the Research Term when Sanofi still has [***], Regulus agrees that it will not work independently of this Agreement for any Third Party (including the grant of any license to any Third Party) to discover, research, develop and/or commercialize [***] in the Target Field or products containing such microRNA Compounds in the Target Field. For clarity, Regulus may (i) conduct its own internal research in the Target Field, subject to Section 3.6; and (ii) work independently of this Agreement for any Third Party (including the grant of any license to any Third Party) to discover, research, develop and/or commercialize microRNA Compounds that target or mimic microRNAs that are not Collaboration Targets so long as such work is [***] outside the Target Field.

2.3.2 During the Research Term if Sanofi [***] and except as otherwise permitted under Section 3.6.5, Regulus agrees that it will not work independently of this Agreement for any Third Party (including the grant of any license to any Third Party) to discover, research, develop and/or commercialize (i) with respect to Collaboration Targets that the Parties are approaching with a microRNA Antagonist, microRNA Compounds that are [***]

such Collaboration Target; and (ii) with respect to Collaboration Targets that the Parties are approaching with a microRNA Mimic, microRNA Compounds with a [***] as the applicable Collaboration Target that are [***] such Collaboration Target.

2.3.3 After the Research Term and except as otherwise permitted under Section 3.6.5, on a Collaboration Target-by-Collaboration Target basis, so long as the exclusive license granted to Sanofi under Section 2.1 is in effect and subject to the limitations set forth in Section 2.4 below, Regulus agrees that it will not work independently of this Agreement for any Third Party (including the grant of any license to any Third Party) to discover, research, develop and/or commercialize (i) with respect to Collaboration Targets that are the subject of the exclusive license under Section 2.1 where the applicable Product contains a microRNA Antagonist, microRNA Compounds that are [***] such Collaboration Target; and (ii) with respect to Collaboration Targets that are the subject of the exclusive license under Section 2.1 where the applicable Product contains a microRNA Mimic, microRNA Compounds with a [***] as the applicable Collaboration Target that are [***] such Collaboration Target.

2.3.4 During the [***] Research Term, Sanofi agrees that it will not work independently of this Agreement in collaboration with any Third Party (including the grant of any license to or from any Third Party) to discover, research, develop and/or commercialize [***] in the Target Field; *provided*, *however*, that at anytime, and from time to time, Sanofi may collaborate with (i) any Third Party (including the grant of any license to or from any Third Party) to discover, research, develop and/or commercialize any microRNA Compound for which an [***] a Third Party, independently of Sanofi, or (ii) any academic or other non-commercial research institution.

2.3.5 During [***], on a Collaboration Target-by-Collaboration Target basis, so long as the exclusive license granted to Sanofi under Section 2.1 is in effect, Sanofi agrees that it will not work independently of this Agreement in collaboration with any Third Party (including the grant of any license to or from any Third Party) to discover, research, develop and/or commercialize (i) with respect to Collaboration Targets that are the subject of the exclusive license under Section 2.1 where the applicable Product contains a microRNA Antagonist, microRNA Compounds that [***] such Collaboration Target; and (ii) with respect to Collaboration Targets that are the subject of the exclusive license under Section 2.1 where the applicable Product contains a microRNA Mimic, microRNA Compounds with a [***] as the applicable Collaboration Target that are [***] such Collaboration Target.

Section 2.4 License Conditions; Limitations.

2.4.1 If Sanofi fails to meet any of its obligations under Section 3.5.1 and Section 6.2, and such failure rises to the level of a material breach of this Agreement, then Regulus will have the termination rights set forth in Section 9.3.

2.4.2 If Sanofi fails to meet its obligations to use Commercially Reasonable Efforts under ARTICLE 5 for a particular Licensed Compound or Product, Regulus will have the termination rights set forth in Section 9.4.

2.4.3 The license and exclusivity granted under Section 2.1 and Section 2.3 are subject to and limited by the (i) Existing Regulus Agreements and (ii) [***], *solely* to the extent Regulus has, prior to the Effective Date, [***].

2.4.4 Without limiting this Section 2.4, Regulus' ability to conduct research and development on [***], and Regulus' ability to grant Sanofi a license under Section 2.1 to Develop and Commercialize [***], is limited by, and subject to, the terms of the [***]. Regulus will use commercially reasonable efforts (and will [***]) to secure the right to conduct research and development on [***] under the R&D Plan, and grant Sanofi a license under Section 2.1 to Develop and Commercialize Licensed Compounds that are [***] to the fullest extent contemplated by this Agreement.

2.4.5 Without limiting this Section 2.4, Regulus' ability to conduct research and development on microRNA Compounds [***], and Regulus' ability to grant Sanofi a license under Section 2.1 to Develop and Commercialize microRNA Compounds [***] is limited until the date [***] (the ***[***]*** which in no event shall be later than [***], as in effect on the Effective Date. Subject to the preceding sentence, Regulus will secure the right to grant Sanofi a license under Section 2.1 to Develop and Commercialize Licensed Compounds [***] to the fullest extent contemplated by this Agreement. The fact that Sanofi has been, or will be granted any rights by Regulus [***]shall be deemed Sanofi Confidential Information [***].

2.4.6 Subject to Section 2.3, Regulus retains the right to grant Permitted Licenses.

2.4.7 The [***] granted to Sanofi under [***] is subject to [***] (including for the avoidance of doubt the [***] obligation [***] to provide reports in accordance [***], and to keep records as set forth in Article 10 of [***], *provided* that Regulus agrees to directly comply

with the reporting obligations under the [***] Agreement with respect to progress of research and development. To the extent necessary to comply with the reporting obligations under the [***] Agreement, Sanofi agrees to provide Regulus with reports of Sanofi's progress through the JSC for so long as the JSC in place, and thereafter as reasonably requested by Regulus, in each case, at intervals and with reasonable lead-times reasonably necessary for Regulus to comply with the [***]. Based on the information reported by Sanofi pursuant to the preceding sentence, Regulus will prepare the necessary reports and submit them to [***]. However, if [***] insists that Sanofi provide written progress, Sanofi agrees to do so. The parties shall cooperate in good faith to facilitate compliance with the Existing Regulus Agreements. Notwithstanding the foregoing, Regulus shall make a good faith effort to [***] so that the [***] of the [***] the reporting obligations that Sanofi has to Regulus under this Agreement.

ARTICLE 3

COLLABORATION

Section 3.1 Objective. The Parties will collaborate in carrying out a program to discover and preclinically develop Licensed Compounds (as further provided for in the R&D Plan, the ***"Research Program"***), for the clinical Development and Commercialization of such Licensed Compounds by Sanofi as Products.

Section 3.2 **R&D Plan.** The Research Program will be carried out in accordance with a written research and development plan (the ***"R&D Plan"***). The initial R&D Plan that has been agreed to by the Parties as of the Effective Date is attached as **APPENDIX 8** hereto. The purpose of the R&D Plan is to detail the responsibilities and activities of Regulus and Sanofi with respect to carrying out the Research Program. The R&D Plan will include a description of the specific activities to be performed by the Parties in support of the Research Program and projected timelines for completion of such activities. The R&D Plan, including the definition of Development Candidate, the Development Candidate selection criteria, and the Target Product Profile, may be amended with the approval of the JSC (with the Senior Representative of Sanofi having the final decision in the case of a dispute between the Parties over such matters, except as set forth in the JSC Charter). The R&D Plan will be updated and amended from time to time, but at least annually. In addition, at the time a Development Candidate is designated, the JSC will meet to update the R&D Plan to implement the Manufacturing Technology transfer under Section 4.3 and to secure supply of API to support Phase 1 Trials, the cost of which will be [***]. If the Parties cannot agree to updates or amendments to the R&D Plan, the Parties will first pursue the dispute resolution provisions of the JSC Charter and thereafter follow the provisions of Section 13.4.

Section 3.3 **Research Term.**

3.3.1 The Research Program will be carried out during the period following the Effective Date and ending on the third anniversary of the Effective Date unless extended pursuant to Section 3.3.2 (such period, including any extensions pursuant to Section 3.3.2, the ***"Research Term"***).

3.3.2 Sanofi will have the option to extend the Research Term for [***] additional [***] periods, such that the Research Term may be extended through the [***] Effective Date. For any extension of the Research Term, the JSC will amend and restate the R&D Plan as necessary, subject to the provisions of the JSC Charter.

3.3.3 In order to exercise its option under Section 3.3.2 to extend the Research Term, Sanofi must provide Regulus a written notice exercising Sanofi's right to extend the Research Term at least [***] prior to the scheduled expiration of the Research Term. If Sanofi does not timely provide such written notice, the Research Term will end when scheduled. In addition, no earlier than the [***] day prior to the scheduled expiration of the Research Term, Regulus may request in writing from Sanofi a nonbinding, good faith indication of whether or not Sanofi intends to extend the Research Term. In such event, Sanofi will provide such nonbinding, good faith indication to Regulus at least [***] days prior to the scheduled expiration of the Research Term.

Section 3.4 **Joint Steering Committee.** The Parties will establish and maintain a joint steering committee (the ***"JSC"***) to oversee the conduct of the Research Program, including, but not limited to approving any changes to the R&D Plan. The JSC will be established, operated and governed in accordance with the policies and procedures set forth in **APPENDIX 4** attached hereto (the ***"JSC Charter"***). The JSC Charter may be amended with the unanimous approval of the JSC members. As needed, the JSC will establish subcommittees and working groups that will report to the JSC to further the objectives of the Research Program. The JSC and any subcommittees and working groups established by the JSC will automatically dissolve at the end of the Research Term.

Section 3.5 **Research Program Staffing; Funding; and Resources.** Regulus will dedicate Regulus employees during the Research Term to perform activities in support of and in accordance with the then-current R&D Plan.

3.5.1 Regulus will invoice Sanofi on or after the Effective Date for, and Sanofi will pay Regulus, an irrevocable, non-creditable and nonrefundable payment of [***] to support Regulus' work under the Research Program for [***] the Research Term. Regulus will invoice Sanofi on or after the [***] of the Effective Date and on or after each subsequent anniversary of the Effective Date during the Research Term (including any extension under Section 3.3.2) for, and Sanofi will pay Regulus, an irrevocable, non-creditable and nonrefundable payment of [***] to support Regulus' work under the Research Program for such year. Regulus will invoice Sanofi for each such payment and Sanofi will pay each such invoice in accordance with Section 6.13.

3.5.2 Except for the payments under Section 3.5.1 above, Regulus will bear all costs, including costs related to research supplies, consumables and animals, in performing its obligations under the R&D Plan. In accordance with the foregoing, if the JSC determines that any of Regulus' obligations under the R&D Plan could be performed better, or faster by Sanofi, then Sanofi shall have the opportunity to perform such work subject to [***] on a scope of work and budget, consistent with [***] require to perform the same; and Regulus will pay Sanofi for such work in accordance with such budget. For clarity, Regulus will perform, and bear all costs of performing, all IND-Enabling Studies to the extent required by the FDA to support the IND

for the Target Product Profile that was approved by the JSC prior to the start of such IND-Enabling Studies.

3.5.3 Regulus shall commit the necessary resources to use commercially reasonable efforts to (a) provide Sanofi with a [***] microRNA targets in [***] Fibrosis [***] by [***], (b) [***] no later than [***], and (c) receive [***] for Licensed Compounds during [***]; in each case consistent with the R&D Plan.

Section 3.6 **Collaboration Targets.** Sanofi will have a license under Section 2.1 for up to four microRNAs (including Mir-21 as of the Effective Date) designated by Sanofi in accordance with Section 3.6.1 below, for research and development under the R&D Plan (each such designated microRNA is a ***"Collaboration Target"***); *provided, however,* that in order to be eligible for designation by Sanofi as a Collaboration Target, a microRNA must be associated with the Target Field, as demonstrated by any one or more of the following: (1) a publication in a peer-reviewed journal; (2) a data set generated by Regulus and/or Sanofi as part of the Research Program; (3) inclusion in Regulus' internal list(s) of microRNAs it accepts as being associated with the Target Field (which list(s) will be shared with Sanofi as described below in this Section); or (4) any other data set that the JSC unanimously accepts (in each case, ***"Associated"***); and *provided, further,* that the Parties hereby acknowledge and agree that Mir-21 is Associated with the field of Fibrosis. At each JSC meeting (including the initial meeting to be held promptly following the Effective Date), Regulus will provide an update to Sanofi regarding all material results of Regulus' research and discovery efforts in the Target Field, including the identity of each microRNA (excluding any microRNA that is encumbered by the [***]) that is the subject of Regulus' efforts in the Target Field. To this end, the Parties agree to hold an audio or video teleconference meeting of the JSC within 10 Business Days after the Effective Date and the initial face-to-face meeting of the JSC within eight (8) weeks after the Effective Date. At least one Collaboration Target must be [***] with the [***] and at least one Collaboration Target must be [***]with the [***] Fibrosis. The Collaboration Targets, including whether they are [***] with the Target Field, and whether Sanofi's rights for such Collaboration Target are for a microRNA Antagonist or a microRNA Mimic will be listed on **APPENDIX 6,** which may be updated from time to time by the Parties in accordance with this

Section 3.6. Sanofi may designate up to four Collaboration Targets at any time during the Research Term; *provided, however,* that if Sanofi wishes to designate a Collaboration Target after the [***], Sanofi must first have extended the Research Term for at least [***] in accordance with Section 3.3.2. During the Research Term, Regulus shall use Commercially Reasonable Efforts to identify and validate microRNAs as Associated with the Target Field in accordance with the R&D Plan.

3.6.1 Designating Collaboration Targets. As of the Effective Date, Sanofi has designated Mir-21 as a Collaboration Target in Fibrosis to approach with a microRNA Antagonist. If during the Research Term there are less than four Collaboration Targets, Sanofi may designate a new microRNA as a Collaboration Target by providing Regulus with a written notice (the ***"Request Notice"***) of the microRNA it wishes to designate as a Collaboration Target (the ***"Proposed Target"***). The Request Notice will include the microRNA name and the miRBase Accession Number, whether Sanofi believes the Proposed Target is Associated with the Target Field, and whether Sanofi wants to approach such Proposed Target with a microRNA Antagonist or a microRNA Mimic. Within 15 Business Days of receipt of the Request Notice, Regulus will give Sanofi written notice (i) stating if any of the criteria set forth in clauses (a), (b)

or (c) below applied to such Proposed Target at the time of Regulus' receipt of the Request Notice (or otherwise confirming that such Proposed Target is available); and (ii) only if none of clauses (a), (b) or (c) below applied to such Proposed Target at the time of Regulus' receipt of the Request Notice, disclosing all relevant Existing Regulus Agreements and Future Regulus Agreements and the [***] and other potential encumbrances known by Regulus and related to the Proposed Target (***"Target Encumbrances"***). If, and only if, at the time of Regulus' receipt of the Request Notice, the Proposed Target:

(a) is the subject of [***] an exclusive license granted by Regulus to a Third Party that would prohibit Regulus from collaborating with Sanofi under this Agreement or from granting a license under Section 2.1 with respect to the Proposed Target;

(b) is not [***] with the [***]; or

(c) has been approved in accordance with [***] procedures, consistently applied to [***] research programs, as an [***] research program [***] with committed resources, as reflected in the minutes of the proceedings of [***]. For purposes of this paragraph, **"[***]"** means the [***] responsible for approving the commitment of resources to an [***];

then, and only then, in each case, the Proposed Target will be rejected and will not become a Collaboration Target. If the Proposed Target is rejected, Sanofi can request another microRNA in accordance with the terms of this Section 3.6.1. If the Proposed Target is not rejected, the Proposed Target will become a Collaboration Target upon payment by Sanofi to Regulus of the applicable target designation milestone under Section 6.3; *provided, however,* that if the Proposed Target has any Target Encumbrances (and Regulus has disclosed such Target Encumbrances to Sanofi), before such Proposed Target can become a Collaboration Target, Sanofi must agree in writing (within 30 days of receiving from Regulus the description of such Target Encumbrances and subject to the allocations set forth in Section 6.8) to assume all applicable Target Encumbrances for such Proposed Target. Whenever a microRNA becomes a Collaboration Target, the JSC will promptly update the R&D Plan and the Parties will promptly update **APPENDIX 6** to add the new Collaboration Target and specify whether the Collaboration Target is [***], and whether Sanofi's rights for such Collaboration Target will be related to a microRNA Antagonist or a microRNA Mimic. If the Parties have a dispute whether a Proposed Target is [***], such dispute will be resolved by an Expert Panel in accordance with Section 13.4.5. For clarity, Sanofi may designate both a microRNA Antagonist and a microRNA Mimic for the same microRNA under this Section 3.6.1, but the microRNA Antagonist and the microRNA Mimic will each count as a separate Collaboration Target.

3.6.2 Right of Substitution. At any time during the Research Term and subject to the procedures set forth below, by written notice to Regulus, Sanofi may substitute a new microRNA for an existing Collaboration Target; *provided* that:

(a) unless unanimously agreed by the JSC, Sanofi may not substitute a Collaboration Target during the first [***] months following the applicable Request Notice for such Collaboration Target;

(b) Sanofi may only substitute Collaboration Targets for which Regulus has not generated a microRNA Compound satisfying the Development Candidate selection criteria set out in the R&D Plan, within [***] months of the applicable Request Notice for such microRNA;

(c) Sanofi may not substitute a Collaboration Target if Regulus has [***] for a Licensed Compound targeting or mimicking such Collaboration Target;

(d) Sanofi may not substitute another microRNA for Mir-21, unless Regulus has not [***] for a Mir-21 Compound by [***]; and

(e) Sanofi may not make more than [***] such substitutions under this Section 3.6.2(e) during the Research Term, provided that if Sanofi extends the Research Term until the [***] anniversary of the Effective Date pursuant to Section 3.3.2, then the maximum number of substitutions under this Section 3.6.2 that Sanofi may make during the Research Term as so extended shall be [***]. Notwithstanding the foregoing, the JSC may unanimously agree to make a Collaboration Target substitution, in which event such substitution shall not count toward the applicable maximum number of substitutions set forth in the preceding sentence.

If Sanofi elects to substitute a Collaboration Target under this Section 3.6.2, then Sanofi will provide written notice to Regulus, which written notice shall include a proposed new microRNA for consideration (including its name, the miRBase accession number for the proposed microRNA, and whether such microRNA is Associated with [***] Fibrosis) as a new Collaboration Target. Regulus shall approve or reject such proposed substitution microRNA in accordance with the criteria on which a Proposed Target becomes a Collaboration Target as set forth in Section 3.6.1. Any microRNA that is substituted-out of the Research Program will no longer be considered a Collaboration Target and Regulus' obligations under this Agreement with respect to such substituted-out microRNA (including but not limited to Section 2.3) will terminate. For purposes of clarity, Sanofi will not have to pay an additional target designation milestone under Section 6.3 for a replacement Collaboration Target under this Section 3.6.2.

3.6.3 Confidentiality. The fact that Sanofi has designated a particular microRNA as a Collaboration Target is Sanofi Confidential Information. The fact that Regulus has rejected a particular microRNA under Section 3.6.1 is Regulus Confidential Information.

3.6.4 End of Research Term. Upon the expiration of the Research Term, (a) Regulus will not be obligated to continue to perform work under the Research Program; (b) Sanofi may not designate any additional (or substituted) Collaboration Targets under Section 3.6; and (c) subject to Regulus' obligations under Section 2.3, Regulus will [***] any data generated under the R&D Plan for any microRNA that is not a Collaboration Target, including any microRNA Compound antagonizing or mimicking such microRNA.

3.6.5 Sanofi Option for other microRNA Compounds. Subject to Section 2.3, 3.6.1 and 3.6.2, Regulus may work independently of this Agreement for itself on a microRNA Compound which targets or mimics a Collaboration Target, which microRNA Compound Sanofi would otherwise not have a license to Develop or Commercialize under Section 2.1 (any such microRNA Compound, an ***"Optional Compound"***). If at any time during

the Term, Regulus identifies an Optional Compound as a candidate for initiation of IND-Enabling Studies, then Sanofi shall have the option (the ***"Option"***) to receive an exclusive royalty-bearing license to Develop and Commercialize such Optional Compound, as follows:

(a) Regulus shall notify Sanofi in writing with the details of such Optional Compound, including but not limited to any available pre-clinical data and the development costs to-date, (i) within [***] of the identification of an Optional Compound as a candidate for initiation of IND-Enabling Studies (the ***"First Option Notice"***) and (ii) if the Option has not yet been exercised, between [***] and [***] prior to the filing of an IND for such Optional Compound (the ***"Second Option Notice"***).

(b) Sanofi may exercise the Option under either the First Option Notice or the Second Option Notice solely by written notice to Regulus (each an ***"Exercise Notice"***); provided that if Sanofi exercises the Option pursuant to the First Option Notice it must provide Regulus with an Exercise Notice within [***] after Sanofi's receipt of the First Option Notice, and if Sanofi exercises the Option pursuant to the Second Option Notice it must provide Regulus with an Exercise Notice within [***] after the filing of the IND for such Optional Compound (the end of each such [***] period, a ***"Second Option Expiration Date"***).

(c) If Sanofi exercises the Option under the First Option Notice within the applicable time period specified in Section 3.6.5(b), then Sanofi shall, in accordance with [***] (i) $[***], (ii) an [***] to [***] specific to such Optional Compound [***] prior to the date of the First Option Notice, (iii) [***] of any [***] in [***] of [***] of [***] and in [***] of [***]by such Optional Compound after Sanofi exercises an Option with respect to such Optional Compound, and (iv) [***] on [***] by such Optional Compound after Sanofi exercises an Option with respect to such Optional Compound at the [***] in [***] of [***] of Section 6.5 with the provisions of Sections [***] through [***] applying *mutatis mutandis*.

(d) If Sanofi exercises the Option under the Second Option Notice within the applicable time period specified in Section 3.6.5(b), then Sanofi shall, in accordance with [***] (i) [***] (ii) an [***] to [***] specific to such Optional Compound [***] prior to the date of the First Option Notice, (iii) [***] of any [***] in [***] of [***] of [***] and in [***] of [***] by such Optional Compound after Sanofi exercises an Option with respect to such Optional Compound, and (iv) any [***] on [***] by such Optional Compound after Sanofi exercises an Option with respect to such Optional Compound at [***] in [***] of [***] of [***] with the provisions of Sections [***] through [***] applying *mutatis mutandis*.

(e) If Sanofi does not exercise an Option by the applicable Second Option Expiration Date, then (i) the applicable Option will expire, (ii) Sanofi's rights (and Regulus' obligations) under this Section 3.6.5 with respect to the applicable Optional Compound will terminate, and (iii) notwithstanding Section 2.3, Regulus may Develop and Commercialize the applicable Optional Compound on its own or with a Third Party (including granting of a license to a Third Party to Develop and Commercialize such Optional Compound).

Section 3.7 Research Program Records. Each Party and its contractors will maintain complete and accurate records of all work conducted in the performance of the Research Program and all results, data, inventions and developments made in the performance of

the Research Program. Such records will be in sufficient detail and in good scientific manner appropriate for patent and regulatory purposes. Upon reasonable prior written notice, Regulus will provide Sanofi the right to inspect such records, and will provide copies of all requested records, to the extent reasonably required for the performance of Sanofi's rights and obligations under this Agreement. Upon reasonable prior written notice, and solely with respect to Discontinued Products, Sanofi will provide Regulus the right to inspect such records, and will provide copies of all requested records, to the extent reasonably required for the performance of Regulus' rights and obligations under this Agreement. In each case, each Party will maintain such records and the information it receives from the other Party in confidence in accordance with Article 7 hereof and will not use such records or information except to the extent otherwise permitted by this Agreement.

Section 3.8 Disclosure of Results of Research Program. The results of all work performed by the Parties as part of the Research Program will be promptly disclosed to the other Party in a reasonable manner as such results are obtained. In addition, Regulus will periodically provide Sanofi with written reports of the work performed under the Research Program and the results achieved by Regulus. Regulus and Sanofi will provide reports and analyses at each JSC meeting, and more frequently on reasonable request by the JSC, detailing the current status of the Research Program. The results, reports, analyses and other information regarding the Research Program 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. Upon reasonable request by Sanofi, Regulus will provide Sanofi with additional data, results and other information with respect to the work performed by Regulus in the performance of the Research Program. Any reports required, excluding reports needed for submission to a Regulatory Agency, under this Section 3.8 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 as agreed upon by the JSC.

Section 3.9 Research Efforts; Resources, Scientific Manner. Each Party will use Commercially Reasonable Efforts to perform the Research Program, including its responsibilities under the R&D Plan.

3.9.1 Throughout the Research Term, Regulus will assign no less than the number of qualified scientists specified in the R&D Plan to perform the work set forth in the then-applicable R&D Plan. The mixture of skills and levels of such employees will be appropriate to the scientific objectives of the Research Program.

3.9.2 Each Party will maintain laboratories, offices, administrative support and all other facilities at its own expense and risk necessary to carry out its responsibilities under the R&D Plan. Each Party agrees to make its employees reasonably available at their respective places of employment to consult with the other Party on issues arising during the performance of the Research Program. Sanofi and Regulus will cooperate with each other in carrying out the Research Program, and each Party will contribute its relevant know-how and experience necessary to carry out the Research Program.

3.9.3 The Research Program will be conducted by each Party in good scientific manner, and in compliance with all applicable GCP, GLP and GMP, and applicable legal requirements, to attempt to achieve efficiently and expeditiously the Objectives of the Research Program. Each Party will comply with all Applicable Laws, in the performance of work under this Agreement.

3.9.4 Regulus will not perform any of its obligations under the R&D Plan through one or more subcontractors or consultants, without the prior written approval of Sanofi, such approval not to be unreasonably withheld; *except* that Regulus may (i) enter Permitted Licenses; and (ii) engage consultants and subcontractors in the ordinary course that generally support Regulus' research and development infrastructure, *provided* that (a) each such consultant and subcontractor agrees in writing to assign to Regulus all Know-How and Patents conceived made or reduced to practice in performing services for Regulus, and (b) Regulus will solely bear any costs associated with Regulus' use of such consultants and subcontractors. Sanofi will promptly notify Regulus regarding any Third Party Sanofi uses to conduct research under the R&D Plan or that Sanofi transfers Compounds or Products to, including identifying such Third Party.

Section 3.10 Materials Transfer. In order to facilitate the Research Program, either Party may provide to the other Party certain materials for use by the other Party in furtherance of the Research Program. All such materials will be used by the receiving Party in accordance with the terms and conditions of this Agreement solely for purposes of performing its rights and 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.

Section 3.11 Pharmacovigilance; Safety Database. Prior to IND transfer, designated staff from the respective Headquarter Pharmacovigilance Department shall be requested by the Joint Steering Committee to establish a detailed Safety Data Exchange Agreement ("***SDEA"***) for the Licensed Products to be in place prior to Sanofi starting any clinical development. Notwithstanding the foregoing, the Parties agree to the following principles:

3.11.1 Sanofi will establish the global safety database for the Licensed Compounds/Products that will be used for regulatory reporting and responses to safety queries from Regulatory Authorities. For that purpose, Regulus will promptly transfer all safety information regarding the Licensed Compounds or Products, including, if applicable, adverse events, and drug exposure during pregnancy data that it has regarding the Licensed Compounds or Products to Sanofi for entry into the global safety database upon request from Sanofi. The timelines, format and content of such transfer shall be agreed in the SDEA.

3.11.2 Regulus maintains a database that includes information regarding the safety and tolerability of its drug compounds, individually and as a class, including information discovered during pre-clinical and clinical development (the ***"Regulus Database"***).

3.11.3 *Safety Monitoring*. In an effort to maximize understanding of the safety profile and pharmacokinetics of Regulus compounds, after IND Approval, Sanofi will cooperate with Regulus and forward safety information to Regulus designated contact persons. This

includes transmission of serious adverse events collected from Sanofi sponsored studies in a timely fashion as agreed in the SDEA. *Vice versa* Regulus shall promptly inform Sanofi on any safety issue or class effect that may come to its attention including those from other license partners to the extent Regulus is not precluded by written agreement with the applicable partner from sharing such information with Sanofi. This includes also non clinical safety information.

3.11.4 *Studies/Regulatory Documents*. To the extent collected by Sanofi and in the form in which Sanofi uses/stores such information for its own purposes, Sanofi will provide Regulus with the results from each of the nonclinical (e.g., toxicology, pharmacokinetics, and safety pharmacology studies) and the clinical studies of each Licensed Compound and Product as soon as practicable following the date such information is available to Sanofi (but not later than [***] after Sanofi's receipt of such information). The clinical results will include, but will not be limited to, subject demographics and characteristics, medical history, prior and concomitant medication usage, adverse event reports and laboratory test results. The clinical results will be accompanied by the clinical study protocol (original and all amendments) and an annotated case report form (CRF) that identifies the variable names in the transferred data associated with each of the data fields in the CRF. In connection with any reported serious adverse event, Sanofi will provide Regulus all serious adverse event reports (including initial, interim, follow-up, amended, and final reports) promptly following the time these reports are submitted to Regulatory Authorities. In addition, with respect to each Licensed Compound and Product, Sanofi will provide Regulus with copies of annual safety updates filed with each IND and the safety sections of any final clinical study reports within [***] following the date such information is filed or is available to Sanofi, as applicable. Furthermore, Sanofi will promptly provide Regulus with any supporting data and answer any follow-up questions reasonably requested by Regulus.

3.11.5 *Confidentiality.* All such information disclosed by Sanofi to Regulus will be Sanofi Confidential Information; *provided*, *however*, that Regulus may disclose any such Sanofi Confidential Information to Regulus' other partners pursuant to ARTICLE 7 below if such information is regarding class generic properties of microRNA Compounds, and/or any Third Party, in each case, so long as Regulus does not disclose the identity of the Product, or Sanofi.

3.11.6 *Contacts.* Sanofi will deliver all such information to Regulus for the Regulus Database to Regulus Therapeutics Inc., 1896 Rutherford Road, Carlsbad, California 92008, Attention: Chief Medical Officer (or to such other address/contact designated in writing by Regulus).

ARTICLE 4

MANUFACTURING

Section 4.1 Supply of microRNA Compound for Research Program. Regulus agrees to manufacture and supply all microRNA Compounds for use in support of the Research Program until the filing of an IND. Regulus will bear its own costs for the manufacture of all microRNA Compound needed for research until the filing of an IND. For clarity, Regulus will not be required to manufacture and supply API or drug product for any human clinical trials.

Section 4.2 Clinical and Commercial Manufacturing and Supply of Licensed Compound and Product.

4.2.1 Product Manufacturing Responsibility. Except as otherwise provided in this Agreement, the Parties acknowledge and agree that Sanofi will be solely responsible for the manufacturing of Licensed Compound and Product for all clinical trials and commercial supply, including management of the overall manufacturing strategy and tactics, formulation, internal or contract manufacturer selection for API and finished Product, associated audits, stability testing, pricing, relationship with contract manufacturer(s) and any work proposals or contract negotiations or contracts themselves.

4.2.2 Supply of Finished Drug Product. Except as otherwise specified in the R&D Plan, the Parties acknowledge and agree that Sanofi will be solely responsible for the manufacturing, stability testing and supply of finished drug Product.

Section 4.3 Transfer of Manufacturing Technology and Assistance. Regulus shall disclose (and provide copies, as applicable) to either Sanofi or a Third Party manufacturer designated by Sanofi all Manufacturing Technology that is required for the manufacture (including the development of the manufacturing process) of the Licensed Compounds and Products and is reasonably necessary or useful to enable Sanofi or such Third Party manufacturer (as appropriate) to manufacture such Products. The steps, planning and obligations of the Parties regarding the transfer of the Manufacturing Technology for each Product (for both the Licensed Compound and the Product) will be set forth in a "Technology Transfer Master Plan API" to be executed between the Parties promptly after the JSC decides such transfer is necessary. Upon request, Regulus will at all times use diligent efforts to provide Sanofi-Aventis with any additional information or on-site support as may be required by Sanofi and its Affiliates in connection with the transfer of the Manufacturing Technology. Sanofi shall reimburse Regulus for any on-site support rendered at the FTE-Day Rate per FTE-day, provided further Regulus shall in no event be obliged to provide more than [***] in total, unless the Parties otherwise agree in writing. For purposes of this Agreement ***"Manufacturing Technology"*** shall mean the Know-How Controlled by Regulus that is reasonably available and reasonably necessary for the Manufacture (including formulation, processing, filling and packaging) of Licensed Compounds and Products. Sanofi and its Third Party manufacturer may only use the Manufacturing Technology only in support of its licenses under Section 2.1 of this Agreement and will not use the Manufacturing Technology in connection with any other compound or product. Sanofi will be responsible and liable to Regulus for any practice of the Manufacturing Technology by Sanofi's Third Party manufacturer that breaches this Section 4.3.

ARTICLE 5

DEVELOPMENT & COMMERCIALIZATION

Section 5.1 Development, Commercialization and Regulatory Responsibilities. Other than Regulus' responsibilities under the R&D Plan (including but not limited to preparing and filing the IND for each Licensed Compound and Product), Sanofi will have sole responsibility, including without limitation sole responsibility for all funding, resourcing and decision-making, for all Development and Commercialization with respect to the Licensed

Compounds and Products after IND Approval. Sanofi hereby assumes all regulatory responsibilities in connection with Licensed Compounds and Products after IND Approval, including sole responsibility for all Regulatory Documentation and for obtaining all Approvals. Sanofi will comply with all Applicable Laws in connection with the Development and Commercialization of Licensed Compounds and Products. Sanofi (by itself or through its Affiliates, sublicensees, (sub)contractors or agents, as applicable) will achieve Initiation of first Phase 1 Trial as soon as practicable following IND Approval for each Licensed Compound and will use Commercially Reasonable Efforts to Develop and Commercialize at least one Licensed Compound or Product for each Collaboration Target. Regulus will make all IND filings under the Research Plan in Regulus' name. Once Sanofi pays Regulus the applicable milestone payment under Section 6.4.1 for IND Approval, Sanofi will own all INDs, NDAs, MAAs and other regulatory filings and Approvals for Products, subject to Regulus reversion rights under ARTICLE 10.

Section 5.2 Reports by Sanofi after the Research Term. After the Research Term with respect to any Licensed Compound or Product that Sanofi is Developing, Sanofi will provide a [***] report to Regulus summarizing Sanofi's activities over the past year with respect to the identified Licensed Compound or Product and an appropriate number of representatives from each Party will meet at least once every year to review Development activities. Sanofi will consider Regulus' input regarding such activities. The reports provided by Sanofi under this Section 5.2 will contain sufficient information to allow Regulus to reasonably determine whether Sanofi is in compliance with its obligations to use Commercially Reasonable Efforts under Section 5.1.

Section 5.3 Product Development Plans; Integrated Product Plans. For each Product that Sanofi is clinically developing under this Agreement, Sanofi will prepare a development plan outlining key aspects of the clinical development of such Product through Approval. Each development plan will contain information customarily contained in Sanofi's development plans for its similar products at similar stages of development (each a ***"Product Development Plan")***. In addition, prior to the launch of a Product, Sanofi will prepare a global integrated Product plan outlining the key aspects of market launch and commercialization (the ***"Integrated Product Plan"*** or ***"IPP"***). Sanofi will prepare each IPP at the same time and containing information and target markets as customarily contained in Sanofi's Commercialization plans for its similar products at similar stages of development. Each Product Development Plan and IPP will be updated annually by Sanofi. Sanofi will provide to Regulus a copy of the final draft of the Product Development Plans and IPPs (original and updates) for each of the U.S., each Major European Country and Japan, if available. Such copies of Product Development Plans and IPPs provided to Regulus may be redacted to the extent necessary to preserve the confidentiality of Sanofi confidential information related to products that are not

Products. Sanofi and Regulus will meet on a yearly basis to discuss the draft of each Product Development Plan and IPP and Sanofi will consider, in its sole discretion, any proposals and comments made by Regulus for incorporation in the final Product Development Plan or IPP (as the case may be).

Section 5.4 Class Generic Claims. To the extent Sanofi intends to make any claims in a Product label that are class generic to microRNA Compounds, Sanofi will provide such

claims to Regulus in advance and will consider, in its sole discretion, any proposals and comments made by Regulus.

ARTICLE 6

FINANCIAL PROVISIONS

Section 6.1 Up-Front Payment. In consideration for the licenses and other rights granted under this Agreement Sanofi will pay Regulus an irrevocable, non-creditable and nonrefundable technology access fee equal to $25,000,000 ($[***] of which Regulus is allocating to the access to Mir-21 in the detailed amounts set forth on **APPENDIX 9**, and $[***] of which Regulus is allocating to the rest of the Research Program in the detailed amounts set forth on **APPENDIX 9**). Regulus shall send Sanofi separate invoices pursuant to Section 6.13 on or after the Effective Date for such $[***] payment and such $[***] payment, and Sanofi shall pay such amounts no later than [***] Business Days following receipt of such invoices.

Section 6.2 Research Program Funding. Sanofi will provide Research Program funding to Regulus as set forth in Section 3.5.1.

Section 6.3 Target Designation Milestone. For each Collaboration Target (other than Mir-21) designated by Sanofi under Section 3.6, Sanofi will pay Regulus an irrevocable, non-creditable, and nonrefundable milestone payment equal to $[***] within 10 Business Days after receipt of invoice from Regulus following such designation. For purposes of clarity, Sanofi will not have to pay an additional target designation milestone under this Section 6.3 for a replacement Collaboration Target under Section 3.6.2.

Section 6.4 Milestone Payments by Sanofi. Sanofi will give Regulus written notice within [***] Business Days of the first achievement of each Milestone Event provided in Table 1; *provided* Regulus will notify Sanofi regarding IND Approval for each Licensed Compound. After receiving such written notice, Regulus shall submit an invoice to Sanofi for the amount of such milestone payment, and Sanofi will pay Regulus the applicable milestone payment within [***] days after receipt of an invoice from Regulus following achievement of the applicable milestone event.

6.4.1 Development/Approval Milestones.

(a) For each Collaboration Target (other than Mir-21), the milestone payments by Sanofi to Regulus under Column 1 of Table 1 below will be triggered by the first achievement of the specified milestone events by Sanofi, its sublicensees or their respective Affiliates for the first Licensed Compound or Product that targets or mimics such Collaboration Target to achieve the specified milestone event.

(b) The milestone payments under Column 2 of Table 1 below will be payable as set forth below for the first achievement of the specified milestone events by Sanofi, its sublicensees or their Affiliates for the first Mir-21 Compound or Mir-21 Product to achieve the specified milestone event.

Table 1

Milestone Event	Column 1 Payment for First Licensed Compound Per Collaboration Target	Column 2 Payment for First Mir-21 Compound
1. IND Approval	[***]	[***]
2. [***]	[***]	[***]
3. [***]	[***]	[***]
4. [***]	[***]	[***]
5. [***]	[***]	[***]
6. [***]	[***]	[***]

(c) In addition, on a Collaboration Target-by-Collaboration Target basis, after the first achievement of milestone event [***] in Table 1 above by the first Licensed Compound or Product associated with a Collaboration Target to achieve such milestone event for any Indication, if a Licensed Compound or Product for such Collaboration Target (whether the same or a different Licensed Compound or Product) subsequently achieves such milestone event(s) for any additional Indication(s) (each, an ***"Additional Indication"***), then Sanofi will promptly notify Regulus and will pay Regulus an additional milestone payment in an amount equal to [***]% of the applicable milestone payment(s) set forth in Column 1 or Column 2 (as applicable) of Table 1 above for the achievement of such milestone event(s) by such Licensed Compound or Product for each Additional Indication (each, an ***"Additional Indication Milestone Payment"***).

(d) If a Licensed Compound or Product for a Collaboration Target fails in development and is replaced by Sanofi with a back-up Licensed Compound or Product targeting the same Collaboration Target, with respect to any milestone payments previously paid with respect to such failed Licensed Compound or Product, Sanofi will not have to pay the same milestone with respect to the corresponding back-up Licensed Compound or Product, and Sanofi will notify Regulus in writing of the selection of the back-up Licensed Compound or Product. All milestone payments due will be payable one time only per Licensed Compound or Product for each Indication.

6.4.2 Sales Milestones. For each Collaboration Target, the milestone payments under Table 2 below will be payable by Sanofi to Regulus for the first achievement of the specified milestone events by Sanofi, its sublicensees or their Affiliates for (i) the first Licensed Compound or Product that targets or mimics such Collaboration Target to achieve the specified milestone event; and (ii) first Mir-21 Compounds or Mir-21 Products to achieve the specified milestone event.

Table 2

Milestone Event	Milestone Payment
[***]	

Section 6.5 Royalty Payments by Sanofi. Subject to the other provisions of this Agreement, Sanofi will pay to Regulus royalties on Net Sales of each Product at the applicable rate(s) set forth under Column 1 of Table 3 below if such Product is not a Mir-21 Product; and at the applicable rate(s) set forth under Column 2 of Table 3 below if such Product is a Mir-21 Product. The royalty rate payable with respect to each particular Product will be based on the level of annual worldwide Net Sales of such Product in a given Calendar Year period by Sanofi, its Affiliates and sublicensees, with the royalty rate tiered based upon the level of such worldwide Net Sales in such Calendar Year period of such Product as set forth in the table below.

Table 3

Annual Worldwide Net Sales	Column 1 Royalty Rate Product	Column 2 Royalty Rate Mir-21 Product
For the portion that is less than or equal to $[***]		

For example, in the instance of a full Calendar Year, if annual Net Sales of a Mir-21 Product in such Calendar Year worldwide are [***].

Section 6.6 Existing Third Party Payment Obligations.

6.6.1 Existing Regulus Agreements. Sanofi acknowledges that certain of the Regulus Technology Controlled by Regulus as of the Effective Date were in-licensed, or otherwise acquired by Regulus, from Third Parties under the Existing Regulus Agreements, and that Regulus is obligated to pay In-License Royalties and/or In-License Milestones to the Licensor(s) under such Existing Regulus Agreements as a result of the Development or Commercialization of Products by Sanofi or any of its Affiliates or sublicensees to the extent that such Products are covered by the applicable Third Party Patents. The Parties acknowledge and agree that Regulus will be responsible for paying [***]% of the In-License Royalties, In-License Milestones and Other In-License Payments that become due to the Licensor(s) under the Existing Regulus Agreements.

6.6.2 Existing Sanofi Agreements. The Parties acknowledge and agree that, if and to the extent that there are any Existing Sanofi Agreements, Sanofi will be responsible for paying [***]% of the In-License Royalties, In-License Milestones and Other In-License Payments that become due to the Licensor(s) under such Existing Sanofi Agreements, and [***] of such payments will be creditable against any payment due to Regulus hereunder.

Section 6.7 Future Third Party Agreements.

6.7.1 Identification of Necessary Patents. Subject to Section 6.7.5, if, after the Effective Date, a Party identifies any Patent that:

(a) is not Controlled by either Party;

(b) covers (i) the [***] thereof (each, a ***"[***]Invention"***), (ii) the [***] (each, a ***"[***]Invention"***), (iii) a [***] (each, a ***"[***]Invention"***), or (iv) [***]that is necessary to [***]to the [***]in order to [***]excluding [***] (each, a ***"[***]Invention"***); and

(c) such Party believes in good faith is, or is likely to be, necessary for the Development or Commercialization of a Product;

then, such Party will inform the other Party thereof, and the Parties (via the JSC for so long as the JSC is in place) shall promptly confer with each other, and attempt in good faith to reach consensus regarding, as to whether in-licensing or acquiring other rights to such Patent is, or is likely to be, necessary for the Development or Commercialization of a Product. [***] with respect to either or both Parties. The [***]as well as [***] The Parties will initially [***]of the [***], provided that promptly after the [***], the Party whose [***]the other Party an [***] [***] of the [***](such that the [***] to the [***] the other Party), and each Party [***]

If the [***]the Party that [***], then such Party shall be [***], provided that (1) such Party shall be responsible for [***] of the [***], (2) if such Party is Sanofi, none of such [***] hereunder, and (3) if such Party is Regulus, then notwithstanding any other provision of this Agreement to the contrary, such [***].

6.7.2 Responsible Party. If the Parties mutually agree, or [***], that in-licensing or acquiring other rights to a Patent meeting the criteria set forth in Section 6.7.1 is necessary for the Development or Commercialization of a Product (each, a ***"Necessary Patent"***), the Party that will be responsible for in-licensing or acquiring other rights to such Necessary Patent (the ***"Responsible Party"***) will be determined based on whether such Necessary Patent covers a Target Invention, a Compound Invention, a Method Invention, or a Formulation Invention, as follows:

Mir-21:
[***]

Other Collaboration Targets:

[***]

\Any agreement entered into by a Responsible Party pursuant to this Section 6.7.2 shall be deemed a ***"Future Regulus Agreement"*** if Regulus is the Responsible Party, and a ***"Future Sanofi Agreement"*** if Sanofi is the Responsible Party.

6.7.3 Consultation; Cooperation. The Responsible Party will consult with the other Party and consider in good faith the reasonable comments and suggestions of the other Party regarding the financial terms of any Future Regulus Agreement or Future Sanofi Agreement (as applicable), and in negotiating such Future Regulus Agreement or Future Sanofi Agreement with the applicable Licensor(s) shall use commercially reasonable efforts to minimize any In-License Royalties, In-License Milestones and Other In-License Payments that (a) are to be borne, in whole or in part, by the other Party pursuant to Section 6.8, (b) are creditable against any amounts payable to Regulus hereunder in accordance with Section 6.10.1 or Section 6.10.4, and/or (c) in the case of In-License Royalties, are to be considered in [***]. Except as set forth in Section 6.7.2 or Section 6.9, Regulus will not enter any Future Regulus Agreement that would impose any additional financial obligations on Sanofi beyond those set forth in this Agreement without first obtaining Sanofi's prior written consent.

6.7.4 Copy of Agreement. Upon entering into any Future Regulus Agreement or Future Sanofi Agreement that includes In-License Royalties, In-License Milestones and/or Other In-License Payments that (a) are to be borne, in whole or in part, by the other Party pursuant to Section 6.8, (b) where Sanofi is the Responsible Party, are creditable against any amounts payable to Regulus hereunder in accordance with Section 6.10.1 or Section 6.10.4, and/or (c) in the case of In-License Royalties, are to be considered in [***], the Responsible Party shall provide to the other Party a copy of the portion of such agreement which sets forth the relevant In-License Royalties, In-License Milestones and/or Other In-License Payments.

6.7.5 [***] Responsibility for [***] and [***] Technology. In the event that after the Effective Date, Sanofi identifies any Patent not Controlled by either Party that covers any [***], in its sole discretion, to be necessary for the Development or Commercialization of a Product, Sanofi shall have the sole responsibility for in-licensing or acquiring other rights to such Patent, including sole responsibility for negotiation and execution of a license or other agreement with respect thereto. Sanofi will be solely responsible for paying [***]% of the In-License Royalties, In-License Milestones and Other In-License Payments that become due to the Licensor(s) under such agreement, and [***] such payments, [***] portion thereof, will be creditable against any of Sanofi's payment obligations to Regulus under this Agreement.

Section 6.8 Allocation of Payments.

6.8.1 In-License Royalties. In-License Royalties payable to Licensors under any Future Regulus Agreement or Future Sanofi Agreement shall be allocated between the Parties based on (a) whether the applicable Third Party Patents cover a [***] Invention, a [***] Invention, a [***] Invention, or a [***] Invention, (b) the identity of the Licensor(s), and/or (c) Indication, as follows:

Mir-21:
[***]
Other Collaboration Targets:
[***]

6.8.2 In-License Milestones. In-License Milestones payable to Licensors under any Future Regulus Agreement or Future Sanofi Agreement shall be allocated between the Parties based on (a) whether the applicable Third Party Patents cover a [***] Invention, a [***]

Invention, a [***] Invention, or a [***] Invention, (b) the identity of the Licensor(s), and/or (c) Indication, as follows:

Mir-21:
[***]

Other Collaboration Targets:
[***]

6.8.3 Other In-License Payments. Other In-License Payments payable to Licensors under any Future Regulus Agreement or Future Sanofi Agreement shall be allocated between the Parties, or among the Parties and one or more Third Parties (as applicable) based on (a) whether the applicable Third Party Patents cover a [***] Invention, a [***] Invention, a [***] Invention, or a [***] Invention, (b) the identity of the Licensor(s), (c) Indication, and/or (d) whether the applicable Third Party Patents are licensed to any Third Party(ies) as follows:

Mir-21:
[***]

Other Collaboration Targets:
[***]

* [***]
[***]

6.8.4 Payment Process. Sanofi will directly pay to Regulus any amounts payable under a Future Regulus In-License in connection with a Product to the extent such amounts are allocated to Sanofi under this Section 6.8. Sanofi will pay directly the applicable Third Party any amounts payable under a Future Sanofi In-License in connection with a Product; *provided*, to the extent any royalty payments are allocated to Regulus under this Section 6.8, Sanofi will be entitled to the royalty reduction as further set forth in Section 6.10.1.

Section 6.9 [***] Technology. After the Effective Date, Regulus may wish to in-license or acquire rights to Patents from a Third Party, which Patents, if in-licensed or acquired, would be within the scope of the definition of [***] Patent (***"[***] Patents"***), with or without associated Know-How. In such event, Regulus shall [***] Sanofi's consent, to negotiate and enter into an in-license or other agreement with the Third Party with respect to such [***] Patents and related Know-How, if any (collectively, ***"[***] Technology"***). In such event (and to the extent permitted by Regulus' confidentiality agreement with the applicable Third Party), Regulus will notify Sanofi regarding the nature of the [***] Technology and status of negotiations related to the [***] Technology through the JSC. Once Regulus and such Third Party have executed an agreement with respect to such [***] Technology (***"[***] Technology Agreement"***), Regulus will offer such [***] Technology to Sanofi (including a description of the upfront and other ongoing non-royalty, non-milestone payments and, except as set forth in Section 6.9.2(b), the royalties and milestone payments paid or potentially payable by Regulus thereunder).

6.9.1 In the case of any such [***] Technology comprising a [***] Invention, [***] Invention, [***] Invention or [***] Invention or patent rights claiming any of the foregoing (in each case, ***"Section 6.9.1 Technology"***), if Sanofi wishes to include such Section 6.9.1 Technology in the Regulus Technology licensed to Sanofi under Section 2.1, Sanofi will notify Regulus of its desire to do so within [***] days after receipt of notice from Regulus, whereupon such Section 6.9.1 Technology shall be included in the Regulus Technology licensed to Sanofi under Section 2.1, and the upfront, royalty, milestone and other ongoing payments paid or potentially payable by Regulus under such [***] Technology Agreement shall be [***] in accordance with Section [***] *mutatis mutandis*. If Sanofi [***] such notification to Regulus within such [***]-day period, then notwithstanding any other provision of this Agreement to the contrary, the applicable Section 6.9.1 Technology will [***] the Regulus Technology licensed to Sanofi under Section 2.1.

6.9.2 In the case of any [***] Technology other than Section 6.9.1 Technology (***"Section 6.9.2 Technology"***), if Sanofi wishes to include such Section 6.9.2 Technology in the Regulus Technology licensed to Sanofi under Section 2.1, Sanofi will notify Regulus of its desire to do so within [***] days after receipt of notice from Regulus, whereupon the Parties will negotiate in good faith regarding:

(a) a fair and commercially reasonable [***] (and/or among the Parties and any Regulus Third Party sublicensee(s) of such Section 6.9.2 Technology) of upfront and other ongoing non-royalty, non-milestone payment obligations (which [***] of such payment obligations). As part of this [***], Regulus will share with Sanofi, in reasonable detail, the assumptions and methodology Regulus used to create the [***]; and

(b) the royalties and milestone payments to be [***] with respect to Licensed Compounds and Products, the Development, manufacture or Commercialization of which is within the scope of Regulus' in-license or other rights to the applicable Section 6.9.2 Technology. For the avoidance of doubt, Regulus will [***] to Sanofi the nature or amount of any of Regulus' royalty and milestone payment obligations to such Third Party.

If the Parties [***] to the [***]in Section 6.9.2(a) and the royalties and milestone payments to be [***] as described in Section 6.9.2(b), then the applicable Section 6.9.2 Technology will be included in the Regulus Technology licensed to Sanofi under Section 2.1. If the Parties [***] to the foregoing, then notwithstanding any other provision of this Agreement to the contrary, the applicable Section 6.9.2 Technology will [***] the Regulus Technology licensed to Sanofi under Section 2.1. For purposes of clarification, any payment obligations [***] under this Section 6.9.2 will be in addition to, and will not be creditable in whole or in part against, Sanofi's payment obligations set forth in this Agreement.

6.9.3 In the event of a dispute between the parties as to whether a particular Patent of a Third Party constitutes a [***] Patent, or whether any particular [***] Technology constitutes Section 6.9.1 Technology or Section 6.9.2 Technology, such dispute shall be [***] in accordance with the provisions of Section 6.7.1, *mutatis mutandis*.

Section 6.10 Royalty Reductions; [***].

6.10.1 Reduction for Third Party Royalties. Subject to Section 6.10.3, Sanofi's royalty obligations under Section 6.5 above with respect to a particular Product in a particular country will be reduced by the applicable percentage (if any) of the amount of aggregate In-License Royalties paid by Sanofi to Licensor(s) under Future Sanofi-Agreements on sales of such Product in such country for which Regulus is responsible, as set forth in Section 6.8; *[***]*.

6.10.2 Generic Competition. Subject to Section 6.10.3, if a Generic Product corresponding to a Product is approved for sale by the applicable Regulatory Authority and then sold in a particular country and the Percentage Reduction of Net Sales is greater than [***]% for any given Calendar Quarter in such country, then the royalty rate set forth in Table 3 of Section 6.5 applicable to such Product and such country for such Calendar Quarter will be reduced to [***]%; *[***]*. As used herein, the ***"Percentage Reduction of Net Sales"*** of a Product in a country for any particular Calendar Quarter means the quotient (expressed as a percentage) obtained by dividing (A) the difference obtained by subtracting the [***]such applicable Calendar Quarter from the [***]by (B) the [***]. In addition, if (i) there [***] Generic Product sold by a Third Party, and (ii) [***], then such Generic Product will [***] the royalty reduction under this Section 6.10.2.

6.10.3 [***]

6.10.4 [***]

6.10.5 No Payments to [***]. For purposes of clarification, and notwithstanding any other provision of this Agreement, in no event shall the [***] to which [***] may be entitled under this Section 6.10 result in [***] being obligated to make any payment to [***].

Section 6.11 Royalty Term. Royalties payable under Section 6.5 (subject to and including any applicable reductions under Section 6.10) will be payable on a Product-by-Product and country-by-country basis from the First Commercial Sale of a Product in a country until the date that is the [***] of (i) [***] years after the First Commercial Sale of such Product in such country or (ii) the expiration of the last to expire Valid Claim within the Regulus Patents which would be infringed by the sale of such Product in such country by an unauthorized party. Such period during which royalties are payable with respect to a Product in a country, including giving effect to any applicable reductions under Section 6.10, is referred to herein as the ***"Royalty Term"*** for such

Product in such country. Notwithstanding expiration of the Royalty Term with respect to a particular Product in a country, [***] with respect to Net Sales of such Product in such country.

Section 6.12 Royalty Report and Payment. During the Royalty Term following the First Commercial Sale of any Product, within [***] after the end of each Calendar Quarter, Sanofi will provide Regulus with a royalty report for such Quarter showing, on a Product-by-Product and country-by-country basis:

(a) the Net Sales of Products sold by Sanofi, its sublicensees and their respective Affiliates during such Calendar Quarter reporting period;

(b) the royalties which will have accrued hereunder with respect to such Net Sales;

(c) the amount of any applicable [***] taken against royalties under Section 6.10.1 and the amount of any applicable [***] accrued against future sales milestone payments under Section 6.10.4;

(d) any adjustment for Generic Products under Section 6.10.2; and

(e) any other information related to the calculation of Net Sales of Products reasonably requested by Regulus that (i) is contained in a report and format that is regularly generated by Sanofi's accounting department in its normal course of business and (ii) is reasonably necessary for Regulus to comply with an Existing Regulus Agreement or an Additional Regulus Third Party Agreement.

Sanofi will keep, and will require its sublicensees and their respective Affiliates to keep, complete, true and accurate books of account and records for the purpose of determining the payments to be made under this Agreement. Upon reasonable request by Regulus (but no more frequently than once in any [***]-month period), Sanofi will report to Regulus the quantity of Product not subject to royalties distributed by Sanofi, its Affiliates or sublicensees as part of an expanded access program to include compassionate use, named patients or other similar use or as part of Phase 4 Trials or as bona fide samples. All information disclosed by Sanofi to Regulus under this Section 6.12 will be Sanofi Confidential Information.

Section 6.13 Manner of Payment and Exchange Rate. Except as otherwise provided in this Agreement, Regulus shall invoice Sanofi for all milestone, royalty and other payments hereunder and Sanofi shall pay all such milestone, royalty and other payments that are due within ten (10) Business Days after the receipt of the applicable invoice. All payments to be made by Sanofi to Regulus hereunder will be made by deposit of U.S. Dollars by wire transfer in immediately available funds in the requisite amount to such bank account Regulus may from time to time designate by notice to Sanofi. For sales that were made in a currency other than U.S. Dollars, such amounts will be converted into U.S. Dollars using the average exchange rates as calculated and utilized by Sanofi's group reporting system and published accounts for the applicable royalty period. All invoices to be provided by Regulus to Sanofi under this Agreement shall include a breakdown of the goods, services and/or activities for which payment is due, as well is payment instructions and shall be sent by express courier service to:

Sanofi-Aventis
Direction Comptable Holding
174 avenue de France
75013 Paris
France

Section 6.14 Audits, including Audits of Royalty Reports.

6.14.1 Audits of Royalty Reports. Upon the written request of Regulus and not more than once in each Calendar Year, Sanofi will permit an independent certified public accounting firm of nationally recognized standing selected by Regulus and reasonably acceptable

to Sanofi, at Regulus' expense to have access during normal business hours to such records of Sanofi and/or its Affiliates as may be reasonably necessary to verify the accuracy of the royalty reports hereunder for any Calendar Year ending not more than 36 months prior to the date of such request. These audit rights (but not any obligation to pay unpaid royalties for such periods) with respect to any Calendar Year will terminate 3 years after the end of such Calendar Year. Regulus will provide Sanofi with a copy of the accounting firm's written report within 30 days of completion of such report.

6.14.2 If such accounting firm concludes that an overpayment or underpayment was made, then the owing Party will pay the amount due within 30 days of the date Regulus delivers to Sanofi such accounting firm's written report so correctly concluding. Regulus will bear the full cost of such audit unless such audit correctly discloses that the additional payment payable by Sanofi for the audited period is more than [***]% of the amount of the royalties paid for that audited period, in which case Sanofi will pay the reasonable fees and expenses charged by the accounting firm.

6.14.3 Sanofi will use Commercially Reasonable Efforts to include in each sublicense granted by it to any sublicensee a provision requiring the sublicensee to maintain records of sales made pursuant to such license and to grant access to such records by Sanofi's independent accountant to the same extent and under substantially similar obligations as required of Sanofi under this Agreement. Sanofi will advise Regulus in advance of each audit of any sublicensee with respect to Product sales. Sanofi will provide Regulus with a summary of the results received from the audit and, if Regulus so requests, a copy of the audit report with respect to Product sales. Sanofi will pay the reasonable fees and expenses charged by the accounting firm, except that Regulus will pay for all additional services requested exclusively by Regulus from Sanofi's independent accountant unless the audit discloses that the additional payments payable to Regulus for the audited period differ by more than [***]% from the amount of the royalties otherwise paid.

6.14.4 All financial information subject to review under this Section or under any license agreement with a sublicensee will be Sanofi Confidential Information and will be treated in accordance with the confidentiality provisions of this Agreement. As a condition precedent to Regulus' audit rights under this Section, Regulus' accounting firm will enter into a confidentiality agreement with Sanofi obligating it to treat all such financial information

in confidence pursuant to such confidentiality agreement. Regulus may provide Third Parties to which Regulus owes royalties on Products information in such audit report that are relevant and required to comply with such Third Party's audit rights under the applicable license agreement between Regulus and such Third Party, *provided* that such Third Party agrees in writing to keep such information confidential under terms no less restrictive than Regulus' obligations of confidentiality under this Agreement.

Section 6.15 Taxes.

6.15.1 Sanofi will make all payments to Regulus under this Agreement without deduction or withholding for taxes except to the extent that any such deduction or withholding is required by Applicable Law in effect at the time of payment.

6.15.2 Sanofi will promptly pay on behalf of Regulus any tax required to be withheld on amounts payable under this Agreement to the appropriate governmental authority, and Sanofi will furnish Regulus with proof of payment of such tax. Any such tax required to be withheld will be an expense of and borne by Regulus.

6.15.3 Sanofi and Regulus will cooperate with respect to all documentation required by any taxing authority or reasonably requested by Sanofi to secure a reduction in the rate of applicable withholding taxes.

Section 6.16 Sublicenses. In the event Sanofi grants licenses or sublicenses to a sublicensee to sell Products which are subject to royalties under Section 6.5, such licenses or sublicenses will include an obligation for the sublicensee to account for and report its sales of Products on the same basis as if such sales were Net Sales by Sanofi.

Section 6.17 [***]

Section 6.18 Sanofi Founding Company License. Notwithstanding any other provision in this Agreement, in the event that Sanofi is granted a license (each such license a ***"Sanofi Founding Company License"***) pursuant to Section 15.3 of the Founding Company License Agreement (entitled "Effects of Termination") from either of the Founding Companies, then, in addition to, and not in lieu of, any other or remedies available to Sanofi:

6.18.1 [***] amounts payable to either of the Founding Companies pursuant to proviso "(ii)" of the final sentence of Section 15.3, [***]; and

6.18.2 subject to Section 6.10.3, any royalty or milestone amounts (including both sales milestones and development milestones) payable to either of the Founding Companies under any Sanofi Parent License, to the extent not [***] than were Regulus' royalty and milestone payment obligations under the Founding Company License Agreement, [***] under this Agreement. If royalty or milestone amounts payable by Sanofi to either of the Founding Companies under any Sanofi Parent License [***] Regulus' royalty or milestone payment obligations under the Founding Company License Agreement, Sanofi [***].

ARTICLE 7

CONFIDENTIALITY; PRESS RELEASES & PUBLICATIONS

Section 7.1 Confidentiality; Exceptions. Except to the extent expressly authorized by this Agreement or otherwise agreed in writing, the Parties agree that, during the Term and for five (5) 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 Know-How or other confidential and proprietary information and materials, patentable or otherwise, in any form (written, oral, photographic, electronic, magnetic, or otherwise) which is disclosed to it by the other Party (the ***"Disclosing Party"***) or its Affiliates or otherwise received or accessed by a Receiving Party in the course of performing its obligations or exercising its rights under this Agreement, including, but not limited to, 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 (collectively, ***"Confidential Information"***), except to the extent that it can be established by the Receiving Party that such Confidential Information:

7.1.1 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;

7.1.2 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;

7.1.3 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

7.1.4 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.

Section 7.2 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) with respect to any such disclosure of Confidential Information, under confidentiality provisions no less restrictive than those in this Agreement, and solely in connection with the performance of its obligations or exercise of its rights granted or reserved in this Agreement (including, without limitation, the rights to Develop and Commercialize Licensed Compounds, Products,

and/or Discontinued Products, and to grant licenses and sublicenses hereunder), *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 with such Receiving Party if such Receiving Party has used reasonable efforts to impose such requirement without success and disclosure to such governmental entity or agency is necessary for the performance of the Receiving Party's obligations hereunder; (ii) to the extent such disclosure is reasonably necessary in filing or prosecuting patent, copyright and trademark applications (subject to Section 8.6 below), complying with applicable governmental regulations, obtaining Approvals, conducting clinical trials, marketing Products, 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, for example, but without limitation, in the event of a medical emergency, 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, arm's-length financial 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 and only to the extent that 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) to prosecute or defend litigation as permitted by this Agreement; or (vi) to the extent mutually agreed to in writing by the Parties.

Section 7.3 Press Release; Disclosure of Agreement. The Parties agree that the public announcement of the execution of this Agreement will be made by individual press releases issued by each Party and will not be made in a joint press release. Furthermore, each such press release will be substantially in the form of the press releases attached as **APPENDIX 7.3-A** and **APPENDIX 7.3-B** (the ***"Initial Press Releases"***). Except for the Initial Press Releases, or to the extent required to comply with applicable law, regulation, rule or legal process or as otherwise permitted in accordance with this Section 7.3, neither Party nor such Party's Affiliates will make any public announcements, press releases or other public disclosures concerning this Agreement or the terms or the subject matter hereof without the prior written consent of the other, which will not be unreasonably withheld. Notwithstanding the foregoing, (a) except for scientific presentations and publications (which will be governed by Section 7.5 below) each Party or its Affiliates may, without the other Party's approval, make disclosures pertaining solely to Products (as to Sanofi) or Discontinued Products (as to Regulus), provided, however, that Sanofi will immediately notify (and provide as much advance notice as possible to) Regulus of any event materially related to Products (including in such notice any disclosure of clinical data or results, material regulatory filings or Approval) so that the Parties may analyze the need for or desirability of publicly disclosing or reporting such event, any press release or other similar public communication by Sanofi related to efficacy or safety data and/or results of a Licensed Product will be submitted to Regulus for review at least five (5) Business Days (to the extent permitted by law) in advance of such proposed public disclosure, Regulus will have the right to expeditiously review and recommend changes to such communication and Sanofi will in good faith consider any changes that are timely recommended by Regulus and (b) to the extent information regarding this Agreement, a Licensed Compound or 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. Each Party will give the other Party a reasonable opportunity (to the extent consistent with law) 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, including without limitation the provisions of this Agreement for which confidential treatment should be sought.

Section 7.4 Remedies. Notwithstanding Section 12.4, each Party will be entitled to seek, in addition to any other right or remedy it may have, at law or in equity, a temporary injunction, without the posting of any bond or other security, enjoining or restraining the other Party from any violation or threatened violation of this Article 7.

Section 7.5 Publications.

7.5.1 Prior to IND Approval. Prior to IND Approval (and Sanofi's payment to Regulus of the applicable milestone under Section 6.5.1) for a given Collaboration Target, Regulus may, consistent with its practice with its other compounds and products, publish and

present data regarding any such Collaboration Targets, Licensed Compounds and/or Products; *provided, however*, that Regulus will provide any such proposed publication to Sanofi at least 30 days prior to submission for publication or presentation. During such 30-day period, Sanofi will have the right to review and comment on any such publications and Regulus will give due consideration to Sanofi's requested changes. In addition, by written notice to Regulus delivered within such 30-day period, Sanofi will have the right, in its discretion, to prohibit Regulus from making such publication or presentation. If Sanofi does not provide such written notice prohibiting publication or presentation by the end of such 30-day period, then Sanofi will be deemed to have consented to such publication or presentation. *Notwithstanding the foregoing*, Regulus may not publish or present any data or information that contains any of Sanofi's Confidential Information without Sanofi's prior written consent.

7.5.2 After IND Approval. After IND Approval (where Sanofi has paid Regulus the applicable milestone payment under Section 6.5.1) for a given Collaboration Target, and subject to this Section 7.5.2, Sanofi will have the right to publish summaries of results from any human clinical trials generated by Sanofi with respect to the Licensed Compounds or Products without obtaining the consent of Regulus and, except as required under Law, Regulus may not publish any of such data, without the prior consent of Sanofi. The Parties acknowledge that scientific lead time is a key element of the value of the Research Program and Products under this Agreement and further agree to use commercially reasonable efforts to control public scientific disclosures of the results of the research and Development activities under this Agreement (including but not limited to any such summaries of human clinical trials data and results as required on the clinical trial registry) to prevent any potential adverse effect of any premature public disclosure of such results. The Parties will establish a procedure for publication review and each Party will first submit to the other Party an early draft of all such publications, whether they are to be presented orally or in written form, at least 45 days prior to submission for publication including, without limitation, to facilitate the publication of any summaries of human clinical trials 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 Research Program. If, as soon as reasonably possible, but no longer than [***] following receipt of an advance copy of a Party's proposed publication, 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 [***] period, the other Party informs such Party that its proposed publication discloses inventions made by either Party in the course of the Research Program 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 Patents or

Know-How solely owned or Controlled by such other Party, then such Party will either (a) delay such proposed publication, for up to [***] [***] 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 (b) remove the identified disclosures prior to publication.

Section 7.6 Acknowledgment. Unless otherwise agreed upon in writing by the Parties, each Party will acknowledge in any press release, public presentation or publication regarding a Collaboration Target, Licensed Compound and/or Product, the other Party's role in

discovering and developing the Collaboration Target, Licensed Compound or Product, as applicable, and that such Collaboration Targets, Compounds or Products are under license from Regulus (including, if requested by Regulus, Regulus' stock ticker) and otherwise acknowledge the contributions from the other Party.

ARTICLE 8

PATENTS

The provisions of this Article 8 (excluding Section 8.1) as they relate to Regulus Patents that are licensed to Regulus under any Existing Regulus Agreement are subject in all respects to the terms of such Existing Regulus Agreement. In the event of any inconsistency between Regulus' obligations under any Existing Regulus Agreement and the rights conferred on Sanofi by this Article 8 (excluding Section 8.1) with respect to the Regulus Patents that are subject to such Existing Regulus, the Existing Regulus Agreement shall control, and the provisions of this Article 8 shall, to the extent inconsistent with the Existing Regulus Agreement, be of no force or effect.

Section 8.1 Ownership of Inventions and Patents.

8.1.1 Title to inventions, discoveries, improvements and other technology, whether or not patentable, conceived, made or reduced to practice in the performance of the Research Program under this Agreement (collectively, the ***"Program Inventions"***) and any Patents claiming such Program Inventions (***"Program Patents"***), are retained by the Party that is the employer of the inventor(s) (or, in the case of consultants and (sub)contractors, the Party for which the consultant or (sub)contractor is providing its services). Each Party will ensure that every employee, consultant, and (sub)contractor employed or contracted by that Party in the performance of the Research Program has a written obligation to assign all Know-How and Patents conceived, made or reduced to practice by each such employee, consultant, and (sub)contractor to such Party. The Parties agree that the United States federal patent law on inventorship will determine the inventorship of any Program Invention and the names of the inventors on any Program Patent filings, whether sole or joint inventions, which arise in connection with activities conducted pursuant to this Agreement. Sanofi will own Program Inventions invented solely by employees, consultants and/or (sub)contractors of Sanofi (the ***"Sanofi Inventions"***) and any Patents claiming such Program Inventions (the ***"Sanofi Program Patents"***). Regulus will own Program Inventions invented solely by employees, consultants and/or (sub)contractors of Regulus (the ***"Regulus Inventions"***) and any Patents claiming such Program Inventions (the ***"Regulus Program Patents"***). Regulus and Sanofi will own jointly such Program Inventions invented jointly by employees, consultants and/or (sub)contractors of Regulus and Sanofi (the ***"Joint Inventions"***) and any Patents claiming such Program Inventions (the ***"Joint Patents"***). Regulus will promptly disclose to Sanofi any such Regulus Invention or Joint Invention, and Sanofi will promptly disclose to Regulus any Sanofi Invention or Joint Invention, arising from or made in the performance of the Research Program and any patent or patent application claiming such Program Invention. It is understood that except as otherwise provided in this Agreement or as the Parties may otherwise agree in writing, neither Party will have any obligation to account to the other Party for profits, or to obtain any approval of the other Party to license, assign, mortgage or exploit a Joint Invention by reason of joint ownership

of any such Joint Invention, and may otherwise undertake all activities a sole owner might undertake with respect to such inventions without the consent of and without accounting to the other joint owner, and each Party hereby waives any right it may have under the laws of any jurisdiction to require such consent or accounting.

8.1.2 CREATE Act. Notwithstanding anything to the contrary in this Article 8, neither Party will have the right to make an election under the Cooperative Research and Technology Enhancement Act of 2004, 35 U.S.C. § 103(c)(2)-(c)(3) (the ***"CREATE Act"***) when exercising its rights under this Article 8 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.

Section 8.2 Filing, Prosecution and Maintenance of Patents. For purposes of this Section 8.2, the terms "prosecute," "prosecuting" and "prosecution," when used in reference to any Patent, shall be deemed to include, without limitation, the control of any interferences, reissue proceedings, oppositions and reexaminations with respect to such Patent.

8.2.1 Product Specific Patents.

(a) Before IND Approval. On a Collaboration Target-by-Collaboration Target basis, for Product Specific Patents filed prior to IND Approval for a Licensed Compound that targets or mimics (as applicable) a particular Collaboration Target, Regulus will be responsible for the preparation, filing, prosecution and maintenance of such Product Specific Patents (including Product Specific Patents that are Joint Patents) directed to such Collaboration Target or to Licensed Compounds or Products that target or mimic (as applicable) such Collaboration Target. Regulus will use Commercially Reasonable Efforts to prepare, file, prosecute and maintain such Product Specific Patents in at least the countries listed in **APPENDIX 7** (each, a ***"Listed Country"***), at Regulus' expense; *provided, however,* that if the applicable patent office in any Listed Country, other than [***] and [***], requires [***] of patent applications [***], Sanofi shall reimburse Regulus for costs incurred by Regulus for [***] of Product Specific Patents [***]. If Sanofi requests in writing that Regulus prepare, file, prosecute and maintain any Product Specific Patent in any country that is not a Listed Country (each, a ***"Sanofi Nominated Country"***), Regulus will use Commercially Reasonable Efforts to prepare, file, prosecute and maintain such Product Specific Patent in such Sanofi Nominated Country, at Sanofi's expense, *provided, however*, that if Sanofi is not the sole licensee or sublicensee of Regulus under such Product Specific

Patent, Regulus will be responsible for such expenses and Sanofi will reimburse Regulus for the amount that is equal to the total of such expenses divided by the number of licensee(s) or sublicense(s) under such product specific patent (such number to also include Regulus).

(b) After IND Approval. On a Collaboration Target-by-Collaboration Target basis, for Product Specific Patents filed after IND Approval for a Licensed Compound that targets or mimics (as applicable) a particular Collaboration Target, Sanofi will be responsible for the preparation, filing, prosecution and maintenance of such Product Specific

Patents (including Product Specific Patents that are Joint Patents) directed to such Collaboration Target or to Licensed Compounds or Products that target or mimic (as applicable) such Collaboration Target, at Sanofi's expense; *provided, however*, that if Sanofi is not the sole licensee or sublicensee of Regulus under such Product Specific Patent, Regulus will be responsible for such expenses and Sanofi will reimburse Regulus for the amount that is equal to the total of such expenses divided by the number of licensee(s) or sublicense(s) under such product specific patent (such number to also include Regulus).

(c) Disclosure; Cooperation. The Party responsible for preparing, filing, prosecuting and maintaining any Product Specific Patent (including any Product Specific Patent that is a Joint Patent) under Section 8.2.1(a) or Section 8.2.1(b) above (the ***"Lead Party"***), or its outside counsel, will provide the other Party with (i) a reasonably detailed monthly update of the filing, prosecution and maintenance status for such Product Specific Patent and (ii) any further information reasonably requested by the other Party from time to time regarding such Product Specific Patent; *provided, however,* that if such Product Specific Patent is licensed to Regulus by a Third Party, Regulus will not be obligated to make disclosure of information regarding such Product Specific Patent to the extent that such disclosure would constitute a breach of Regulus' confidentiality obligations to the Third Party licensor. Regulus will consider in good faith, and give effect to, all reasonable requests or recommendations of Sanofi regarding the preparation, filing, prosecution and maintenance of Product Specific Patents. Sanofi will consider in good faith all reasonable requests or recommendations of Regulus regarding the preparation, filing, prosecution and maintenance of Product Specific Patents.

(d) Election Not to File, Prosecute, or Maintain Product Specific Patents. In the event that the Lead Party decides not to pursue or continue the filing, prosecution or maintenance of any Product Specific Patent in any country, the Lead Party, or its outside counsel, will provide the other Party with written notice of such decision at least 60 days in advance of any relevant filing, prosecution or maintenance deadline, and the other Party will provide the Lead Party with prompt notice as to whether the other Party desires to assume responsibility and costs for such filing, prosecution or maintenance of such Product Specific Patent. The Lead Party will not knowingly permit any such Product Specific Patent to be abandoned in any Listed Country (or, in the case of Regulus, any Sanofi Nominated Country for which Sanofi is bearing the expense of preparation, filing, prosecution and maintenance of Product Specific Patents), or elect not to file a new patent application claiming priority to a patent application within the Product Specific Patents either before such patent application's issuance or within the time period required for the filing of an international (i.e., Patent Cooperation Treaty), regional (including European Patent Office) or national application, without the other Party's written consent or without the other Party otherwise first being given an opportunity to assume full responsibility (at the other Party's expense) for the continued prosecution and maintenance of such Product Specific Patents, or the filing of such new patent application. In the event that the other Party assumes responsibility for the preparation, filing, prosecution or maintenance of any patent or patent application as set forth above, the other Party will not be liable to the Lead Party in any way with respect to its handling of, or the results obtained from, the filing, prosecution, issuance, extension or maintenance of such application or any resulting patent or any failure by it to so file, prosecute, extend or maintain. In the event that Sanofi assumes responsibility for the preparation, filing, prosecution or maintenance of any such Product Specific Patent as set forth above, Regulus will assign such Product Specific Patent to

Sanofi, for no additional consideration, and such Product Specific Patent (if later granted) will be disregarded for the purposes of calculating the Royalty Term under Section 6.11.

8.2.2 Regulus Core Technology Patents Other Than Joint Patents. Regulus (or its Third Party licensors of Regulus Core Technology Patents, as applicable) will be solely responsible for the preparation, filing, prosecution and maintenance of Regulus Core Technology Patents (other than Joint Patents that are Regulus Core Technology Patents), at Regulus' sole expense. At Sanofi's reasonable request from time to time, Regulus, or its outside counsel, will promptly provide Sanofi with an update of the filing, prosecution and maintenance status for each of such Regulus Core Technology Patents, including without limitation an update of **APPENDIX 3**.

8.2.3 Joint Core Technology Patents. This Section 8.2.3 will apply only to: (i) Regulus Core Technology Patents that are Joint Patents (each, a ***"Joint Core Technology Patent"***); and (ii) any Joint Invention that is not claimed by any patent application in a country, provided that if a patent application claiming such Joint Invention were filed in such country, such patent application would be a Joint Core Technology Patent (such Joint Invention, a ***"Joint Core Technology Invention"***).

(a) Regulus First Right to File, Prosecute and Maintain. Regulus will have the first right to prepare, file, prosecute and maintain any new patent application claiming a Joint Core Technology Invention, at Regulus' expense. Regulus shall consult with Sanofi as to the preparation, filing, prosecution and maintenance of Joint Core Technology Patents and draft patent applications claiming Joint Core Technology Inventions reasonably prior to any deadline or action with any patent office, shall furnish to Sanofi copies of all relevant documents reasonably in advance of such consultation, and shall consider in good faith the reasonable comments and suggestions of Sanofi. Regulus, or its outside counsel, will provide Sanofi with an update of the filing, prosecution and maintenance status for each Joint Core Technology Patent on a periodic basis, and will provide to Sanofi copies of any papers relating to the filing, prosecution and maintenance of such Joint Core Technology Patents promptly upon their being filed or received.

(b) Disclosure; Cooperation. Regulus or its outside counsel, will provide Sanofi with (i) a reasonably detailed monthly update of the filing, prosecution and maintenance status for such Joint Core Technology Patent and (ii) any further information reasonably requested by Sanofi from time to time regarding such Joint Core Technology Patent. Regulus will consider in good faith all reasonable requests or recommendations of Sanofi regarding the preparation, filing, prosecution and maintenance of Joint Core Technology Patents.

(c) Election Not to File, Prosecute, or Maintain Joint Core Technology Patents. In the event that Regulus decides not to pursue or continue the filing, prosecution or maintenance of any Joint Core Technology Patent in any country, Regulus, or its outside counsel, will provide Sanofi with written notice of such decision at least 60 days in advance of any relevant filing, prosecution or maintenance deadline, and Sanofi will provide

Regulus with prompt notice as to whether Sanofi desires to assume responsibility and costs for such filing, prosecution or maintenance of such Joint Core Technology Patent. Regulus will not knowingly permit any such Joint Core Technology Patent to be abandoned, or elect not to file a

new patent application claiming priority to a patent application within the Joint Core Technology Patents either before such patent application's issuance or within the time period required for the filing of an international (i.e., Patent Cooperation Treaty), regional (including European Patent Office) or national application, without Sanofi's written consent or without Sanofi otherwise first being given an opportunity to assume full responsibility (at Sanofi's expense) for the continued prosecution and maintenance of such Joint Core Technology Patent, or the filing of such new patent application. In the event that Sanofi assumes responsibility for the preparation, filing, prosecution or maintenance of any Joint Core Technology Patent as set forth above, such Joint Core Technology Patent (if later granted) will be disregarded for the purposes of calculating the Royalty Term under Section 6.7, provided that Regulus shall retain its joint ownership interest in such Joint Core Technology Patent.

8.2.4 Joint Patents Other Than Joint Core Technology Patents and Product Specific Patents. This Section 8.2.4 will apply only to: (i) Joint Patents that are neither Joint Core Technology Patents nor Product Specific Patents (each, an ***"Other Joint Patent"***); and (ii) any Joint Invention that is not claimed by any patent application in a country, provided that if a patent application claiming such Joint Invention were filed in such country, such patent application would be neither a Joint Core Technology Patent nor a Product Specific Patent (such Joint Invention, an ***"Other Joint Invention"***).

(a) Sanofi First Right to File, Prosecute and Maintain. Sanofi will have the first right to prepare, file, prosecute and maintain any new patent application claiming an Other Joint Invention, at Sanofi's expense. Sanofi shall consult with Regulus as to the preparation, filing, prosecution and maintenance of Other Joint Patents and draft patent applications claiming Other Joint Inventions reasonably prior to any deadline or action with any patent office, shall furnish to Regulus copies of all relevant documents reasonably in advance of such consultation, and shall consider in good faith the reasonable comments and suggestions of Regulus. Sanofi, or its outside counsel, will provide Regulus with an update of the filing, prosecution and maintenance status for each Other Joint Patent on a periodic basis, and will provide to Regulus copies of any papers relating to the filing, prosecution and maintenance of such Other Joint Patents promptly upon their being filed or received.

(b) Election Not to File, Prosecute, or Maintain Other Joint Patents. In the event that Sanofi decides not to pursue or continue the filing, prosecution or maintenance of any Other Joint Patent in any country, Sanofi, or its outside counsel, will provide Regulus with written notice of such decision at least 60 days in advance of any relevant filing, prosecution or maintenance deadline, and Regulus will provide Sanofi with prompt notice as to whether Regulus desires to assume responsibility and costs for such filing, prosecution or maintenance of such Other Joint Patent. Sanofi will not knowingly permit any such Other Joint Patent to be abandoned, or elect not to file a new patent application claiming priority to a patent application within the Other Joint Patents either before such patent application's issuance or within the time period required for the filing of an international (i.e., Patent Cooperation Treaty), regional (including European Patent Office) or national application, without Regulus' written consent or without Regulus otherwise first being given an opportunity to assume full responsibility (at Regulus' expense) for the continued prosecution and maintenance of such Other Joint Patent, or the filing of such new patent application. In the event that Regulus assumes responsibility for the preparation, filing, prosecution or maintenance of any patent or

patent application as set forth above, Regulus will not be liable to Sanofi in any way with respect to its handling of, or the results obtained from, the filing, prosecution, issuance, extension or maintenance of such application or any resulting patent or any failure by it to so file, prosecute, extend or maintain.

8.2.5 Cooperation. Each Party agrees to cooperate fully in the preparation, filing, prosecution and maintenance of Patents pursuant to this Section 8.2. Such cooperation includes, but is not limited to: (a) executing all papers and instruments, or requiring its employees or contractors, to execute such papers and instruments, so as to enable the other Party to exercise its rights and perform its obligations under this Section 8.2; and (b) promptly informing the other Party of any matters coming to such Party's attention that may affect the preparation, filing, prosecution or maintenance of any such patent applications.

Section 8.3 Patent Term Extension. Regulus and Sanofi will each cooperate with one another and will use Commercially Reasonable Efforts in obtaining patent term restorations and/or extensions (including without limitation, any pediatric exclusivity extensions as may be available) or supplemental protection certificates or their equivalents in any country with respect to patent rights covering those Products licensed by Sanofi hereunder. If elections with respect to obtaining such patent term extensions or supplemental protection are to be made, Sanofi will have the right to make such election, *provided* that (i) such election will be made in accordance with applicable Law so as to maximize the period of marketing exclusivity for the Product, and (ii) Sanofi may not elect to extend a Regulus Core Technology Patent (other than a Joint Core Technology Patent) under this Section 8.3 without Regulus' prior written consent.

Section 8.4 Enforcement of Patents

8.4.1 Product Specific Patents.

(a) Enforcement by Sanofi. In the event that Regulus or Sanofi becomes aware of a suspected infringement of any Product Specific Patent, or any such Product Specific Patent is challenged in any action or proceeding (other than any interferences, reissue proceedings, oppositions or reexaminations, which are addressed above), such Party will notify the other Party promptly, and following such notification, the Parties will confer and determine an appropriate course of action in response to such suspected infringement or action or proceeding. Sanofi will have the right, but will not be obligated, to defend any such action or proceeding or bring an infringement action with respect to such suspected infringement at its own expense, in its own name and entirely under its own direction and control, or settle any such action, proceeding or dispute by license (to the extent such sublicense is permitted under this Agreement). Regulus will reasonably assist Sanofi in any action or proceeding being defended or prosecuted if so requested, and will lend its name to such actions or proceedings if reasonably requested by Sanofi or required by Applicable Law. Sanofi will reimburse Regulus for the documented out-of-pocket costs Regulus reasonably incurs in providing such assistance as specifically requested in writing by Sanofi. In the event Regulus is a required party to the proceeding or action, Regulus will have the right to be represented by its own counsel (such selection to be subject to Sanofi's approval, such approval not to be unreasonably withheld), and Sanofi will reimburse Regulus for the documented external costs Regulus reasonably incurs that are reasonably related to the proceeding or action, including attorneys fees, *provided* that Sanofi

will retain overall responsibility for the prosecution of such action or proceeding in such event. In the event that Regulus is not a necessary party to the proceeding or action, Regulus will have the right to participate and be represented in any such suit by its own counsel at its own expense, *provided* that Sanofi will retain overall responsibility for the prosecution of such action or proceedings in such event. Sanofi may not enter any settlement of any such action or proceeding which restricts the scope, or adversely affects the enforceability, of a Product Specific Patent, or which could be reasonably expected to have a material adverse financial impact on Regulus, without Regulus' prior written consent, which consent will not be unreasonably withheld, conditioned or delayed.

(b) Enforcement by Regulus. If Sanofi elects not to settle, defend or bring any action for infringement described in Section 8.4.1(a) and so notifies Regulus, including following any request by Regulus to do so, then Regulus may defend or bring such action at its own expense, in its own name, *provided however* that, Regulus agrees not to so settle, defend or bring any action for infringement of a Product Specific Patent Right upon Sanofi's request based on Sanofi's good faith reasonable determination, the basis for which will be provided to Regulus, that it is not in the best interest of the Parties to so settle, defend or bring such action for infringement. In the case where Regulus proceeds to settle, defend or bring an action for such infringement, the following will apply: (i) Sanofi will reasonably assist Regulus in any action or proceeding being defended or prosecuted if so requested, and will lend its name to such actions or proceedings if requested by Regulus or required by Applicable Law; (ii) Regulus will reimburse Sanofi for the documented external costs Sanofi reasonably incurs, including attorneys fees, in providing such assistance as specifically requested in writing by Regulus; (iii) Sanofi will have the right to participate and be represented in any such suit by its own counsel at its own expense, *provided* that Regulus will retain overall responsibility for the prosecution of such suit or proceedings in such event; and (iv) Regulus may not enter any settlement of any action or proceeding defended or brought by Regulus with respect to a Product Specific Patent, which restricts the scope, or adversely affects the enforceability, of a Product Specific Patent, or which could be reasonably expected to have a material adverse financial impact on Sanofi without Sanofi's prior written consent, which consent will not be unreasonably withheld, conditioned or delayed.

(c) Withdrawal. If either Party brings an action or proceeding under this Section 8.4.1 and subsequently ceases to pursue or withdraws from such action or proceeding, it will promptly notify the other Party and the other Party may substitute itself for the withdrawing Party and pursue such action or proceeding in accordance with the terms of this Section 8.4.1 (including but not limited to the proviso in the first sentence of Section 8.4.1(b)).

(d) Damages. In the event that either Party exercises the rights conferred above in this Section 8.4.1 and recovers any damages or other sums in such action, suit or proceeding or in settlement thereof, such damages or other sums recovered will first be applied to all out-of-pocket costs and expenses incurred by the Party which initiated such action, suit or proceeding, including, without limitation, attorneys fees, and second to any out-of-pocket costs and expenses incurred by the other Party and not previously reimbursed by the Party which initiated such action, suit or proceeding according to this Section 8.4.1. Any remaining amounts will: (i) if recovered by Sanofi, be divided as follows: (A) as to ordinary damages based on lost sales or profit, Sanofi will retain such funds and such funds will be treated as Net Sales and

royalties will be payable by Sanofi to Regulus with respect to such Net Sales in accordance with Section 6.5 of this Agreement and (B) as to special or punitive damages, Sanofi will receive [***]% of the amount of such special or punitive damages and Regulus will receive [***]% of the amount of such special or punitive damages; or (ii) if recovered by Regulus, [***].

8.4.2 Regulus Core Technology Patents Other Than Joint Core Technology Patents. Regulus will have the sole right to enforce Regulus Core Technology Patents (other than Joint Core Technology Patents) and to defend Regulus Core Technology Patents (other than Joint Core Technology Patents) against challenge in any action or proceeding (other than any interferences, reissue proceedings, oppositions or reexaminations, which are addressed above). In the event of suspected infringement of a Regulus Core Technology Patent (other than a Joint Core Technology Patent) by a Third Party in a country, wherein (a) the suspected infringing activity competes with a Product being commercialized by or on behalf of Sanofi in such country, and (b) no other Patent Controlled by Sanofi (whether by license under this Agreement or otherwise) is infringed or suspected to be infringed by the suspected infringing activity, Section [***] to apply to such Product in such country (with the suspected infringing product [***]), unless Regulus permits Sanofi to enforce the applicable Regulus Core Technology Patent against such Third Party.

8.4.3 Joint Core Technology Patents. In the event of suspected infringement of a Joint Core Technology Patent by a Third Party in a country, wherein the suspected infringing activity competes with a Product being commercialized by or on behalf of Sanofi in such country, the Parties' respective rights and obligations with respect to enforcement of such Joint Core Technology Patent in such country (including damages or settlement amounts received as a result thereof) shall be as set forth in Section 8.4.1, *mutatis mutandis*. In the event of any other suspected infringement of a Joint Core Technology Patent, the Parties' respective rights and obligations with respect to enforcement of such Joint Core Technology Patent in such country will be the reverse of their respective rights and obligations under Section 8.4.1, *mutatis mutandis*; *provided*, *however*, that after reimbursement of costs, any remaining damages or other amounts recovered will be allocated [***]% to the Party that brought and controlled the action, and [***]% to the other Party.

8.4.4 Other Joint Patents. In the event of suspected infringement of an Other Joint Patent by a Third Party in a country, wherein the suspected infringing activity competes with a Product being commercialized by or on behalf of Sanofi in such country, the Parties' respective rights and obligations with respect to enforcement of such Other Joint Patent in such country shall be as set forth in Section 8.4.1, *mutatis mutandis*. In the event of any other suspected infringement of an Other Joint Patent, the Parties shall mutually agree in good faith on a case-by-case basis on the course of action to be taken and the allocation of costs and recovered amounts.

8.4.5 Cooperation. The Party not enforcing a particular Patent under any of the preceding provisions of this Section 8.4 will provide reasonable assistance to the other Party (at such other Party's expense), including providing access to relevant documents and other evidence, making its employees available at reasonable business hours, and joining the action to the extent necessary to allow the enforcing Party to initiate or maintain the action.

Section 8.5 Determination of Certain Patent Matters. The Parties, acting in good faith and on the advice of their respective internal or external patent counsel, agree in good faith on: (i) the inventorship of Program Inventions under Section 8.1.1, consistent with U.S. patent laws; (ii) whether any particular Regulus Patent is a Regulus Core Technology Patent or a Product Specific Patent, taking into full consideration the definitions of such terms set forth in **APPENDIX 1** and the Regulus Patents listed in **APPENDIX 2** and **APPENDIX 3** hereto; and (iii) whether there exists a Product Specific Patent that is suspected to be infringed by a suspected infringement under Section 8.4.1. If the Parties cannot agree upon any such matter within 30 days of good faith discussions, the Parties will refer such matter to independent patent counsel, not engaged by either Party or any of its Affiliates for any matter in the previous three (3) years and reasonably acceptable to both Parties. The determination of the independent patent counsel with respect to such matter will be binding on the Parties. The costs and expenses of the independent patent counsel will be shared equally between the Parties.

Section 8.6 Data Exclusivity and Orange Book Listings. With respect to data exclusivity periods (such as those periods listed in the FDA's Orange Book (including without limitation any available pediatric extensions) or periods under national implementations of Article 11.1(a)(iii) of Directive 2001/EC/83, or similar periods as may be applicable to a biologic, and all international equivalents), Sanofi will use Commercially Reasonable Efforts consistent with its obligations under applicable law (including any applicable consent order) to seek, maintain and enforce all such data exclusivity periods available for the Products exclusively licensed by Sanofi hereunder. With respect to filings in the FDA Orange Book or other similar filings or listings as may be applicable (and foreign equivalents) for issued patents for a Product, upon reasonable request by Sanofi, Regulus will provide reasonable cooperation to Sanofi in filing and maintaining any such listing and filings. All listing and filing decisions will be at the sole discretion of Sanofi; *provided, however* that Sanofi will not list Regulus Core Technology Patents in the FDA Orange Book without Regulus' prior written consent, such consent not to be unreasonably withheld or delayed. In no event will Regulus withhold or delay such consent where the listing of such Regulus Core Technology Patent is required under applicable law.

Section 8.7 Further Actions. Each Party will, upon the reasonable request of the other Party, provide such assistance and execute such documents as are reasonably necessary for such Party to exercise its rights and/or perform its obligations pursuant to this Article 8; *provided however*, that neither Party will be required to take any action pursuant to Article 8 that such Party reasonably determines in its sole judgment and discretion conflicts with or violates any applicable court or government order or decree.

Section 8.8 Infringement Claims; Oppositions. Sanofi and Regulus will promptly inform the other in writing of any written notice to it of alleged infringement or misappropriation, based on the research, development, making, using, importing, exporting or selling of a Licensed Compound or Product, of a Third Party's intellectual property rights of which it will become aware. The Parties will confer on the handling of such matter. Regulus will not acknowledge to a Third Party the validity of any such allegation or admit liability without the prior written consent of Sanofi, and Sanofi will not acknowledge to a Third Party the validity of any such allegation or admit liability without the prior written consent of Regulus. Sanofi and Regulus will each keep the other advised of all material developments in the conduct

of any proceedings in defending any claim of such alleged infringement or misappropriation and will cooperate with the other in the conduct of such defense. In no event may either Party settle any such infringement or misappropriation claim in a manner that would limit the rights of the other Party or impose any obligation on the other Party, without such other Party's prior written consent, such consent not to be unreasonably withheld or delayed. Sanofi and Regulus will promptly inform the other in writing of any written notice to it of actual or threatened opposition related to the Product Specific Patents. The Parties will confer on the handling of such matter and such matters will be handled in accordance with Section 8.2 above.

Section 8.9 Records Regarding Regulus Patents. Each Party will assign patent counsel representatives who will be responsible for coordinating activities between the Parties in accordance with this Article 8. Such representatives will use commercially reasonable efforts to maintain a report listing the Regulus Patents that are subject to the license granted to Sanofi under Section 2.1. Such report will be used to facilitate the identification and tracking of the Regulus Patents licensed under this Agreement, but will not, unless specifically agreed to in a separate written agreement signed by authorized representatives of both Parties, be considered to be a then-current complete and binding list of the Regulus Patents licensed under this Agreement.

Section 8.10 No Challenge. As a material inducement for entering into this Agreement, Sanofi covenants to Regulus that during the term of this Agreement, solely with respect to claims within the Regulus Patents that are included in the license granted to Sanofi under Section 2.1, Sanofi, its Affiliates or sublicensees will not (a) commence or otherwise voluntarily determine to participate in (other than as may be necessary or reasonably required to respond to a court request or order or administrative law request or order) any action or proceeding, challenging or denying the validity of any claim within an issued patent or patent application within the Regulus Patents, or (b) direct, support or actively assist any other Person (other than as may be necessary or reasonably required 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 the Regulus Patents. For purposes of clarification, any breach of this Section 8.10 will be a material breach of this Agreement and will be grounds for termination by Regulus of this Agreement under Section 9.3.

Section 8.11 Amendments to Third Party Agreements. Regulus will not amend or agree to amend any Existing Regulus Agreement, Future Regulus Agreement, or New Core Technology Agreement for New Core Technology included in the Regulus Technology licensed to Sanofi under Section 2.1, in any manner that would increase Sanofi's payment obligations or reduce the scope of Sanofi's license under Section 2.1, without the prior written consent of Sanofi.

ARTICLE 9

TERM AND TERMINATION

Section 9.1 Term. The term of this Agreement (the ***"Term"***) commences upon the Effective Date and, unless earlier terminated in accordance with the provisions of this Article 9, will continue until the expiration of all payment obligations on all Products to Regulus.

Section 9.2 Sanofi Right to Terminate.

9.2.1 After the expiration of the Research Term, Sanofi may terminate this Agreement (including its license rights under this Agreement) in full, or on a Product-by-Product basis, effective upon 30 days prior written notice. For purposes of clarification, milestone and royalty payments will be due on milestones achieved and Products sold during the period between notice of termination and the effective date of termination.

9.2.2 At any time during the Research Term, but following payment by Sanofi of the technology access fee under Section 6.1, Sanofi will be entitled to terminate the license granted under Section 2.1 at any time on a Product-by-Product basis for any safety, efficacy or regulatory viability issues, including but not limited to the detection in a test population of adverse experiences associated with the administration of the Product that are significant, serious or life threatening to the patient or demonstrate significant toxicological effect(s) of such Product on one or more body tissues that are not balanced by a countervailing benefit to the patient. The safety, efficacy and regulatory viability of a Product will be determined by Sanofi in view of the risk to benefit relationship of such Product in the relevant patient population.

Section 9.3 Material Breach.

(a) If either Party believes that the other is in material breach of this Agreement (other than with respect to a breach of Sanofi's obligations under Section 5.1, which is governed by Section 9.4), then the non-breaching Party may deliver notice of such breach to the other Party. In such notice the non-breaching Party will identify the actions or conduct that it wishes such Party to take for an acceptable and prompt cure of such breach (or will otherwise state its good faith belief that such breach is incurable); *provided* that such identified actions or conduct will not be binding upon the other Party with respect to the actions that it may need to take to cure such breach. If the breach is curable, the allegedly breaching Party will have [***] days to either 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) or, if a cure cannot be reasonably effected within such 120-day period, to deliver to the non-breaching Party a plan for curing such breach which is reasonably sufficient to effect a cure within a reasonable period. If the breaching Party fails to (i) cure such breach within the [***]-day (or 30-day, as applicable) period or (ii) use Commercially Reasonable Efforts to carry out the plan and cure the breach, the non-breaching Party may terminate this Agreement on a Product-by-Product basis by providing written notice to the breaching Party.

(b) Notwithstanding the foregoing, if the allegedly breaching Party 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 (the ***"Other Party"***) of such dispute within such [***]-day period, the Other Party will not have the right to terminate this Agreement in accordance with this Section 9.3 unless and until it has been determined in accordance with Section 12.4 that this Agreement was materially breached by the allegedly breaching Party and that Party fails to cure such breach within [***] days following such determination. It is understood and acknowledged that during the pendency of such a dispute, all of the terms and conditions of this Agreement will remain in effect and the Parties will continue to perform all of their respective obligations hereunder.

(c) This Section 9.3 will be subject to and will not limit the provisions of Section 9.4 and Section 9.5.

Section 9.4 Termination by Regulus For Failure of Sanofi to Use Commercially Reasonable Efforts.

9.4.1 Subject to Section 9.4.2 and 9.4.3, at any time after the expiration of the Research Term, Regulus will have the right to terminate the license granted under Section 2.1 (and the corresponding exclusivity obligation under Section 2.3) on a Product-by-Product basis and country-by-country basis, if Sanofi is in breach of its obligations to use Commercially Reasonable Efforts as set forth in Section 5.1, *provided however*, that the Agreement will not so terminate unless (i) Sanofi is given 30 days prior written notice by Regulus of Regulus' intent to terminate, stating the reasons and justification for such termination and recommending steps which Sanofi should take, and (ii) Sanofi, or its sublicensee, has not used good faith Commercially Reasonable Efforts during the [***]-day period following such notice to diligently pursue the Development and/or Commercialization of at least one Licensed Compound or Product for each Collaboration Target in the applicable country. Any such termination will be limited in force and effect to the country or countries and Products to which such breach relates.

9.4.2 It is understood and acknowledged that if Sanofi (by itself or through its Affiliates or sublicensees) uses Commercially Reasonable Efforts to Develop and Commercialize a Product for each Collaboration Target in each and every Major Market Country, Sanofi will be deemed to be in compliance with its obligation under Section 5.1 to use Commercially Reasonable Efforts to Develop and Commercialize a Product for such Collaboration Target with respect to all countries in the world.

9.4.3 If Sanofi disputes in good faith the existence or materiality of an alleged breach specified in a notice provided by Regulus pursuant to Section 9.4.1, and provides notice to Regulus of such dispute within the 30 days following such notice provided by Regulus, Regulus will not have the right to terminate this Agreement unless and until the existence of such material breach or failure by Sanofi has been determined in accordance with Section 12.4 and Sanofi fails to cure such breach within 30 days following such determination. It is understood and acknowledged that during the pendency of such a dispute, all of the terms and conditions of this Agreement will remain in effect and the Parties will continue to perform all of their respective obligations hereunder.

Section 9.5 Consequences of Termination.

9.5.1 Licenses. Upon termination of this Agreement in its entirety by either Party pursuant to this Article 9, the licenses granted by Regulus to Sanofi hereunder will terminate.

9.5.2 Return of Information and Materials. Upon termination of this Agreement in its entirety by either Party pursuant to this Article 9, 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 purposes, and with respect to Regulus, to practice its rights under Section 10.1.

Section 9.6 Accrued Rights; Surviving Obligations.

9.6.1 Accrued Rights. Termination or expiration 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 or expiration. Such termination or expiration will not relieve a Party from obligations that are expressly indicated to survive the termination or expiration of this Agreement.

9.6.2 Survival. Articles 7, 9, 10, 11 and 13; and Section 3.6.4, Section 6.14, Section 6.17, and Section 12.4 of this Agreement will survive expiration or termination of this Agreement for any reason. Furthermore, Regulus hereby grants to Sanofi a worldwide non-exclusive license, with the right to grant sublicenses under Section 2.2, to Regulus Know-How existing now or in the future and disclosed to Sanofi during the Term, solely for the further manufacture and sale of Licensed Compounds and Products after the expiration (but not the termination) of the Term.

Section 9.7 Rights in Bankruptcy. All rights and licenses granted under or pursuant to this Agreement by Regulus or Sanofi are, and will otherwise be deemed to be, for purposes of Section 365(n) of the U.S. Bankruptcy Code (i.e., Title 11 of the U.S. Code) or analogous provisions of Applicable Law outside the United States, licenses of rights to "intellectual property" as defined under Section 101 of the U.S. Bankruptcy Code or analogous provisions of Applicable Law outside the United States. The Parties agree that each Party, as licensee of such rights under this Agreement, will retain and may fully exercise all of its rights and elections under the U.S. Bankruptcy Code or any other provisions of Applicable Law outside the United States that provide similar protection for 'intellectual property.' The Parties further agree that, in the event of the commencement of a bankruptcy proceeding by or against a Party under the U.S. Bankruptcy Code or analogous provisions of Applicable Law outside the United States, the Party that is not subject to such proceeding will be entitled to a complete duplicate of (or complete access to, as appropriate) such intellectual property and all embodiments of such intellectual property, which, if not already in the non subject Party's possession, will be promptly delivered to it upon the non subject Party's written request therefor. Any agreements supplemental hereto will be deemed to be "agreements supplementary to" this Agreement for purposes of Section 365(n) of the U.S. Bankruptcy Code.

ARTICLE 10

REGULUS REVERSION RIGHT

Section 10.1 Regulus Reversion Rights. If (i) Sanofi terminates the Agreement (in full or on a Product-by-Product basis) under Section 9.2, (ii) Sanofi makes a substitution under Section 3.6.2, or (iii) Regulus terminates the Agreement under Section 9.3 or 9.4, Regulus may continue to Develop and Commercialize any Licensed Compound or Product that is the subject of such termination or substitution (a ***"Discontinued Product"***). If Regulus provides a notice in writing to Sanofi within 90 days of such termination (an ***"Election Notice"***) that Regulus is exercising its rights under this Section 10.1, subject to Regulus' payment obligations in Section 10.2, Sanofi will, and it hereby does: (x) grant to Regulus a sublicensable, [***] license or sublicense, as the case may be, to all [***] and [***] by Sanofi as of the date of the Election Notice solely as they are necessary to make, have made, use, sell, offer for sale, have sold and import Discontinued Products, (y) transfer to Regulus, for Regulus' use with respect to the Development and Commercialization of the Discontinued Products, [***] and [***] as of the date of the Election Notice that relate to such Discontinued Products, and (z) [***] to Regulus [***] with respect to such Discontinued Product (including but not limited to [***] for Regulus, and [***] Regulus to [***], any [***] with a [***] related to such Discontinued Product).

Section 10.2 Regulus Payment Obligations for Reversion Rights. If Regulus provides an Election Notice for any Discontinued Product which has completed a [***] prior to the applicable termination under this Agreement, then Regulus shall pay to Sanofi (i) [***] with the provisions of Section 6.6 through Section 6.17 applying *mutatis mutandis*. For purposes of this Agreement, ***"Licensing Revenues"*** will mean any payments that Regulus receives from a Third Party in consideration of a license to further the Development and Commercialization of a Discontinued Product, in each case including, but not limited to, upfront payments, license fees, regulatory or sales milestone payments, royalties and/or profit sharing payments, but *excluding*: (i) [***]

ARTICLE 11

INDEMNIFICATION, INSURANCE AND LIMITATION OF LIABILITY

Section 11.1 Indemnification of Regulus. Sanofi agrees to defend Regulus, its Affiliates and their respective directors, officers, stockholders, employees and agents, and their respective successors, heirs and assigns (collectively, the ***"Regulus Indemnitees"***), and will indemnify and hold harmless the Regulus 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 Regulus Indemnitee and resulting from or occurring as a result of: (a) the Development, manufacture, use, handling, storage, sale or other Commercialization or disposition of any Licensed Compound or Product in the Territory by Sanofi or its Affiliates, sublicensees or contractors, (b) any breach by Sanofi of any of its representations, warranties or covenants pursuant to this Agreement or (c) the negligence or willful misconduct of Sanofi or any Sanofi Affiliate or sublicensee in connection with this Agreement; *except* in any such case to

the extent such Losses result from: (i) the negligence or willful misconduct of any Regulus Indemnitee, (ii) any breach by Regulus of any of its representations, warranties, covenants or obligations pursuant to this Agreement, or (iii) any breach of Applicable Law by any Regulus Indemnitee.

Section 11.2 Indemnification of Sanofi. Regulus agrees to defend Sanofi, its Affiliates and their respective directors, officers, stockholders, employees and agents, and their respective successors, heirs and assigns (collectively, the ***"Sanofi Indemnitees"***), and will indemnify and hold harmless the Sanofi Indemnitees, from and against any Losses and Third Party Claims brought against any Sanofi Indemnitee and resulting from or occurring as a result of: (a) any activities conducted by a Regulus employee, consultant or (sub)contractor in the performance of the Research Program (unless such activities were the subject of a dispute between Regulus' and Sanofi's representatives on the JSC that was finally resolved by Sanofi's Senior Representative, as reflected in the minutes of JSC proceedings); (b) any breach by Regulus of any of its representations, warranties or covenants pursuant to this Agreement or (c) the negligence or willful misconduct of any Regulus Indemnitee or any (sub)contractor of Sanofi in connection with this Agreement; *except* in any such case to

the extent such Losses result from: (i) the negligence or willful misconduct of any Sanofi Indemnitee, (ii) any breach by Sanofi of any of its representations, warranties, covenants or obligations pursuant to this Agreement, or (iii) any breach of Applicable Law by any Sanofi Indemnitee.

Section 11.3 Notice of Claim. All indemnification claims provided for in Sections 11.1 and 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 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.

Section 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 calendar 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 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 (i) the employment thereof has been specifically authorized by the indemnifying Party in writing, (ii) 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 (iii) 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 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 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.

Section 11.5 Insurance.

11.5.1 Regulus' Insurance Obligations. Regulus shall 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, provided, that, at a minimum, Regulus shall maintain, in force at its sole cost, a general liability insurance policy providing coverage of at least $[***] per claim and $[***] annual aggregate. In addition to the

foregoing, in the event that Regulus plans to Commercialize any Discontinued Product, then Regulus shall increase its insurance coverage commensurate with the additional liability and other risks associated with Commercialization activities, and at a minimum provide that the annual aggregate amount of such coverage is increased to at least $[***] at least thirty (30) days before Regulus initiates the First Commercial Sale of any Discontinued Product hereunder. Regulus shall furnish to Sanofi evidence of any insurance required under this Section 11.5, upon request.

11.5.2 Sanofi's Insurance Obligations. Sanofi hereby represents and warrants to Regulus that it is self-insured against liability and other risks associated with its activities and obligations under this Agreement 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 Sanofi under this Agreement. Sanofi shall maintain such self insurance throughout the term of this Agreement and shall furnish to Regulus evidence of such self-insurance, upon request.

ARTICLE 12

REPRESENTATIONS AND WARRANTIES

Section 12.1 Representations, Warranties and Covenants. Each Party hereby represents and warrants as of both the Effective Date and covenants to the other Party that:

12.1.1 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;

12.1.2 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;

12.1.3 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; and

12.1.4 the execution and delivery of this Agreement and the performance of such Party's obligations hereunder (i) 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 (ii) 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.

Section 12.2 Regulus Representations, Warranties, and Covenants. Regulus hereby represents and warrants to Sanofi as of the Effective Date that:

12.2.1 Regulus is the owner of, or otherwise has the right to grant all rights and licenses it purports to grant to Sanofi with respect to the Regulus Patents under this Agreement for Mir-21 and Licensed Compounds identified by Regulus on or before the Effective Date that target Mir-21;

12.2.2 To the best of its knowledge and belief, Regulus does not require any additional licenses or other intellectual property rights in order for Regulus to conduct its obligation under the R&D Plan with respect to Mir-21 and Licensed Compounds identified by Regulus on or before the Effective Date that target Mir-21;

12.2.3 Regulus has not received any written claim alleging that any of the Regulus Patents are invalid or unenforceable;

12.2.4 Regulus has not received any written claim alleging that any of Regulus' activities relating to Mir-21 and Licensed Compounds identified by Regulus on or before the Effective Date that target Mir-21, or any of Regulus' activities of the type proposed to be undertaken pursuant to the R&D Plan, infringe any intellectual property rights of a Third Party;

12.2.5 All employees, consultants, or (sub)contractors of Regulus or Affiliates performing Development activities hereunder on behalf of Regulus are, and Regulus hereby covenants to Sanofi 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 Regulus or Affiliate, respectively, as the sole owner thereof;

12.2.6 Regulus will, and Regulus hereby covenants to, as appropriate, hire and maintain sufficient staff and management to support and conduct all the Research Program hereunder in a timely fashion;

12.2.7 If reasonably requested by Sanofi in writing, Regulus will, and Regulus hereby covenants to, take reasonable, good faith measures and cooperate with Sanofi to help to facilitate a good faith negotiation between Sanofi and any Existing Regulus Agreement in the event that Sanofi desires to pursue the Development or Commercialization of any Licensed Compound or Product and would require a license directly from any such Third Party;

12.2.8 Regulus will not, and Regulus hereby covenants to Sanofi not to, withhold from Sanofi any material information or correspondence, including to or from any Regulatory Authority, that would be material and relevant to a reasonable assessment of the scientific, commercial, safety, and regulatory liabilities or commercial value of the Licensed Compounds;

12.2.9 Regulus will, and Regulus hereby covenants to Sanofi that it 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, and with respect to the care, handling and use in Development activities hereunder of any non-human animals by or on behalf of Regulus, will at all times comply (and will ensure compliance by any of its subcontractors) with all applicable federal, state and local laws, regulations and ordinances and the guiding principles of the "3R's", namely, wherever reasonably possible, reducing the number of animals used, replacing animals with non-animal methods and refining the research techniques used for the proper care, handling and use of animals in pharmaceutical research and development activities; and

12.2.10 The licenses granted to Regulus under the Existing Regulus Agreements are in full force and effect and Regulus has not received any written notice, and is not aware, of any breach by any party to the Existing Regulus Agreements.

Section 12.3 Sanofi Covenants. Sanofi hereby covenants to Regulus that it 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, and with respect to the care, handling and use in Development activities hereunder of any non-human animals by or on behalf of Sanofi, will at all times comply (and will ensure compliance by any of its subcontractors) with all Applicable Laws and the guiding principles of the "3R's", namely, wherever reasonably possible, reducing the number of animals used, replacing animals with non-animal methods and refining the research techniques used for the proper care, handling and use of animals in pharmaceutical research and development activities.

Section 12.4 DISCLAIMER OF WARRANTY. EXCEPT FOR THE EXPRESS WARRANTIES SET FORTH IN THIS ARTICLE 12, SANOFI AND REGULUS MAKE NO REPRESENTATIONS AND GRANT NO WARRANTIES, EXPRESS OR IMPLIED, EITHER IN FACT OR BY OPERATION OF LAW, BY STATUTE OR OTHERWISE, AND SANOFI AND REGULUS 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 PATENTS OR THE NON-INFRINGEMENT OF ANY INTELLECTUAL PROPERTY RIGHTS OF THIRD PARTIES.

ARTICLE 13

MISCELLANEOUS

Section 13.1 Assignment; Sanofi Affiliates. Except as expressly set forth in this Agreement, without the prior written consent of the other Party hereto, neither Party will sell, transfer, assign, delegate, pledge or otherwise dispose of, whether voluntarily, involuntarily, by operation of law or otherwise, this Agreement or any of its rights or duties hereunder; *provided*, *however,* that:

(a) either Party may assign this Agreement and its rights and obligations hereunder without the other Party's consent in connection with the transfer or sale of all or substantially all of the business of such Party to which this Agreement relates to a Third Party, whether by merger, sale of stock, sale of assets or otherwise, provided that in the event of such a sale or transfer (whether this Agreement is actually assigned or is assumed by the acquiring party by operation of law (*e.g.*, in the context of a reverse triangular merger)), intellectual property rights of the acquiring party in such sale or transfer (if other than one of the Parties to this Agreement) shall not be included in the technology licensed hereunder or otherwise subject to this Agreement;

(b) Sanofi may, without Regulus' consent, assign this Agreement and its rights and obligations hereunder to an Affiliate of Sanofi, provided that such Affiliate agrees to be bound by the terms and conditions of this Agreement and that no such assignment to an Affiliate will relieve Sanofi of its obligations hereunder; and

(c) Regulus may assign or transfer its rights under Article 6 (but no liabilities) to a Third Party in connection with a royalty factoring transaction.

The rights and obligations of the Parties under this Agreement shall be binding upon and inure to the benefit of the successors and permitted assigns of the Parties, and the name of a Party appearing herein will be deemed to include the name of such Party's successors and permitted assigns to the extent necessary to carry out the intent of this section. Any purported assignment or transfer in violation of this Section 13.1 will be void *ab initio* and of no force or effect.

Section 13.2 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.

Section 13.3 Governing Law; Jurisdiction. 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.

Section 13.4 Dispute Resolution.

13.4.1 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 within the JSC's decision-making authority will be finally decided as set forth in **APPENDIX 5**. Any dispute between the Parties which is outside the JSC's decision-making authority and is not subject to resolution under Section 6.7.1 or

Section 13.4.5 will be promptly presented to each Party's respective co-chair of the JSC for resolution, and if the co-chairs of the JSC are unable to resolve such dispute, such dispute will then be presented to the Executive VP of R&D of Sanofi and the Executive Vice President of Regulus (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.

13.4.2 Request for Arbitration. If after negotiating in good faith pursuant to Section 13.4.1, 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 13.4.3 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.

13.4.3 Arbitration.

(a) 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 13.4.1 will be resolved by final and binding arbitration conducted in accordance with the terms of this Section 13.4.3. 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 (3) 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 (6) 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 13.4.3. 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 7. 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 7. 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.

(c) EXCEPT FOR LOSSES COVERED BY THE INDEMNITIES PROVIDED UNDER ARTICLE 11, AND ANY BREACH OF THE CONFIDENTIALITY RESTRICTIONS UNDER ARTICLE 7, EACH PARTY HERETO WAIVES (1) ANY CLAIM TO PUNITIVE, EXEMPLARY OR MULTIPLIED DAMAGES FROM THE OTHER; AND (2) ANY CLAIM OF CONSEQUENTIAL, INDIRECT OR INCIDENTAL DAMAGES FROM THE OTHER.

13.4.4 Disputes Regarding Material Breach. If the Parties are in dispute as to whether one Party is in material breach of this Agreement, then the arbitrator will first determine if material breach has in fact occurred, and if so, will grant the defaulting Party the cure period provided pursuant to Section 9.3 (or 9.2, as applicable). If the material breach is not cured within the time period provided pursuant to Section 9.3 (or 9.2, as applicable), the arbitration will continue and the arbitrator will, as part of the same arbitration, award actual direct damages to the non-defaulting Party.

13.4.5 Certain Matters Subject to Expert Panel. If, at any time during the Research Term, the parties disagree whether a Proposed Target under Section 3.6.1 is Associated with the Target Field, the Parties will submit such matter to a panel of three (3) experts who are experienced in the field of biopharmaceuticals (an ***"Expert Panel"***). All members of the Expert Panel must be mutually agreed by the Parties in good faith and as promptly as possible and must be free of any conflicts of interest with respect to either or both Parties. The Expert Panel will promptly hold a hearing to review the matter, at which they will consider briefs submitted by each Party at least 15 days before the hearing, as well as reasonable presentations that each Party may present. The determination of the relevant Expert Panel as to such dispute will be binding on both Parties. The Parties will share equally in the costs of the Expert Panel, and each Party will bear its own costs associated with preparing for and presenting to the Expert Panel. The Parties may also elect by mutual agreement to use an Expert Panel (or other panels of key opinion leaders) for guidance on other issues that may arise during the Research Term.

13.4.6 Court Actions. Nothing contained in this Agreement shall 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 shall be subject to arbitration pursuant to Section 13.4.3.

Section 13.5 Notices. Except as otherwise provided for in this Agreement, all notices or other communications that are required or permitted hereunder will be in the English

Language and in writing and delivered personally with acknowledgement of receipt, sent by facsimile (and promptly confirmed by personal delivery, registered or certified mail or overnight courier as provided herein), sent by nationally-recognized overnight courier or sent by registered or certified mail, postage prepaid, return receipt requested, addressed as follows:

If to Sanofi, to:

Sanofi-Aventis
174, avenue de France

75013 Paris, France
Attention: General Counsel
Facsimile No.: +33 11.4.1 53 77 43 03

If to Regulus, to:

Regulus Therapeutics Inc.
1896 Rutherford Road
Carlsbad, California 92008
USA
Attention: Executive Vice President
Facsimile: +1 (760) 268-6868

With a copy to:

Attention: General Counsel
Facsimile: +1 (760) 268-4922

With a copy to:

Attention: Thomas Coll
Cooley LLP
4401 Eastgate Mall
San Diego, CA 92121
USA
Facsimile: +1 (858) 550-6420

or to such other address as the Party to whom notice is to be given may have furnished to the other Party in writing in accordance herewith. Any such communication will be deemed to have been given (i) when delivered, if personally delivered or sent by facsimile on a Business Day, (ii) on the Business Day after dispatch, if sent by nationally-recognized overnight courier, and (iii) on the third Business Day following the date of mailing, if sent by mail. It is understood and agreed that this Section 13.5 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.

Section 13.6 Entire Agreement; Modifications. This Agreement (including the attached Appendices and the R&D Plan), together with the Technology Alliance Agreement and the Stock Purchase Agreement, sets forth and constitutes the entire agreement and understanding

between the Parties with respect to the subject matter hereof and thereof, 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.

Section 13.7 Headings. The headings of Articles and Sections of this Agreement are for ease of reference only and will not affect the meaning or interpretation of this Agreement in any way.

Section 13.8 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.

Section 13.9 Waiver. Any term or condition of this Agreement may be waived at any time by the Party that is entitled to the benefit thereof, but no such waiver will be effective unless set forth in a written instrument duly executed by or on behalf of the Party waiving such term or condition. Any such waiver will not be deemed a waiver of any other right or breach hereunder.

Section 13.10 Counterparts. This Agreement may be executed in two or more counterparts, each of which will be deemed an original, but all of which together will constitute one and the same instrument.

Section 13.11 No Benefit to Third Parties. The representations, warranties, covenants and agreements set forth in this Agreement are for the sole benefit of the Parties hereto and their successors and permitted assigns, and they will not be construed as conferring any rights on any other parties.

Section 13.12 Further Assurances. Each Party will duly execute and deliver, or cause to be duly executed and delivered, such further instruments and do and cause to be done such further acts and things, including the filing of such assignments, agreements, documents and instruments, as may be necessary to carry out the provisions and purposes of this Agreement.

Section 13.13 Force Majeure. Neither Party will be charged with any liability for delay in performance of an obligation under this Agreement to the extent such delay is due to a cause beyond the reasonable control of the affected Party, such as war, riots, labor disturbances, fire, explosion, earthquake, and compliance in good faith with any governmental Law, regulation or order. The Party affected will give prompt written notice to the other Party of any material delay due to such causes.

Section 13.14 Interpretation.

13.14.1 Each of the Parties acknowledges and agrees that this Agreement has been diligently reviewed by and negotiated by and between them, that in such negotiations each of them has been represented by competent counsel and that the final agreement contained herein, including the language whereby it has been expressed, represents the joint efforts of the Parties hereto and their counsel. Accordingly, in the event an ambiguity or a question of intent or

interpretation arises, this Agreement will be construed as if drafted jointly by the Parties and no presumption or burden of proof will arise favoring or disfavoring any Party by virtue of the authorship of any provisions of this Agreement. This Agreement has been prepared in the English language and the English language shall control its interpretation.

13.14.2 The definitions of the terms herein will apply equally to the singular and plural forms of the terms defined. Whenever the context may require, any pronoun will include the corresponding masculine, feminine and neuter forms. The words "include", "includes" and "including" will be deemed to be followed by the phrase "without limitation". The word "will" will be construed to have the same meaning and effect as the word "will". The word "any" will mean "any and all" unless otherwise clearly indicated by context.

13.14.3 Unless the context requires otherwise, (i) any definition of or reference to any agreement, instrument or other document herein will be construed as referring to such agreement, instrument or other document as from time to time amended, supplemented or otherwise modified (subject to any restrictions on such amendments, supplements or modifications set forth herein or therein), (ii) any reference to any Applicable Laws herein will be construed as referring to such Applicable Laws as from time to time enacted, repealed or amended, (iii) any reference herein to any person will be construed to include the person's successors and assigns, (iv) the words "herein", "hereof" and "hereunder", and words of similar import, will be construed to refer to this Agreement in its entirety and not to any particular provision hereof, and (v) all references herein to Articles, Sections or Appendices, unless otherwise specifically provided, will be construed to refer to Articles, Sections and Appendices of this Agreement.

13.14.4 References to sections of the Code of Federal Regulations and to the United States Code will mean the cited sections, as these may be amended from time to time.

[SIGNATURE PAGE FOLLOWS]

IN WITNESS WHEREOF, the Parties hereto have caused this Agreement to be executed by their duly authorized representatives as of the date first above written.

REGULUS THERAPEUTICS INC.:

By: /s/ Kleanthis G. Xanthopoulos

Title: President and CEO

SANOFI-AVENTIS:

By: /s/ Philippe GOUPIT

Title: VP Corporate Licenses

SIGNATURE PAGE -COLLABORATION AND LICENSE AGREEMENT

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APPENDIX 1

DEFINITIONS

"Additional Indication" has the meaning set forth in Section 6.4.1(c).

"Additional Indication Milestone Payment" has the meaning set forth in Section 6.4.1(c).

"Affiliate" means any Person, whether *de jure or de facto*, which directly or indirectly through one (1) or more intermediaries controls, is controlled by or is under common control with another Person. A Person will be deemed to "control" another Person if it (a) owns, directly or indirectly, beneficially or legally, 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 Person in a particular jurisdiction) of such other Person, or has other comparable ownership interest with respect to any Person other than a corporation; or (b) has the power, whether pursuant to contract, ownership of securities or otherwise, to direct the management and policies of the Person. Notwithstanding the above, neither of the Founding Companies of Regulus will be deemed an Affiliate of Regulus for the purposes of this Agreement under any circumstances.

"Agreement" means this Collaboration and License Agreement, together with all Appendices attached hereto, and the R&D Plan, as the same may be amended or supplemented from time to time in accordance with the terms of this Agreement.

"API" means, with respect to a Product, the bulk active pharmaceutical ingredient for a Licensed Compound manufactured in accordance with GMP for such 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 but not limited to any applicable rules, regulations, guidelines, or other requirements of the Regulatory Authorities that may be in effect from time to time, but excluding patent laws.

"Approval" means, with respect to any Product in any regulatory jurisdiction, approval from the applicable Regulatory Authority sufficient for the manufacture, distribution, use and sale of the Product in such jurisdiction in accordance with Applicable Laws. In jurisdictions where the applicable Regulatory Authority sets the pricing authorizations necessary for a Product, Approval will not be deemed to have occurred if the final approval to market and sell the Product is being withheld because Sanofi (or its Affiliates or sublicensee) and the Regulatory Authority have not yet determined pricing; *provided*, *however*, that the First Commercial Sale in such jurisdiction will be considered Approval in such jurisdiction.

"Associated" has the meaning provided in Section 3.6.

"Business Day" means a day on which banking institutions in New York, New York, United States and Paris, France are both open for business.

"Calendar Quarter" means the respective periods of three consecutive calendar months ending on March 31, June 30, September 30 and December 31.

"Combination Product" means a Product that includes at least one additional active ingredient (whether coformulated or copackaged) which is not a Licensed Compound.

"Commercialize", **"Commercializing"** and **"Commercialization"** means activities directed to manufacturing, obtaining pricing and reimbursement approvals, for, marketing, promoting, distributing, importing or selling a Product, including, without limitation, 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.

"Collaboration Target" has the meaning set forth in Section 3.6.

"Commercially Reasonable Efforts" means, with respect to a Licensed Compound and Product, the carrying out of discovery, research, Development or Commercialization activities using the efforts that the applicable Party would reasonably devote to a compound or product of similar market potential at a similar stage in development or product life resulting from its own research efforts, taking into account product profile, the competitive landscape and other relevant scientific, technical and commercial factors.

"Confidential Information" has the meaning set forth in Section 7.1.

"Control" means, with respect to any Know-How, Patent or other intellectual property right, possession by a Party (including its Affiliates) of the right (whether by ownership, license or otherwise) to grant to the other Party ownership, a license, sublicense and/or other right to practice under such Know How, Patent or other intellectual property right as provided for herein without violating the terms of any agreement or other arrangement with any Third Party. Notwithstanding anything to the contrary under this Agreement, with respect to any Third Party acquirer that later becomes an Affiliate of Regulus after the Effective Date, no intellectual property of such Third Party acquirer will be included in the licenses granted hereunder by virtue of such Third Party acquirer becoming an Affiliate of Regulus.

"Cover", **"Covered"** or **"Covering"** means, with respect to a Patent, that, but for rights granted to a Person under such Patent, the practice by such Person of an invention claimed in such Patent 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.

"Development" means non-clinical (such as, but not limited to, IND-enabling toxicology and production of GMP quality Product) and clinical development activities reasonably related to the development and submission of information to a Regulatory Authority, including, without limitation, chemical synthesis, toxicology, pharmacology, test method development and stability testing, manufacturing process development, formulation development, delivery system development, quality assurance and quality control development, manufacturing, statistical analysis, and clinical studies. When used as a verb, **"Develop"** means to engage in Development.

"Development Candidate" has the meaning provided in the R&D Plan.

"Disclosing Party" has the meaning set forth in Section 7.1.

"Discontinued Product" has the meaning set forth in Section 10.1.

"Dollars" or **"$"** means the lawful currency of the United States.

"Effective Date" has the meaning set forth in the opening paragraph of this Agreement.

"Election Notice" has the meaning set forth in Section 10.1.

"EMEA" means the European Regulatory Authority known as the European Medicines Agency and any successor agency thereto.

"EU" means the European Union, as its membership may be altered from time to time, and any successor thereto, and which, as of the Effective Date, consists of Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, The Netherlands, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden and the United Kingdom, and that certain portion of Cyprus included in such organization.

"Existing Regulus Agreement" means any of the agreements listed on **APPENDIX 5**.

"Existing Sanofi Agreement" means any agreement to which Sanofi is a party as of the Effective Date under which Sanofi has in-licensed or acquired rights to Patents from a Third Party.

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

"Fibrosis" means [***].

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

"Founding Company" means individually, either Isis Pharmaceuticals, Inc. or Alnylam Pharmaceuticals, Inc.; and collectively, both Isis Pharmaceuticals, Inc. and Alnylam Pharmaceuticals, Inc.

"Founding Company License Agreement" means the Amended and Restated License and Collaboration Agreement among Regulus and the Founding Companies dated January 1, 2009, as amended as of the Effective Date.

"FTE-Day Rate" means US $[***] per FTE-day, subject to adjustment on an annual basis as of January 1 of each year beginning in 2011 by a factor which reflects changes in the Consumer Price Index for San Diego, California as reported as of January 1 by the U.S.

Department of Labor's Bureau of Labor Statistics in each applicable year during the Research Term when compared to the comparable statistic for January 1 of the preceding year. The FTE-Day Rate shall be inclusive of all allocated overhead costs, administrative expenses and other expenses for the employee(s) providing services under this Agreement, excluding [***] costs (which Sanofi will either pay directly or reimburse to Regulus within 30 days of invoice).

"Future Regulus Agreement" has the meaning provided in Section 6.7.2.

"Future Sanofi Agreement" has the meaning provided in Section 6.7.2.

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

"[***] Agreement" means the License Agreement among [***] and [***] dated [***].

"Generic Product(s)" means a Third Party's product(s) or Third Parties' product(s) that has the same or substantially the same active pharmaceutical ingredient as a Product and receives Approval through a regulatory approval process in which either: (i) the applicant for, or sponsor of such Approval; or (ii) the Regulatory Authority that granted such Approval, relied, in whole or in part, upon [***] submitted by, or on behalf of, Sanofi (or its Affiliate or sublicensee), to any Regulatory Authority, to support the Approval of a Product.

"Good Clinical Practice" or **"GCP"** will mean the then current standards for clinical trials for pharmaceuticals, as set forth in the United States Code of Federal Regulations, ICH guidelines and applicable regulations, laws or rules as promulgated thereunder, as amended from time to time, and such standards of good clinical practice as are required by the European Union and other organizations and governmental agencies in countries in which a Licensed Product is intended to be sold to the extent such standards are not less stringent than United States GCP.

"Good Laboratory Practice" or **"GLP"** will mean the then current standards for laboratory activities for pharmaceuticals, as set forth in the FDA's GLP regulations and/or ICH guidelines and applicable regulations.

"Good Manufacturing Practice(s)" or **"GMP"** will mean the regulatory requirements for current good manufacturing practices promulgated in the United States Code of Federal Regulations including those rules promulgated by the United States Food and Drug Administration under the U.S. Food, Drug and Cosmetic Act, 21 C.F.R. § 210 et seq., and ICH Guidelines and applicable regulations, as the same may be amended from time to time.

"[***]" means the [***] and [***] Agreement dated [***], between [***] and [***] as amended.

"[***]

"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 Approval" means the acceptance (or deemed acceptance) of the filing of an IND by the applicable Regulatory Authority. For purposes of clarity, acceptance (or deemed

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acceptance) of the filing of the foreign equivalent of an IND by the applicable Regulatory Authority in such country will be an IND Approval.

"IND-Enabling Studies" means the pharmacokinetic and toxicology studies required to meet the regulations for filing an IND.

"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 mean any human or animal disease or condition, or sign or symptom of a human or animal disease or condition.

"Initiation of Phase 1 Trial" means the dosing of the first human subject in a Phase 1 Trial.

"Initiation of Phase 2 Trial" means the dosing of the first human subject in the first Phase 2 Trial.

"Initiation of Phase 3 Trial" means the dosing of the first human subject in a Phase 3 Trial. In the case where a Phase 2b/3 Trial precedes any Phase 3 Trial for a given Product, the first dosing of such Product in a human subject following the review of interim data and decision to extend the period of such Phase 2b/3 Trial in order to provide sufficient evidence of safety and efficacy to be included as a Phase 3 Trial in filings with Regulatory Authorities will be deemed to be the "start of Phase 3 Trial" for such Product.

"In-License Milestones" means, with respect to a particular Third Party Agreement, all milestone payments that become payable by a Party to the Licensor(s) under such Third Party Agreement with respect to the applicable Third Party Patents as a result of the achievement of Development, regulatory and/or Commercialization events by a Product. For clarity, "In-License Milestones" shall not include any upfront payments under Third Party Agreements.

"In-License Royalties" means, with respect to a particular Third Party Agreement, all royalties on sales of Products by Sanofi, its Affiliates and its sublicensees that become payable by a Party to the Licensor(s) under such Third Party Agreement with respect to the applicable Third Party Patents.

"Integrated Product Plan" or **"IPP"** has the meaning set forth in Section 5.3.

"Intellectual Property Panel" has the meaning set forth in Section 6.7.1.

"Joint Invention" has the meaning set forth in Section 8.1.

"Joint Patent" means any Patent that claims, and only to the extent that it claims, a Joint Invention(s).

"JSC Charter" has the meaning set forth in Section 3.4.

"JSC" has the meaning set forth in Section 3.4.

"Know-How" means technical information and materials, including without limitation, technology, software, instrumentation, devices, data, biological materials, assays, constructs, compounds, inventions, practices, methods, knowledge, know-how, trade secrets, skill and experience.

"Licensed Compound" means either (i) with respect to any Collaboration Target identified on **APPENDIX 6** as approached via a microRNA Antagonist, any microRNA Antagonist that modulates the expression of such Collaboration Target where its primary mechanism of action is [***], or (ii) with respect to any Collaboration Target identified on **APPENDIX 6** as approached via a microRNA Mimic, a microRNA Mimic with a substantially similar base composition as such Collaboration Target and which is [***] such Collaboration Target; in each case that is identified by Regulus as of the Effective Date or in the performance of the Research Program. For purposes of clarity, so long as Mir-21 remains a Collaboration Target, a Mir-21 Compound will be a Licensed Compound under this Agreement.

"Licensing Revenues" has the meaning set forth in Section 10.2.

"Licensor" means, with respect to a particular Third Party Agreement, any Third Party that is a party to such Third Party Agreement.

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

"Major European Country" means France, Germany, Italy, Spain or the United Kingdom.

"Major Market Country" means Canada, France, Germany, Italy, Japan, Spain, the United Kingdom, and the United States.

"Manufacturing Technology" has the meaning set forth in Section 4.3.

"microRNA" means a structurally defined functional RNA molecule usually between 21 and 25 nucleotides in length, which is derived from genetically-encoded non-coding RNA which is predicted to be processed into a hairpin RNA structure that is a substrate for the double-stranded RNA-specific ribonuclease Drosha and subsequently is predicted to serve as a substrate for the enzyme Dicer, a member of the RNase III enzyme family; including, without limitation, those microRNAs exemplified in miRBase (http://microrna.sanger.ac.uk/). To the extent that [***] for purposes of this Agreement; *provided, however*, that nothing contained herein will require any Party hereto to [***].

"microRNA Antagonist" means a single-stranded oligonucleotide (or a single stranded analog thereof) that is designed to interfere with or inhibit a particular microRNA. For purposes of clarity, the definition of "microRNA Antagonist" excludes oligonucleotides that function predominantly through the RNAi mechanism of action or the RNase H mechanism of action.

"microRNA Compound" means a compound consisting of (a) a microRNA Antagonist, or (b) a microRNA Mimic.

"microRNA Mimic" means a double-stranded or single-stranded oligonucleotide or analog thereof with a substantially similar base composition as a particular microRNA and which is designed to mimic the activity of such microRNA.

"Mir-21" means the microRNA having (i) miRBase ID: hsa-miR-21; (ii) the miRBase Accession Number MIMAT0000076, and (iii) the sequence UAGCUUAUCAGACUGAUGUUGA.

"Mir-21 Compound" means any microRNA Antagonist that modulates the expression of Mir-21 whose primary mechanism of action is through [***] to Mir-21 and that is specifically identified by Regulus as of the Effective Date or in the performance of the Research Program.

"Mir-21 Product" means any pharmaceutical product containing a Mir-21 Compound (alone or with other active ingredients), in all forms, presentations, formulations and dosage forms.

"NDA" means a New Drug Application filed with the FDA after completion of clinical trials to obtain marketing approval for the applicable Product in the United States.

"NDA Filing" means the acceptance by the FDA of the filing of an NDA for the applicable Product, or the acceptance of the foreign equivalent of an NDA by the applicable Regulatory Authority.

"Necessary Patent" has the meaning provided in Section 6.7.1.

"Net Sales" means, with respect to a Product, the gross invoice price of all units of such Products sold by Sanofi, its Affiliates and/or their sublicensees to any Third Party, less the following items: (a) trade discounts, credits or allowances, (b) credits or allowances additionally granted upon returns, rejections or recalls, (c) freight, shipping and insurance charges, (d) taxes, duties or other governmental tariffs (other than income taxes), (e) government-mandated rebates, and (f) a reasonable reserve for bad debts. "Net Sales" under the following circumstances will mean the fair market value of such Product: (i) Products which are used by Sanofi, its Affiliates or sublicensees for any commercial purpose without charge or provision of invoice, (ii) Products which are sold or disposed of in whole or in part for non cash consideration, or (iii) Products which are provided to a Third Party by Sanofi, its Affiliates or sublicensees without charge or provision of invoice and used by such Third Party except in the cases of Products used to conduct clinical trials, reasonable amounts of Products used as marketing samples and Product provided without charge for compassionate or similar uses.

Net Sales will not include any transfer between or among Sanofi and any of its Affiliates or sublicensees for resale.

In the event a Product is sold as part of a Combination Product, the Net Sales from the Combination 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 average sale price of the Product when sold separately in finished form and B is the average sale price of the other therapeutically active pharmaceutical compound(s) included in the Combination Product when sold separately in

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finished form, 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 which sales of all occurred. In the event that such average sale price cannot be determined for both the Product and all other therapeutically active pharmaceutical compounds included in the Combination Product, Net Sales for the purposes of determining royalty payments will be calculated as above, but the average sales price in the above equation will be replaced by a good faith estimate of the fair market value of the compound(s) for which no such price exists.

"New Core Patents" has the meaning set forth in Section 6.9.

"New Core Technology" has the meaning set forth in Section 6.9.

"New Core Technology Agreement" has the meaning set forth in Section 6.9.

"Objective" means the objective of the R&D Plan set forth in Section 3.1.

"Other In-License Payments" means, with respect to a particular Third Party Agreement, all payments (*excluding* In-License Royalties and In-License Milestones) that become payable by a Party to the applicable Licensor(s) under such Third Party Agreement with respect to the applicable Third Party Patents.

"Other Licensor" means any Licensor that is not a Founding Company.

"Other Party" has the meaning set forth in Section 9.3.

"Party(ies)" has the meaning set forth in the opening paragraph of this Agreement.

"Patents" means (a) patents and patent applications in any country or jurisdiction, (b) all priority applications, divisionals, continuations, and continuations-in-part of any of the foregoing, and (c) all patents issuing on any of the foregoing patent applications, together with all registrations, reissues, renewals, re-examinations, confirmations, supplementary protection certificates, and extensions of any of (a), (b) or (c).

"Permitted License" means a license granted by Regulus to a Third Party (i) under the Regulus Core Technology Patents (but not under the Product Specific Patents) to [***] (or [***] to [***]) solely to conduct Research, or (ii) under the Regulus Core Technology Patents (but not under the Product Specific Patents) to enable such Third Party to [***] or [***] microRNA Compounds, where such Third Party is [***] and is not [***] or [***]

"Person" means any individual, firm, corporation, partnership, limited liability company, trust, business trust, joint venture company, governmental authority, association or other entity.

"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 2 Trial" means a human clinical trial of a Product, the principal purpose of which is a determination of preliminary short-term safety and efficacy in the target patient

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population, as described in 21 C.F.R. 312.21(b) for the United States, or a similar clinical study prescribed by the Regulatory Authorities in a foreign country.

"Phase 2b/3 Trial" means a human clinical trial of a Product, the principal purpose of which is a further determination of efficacy and safety, 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 (dose and dose regimen) prior to initiation of the pivotal Phase 3 Trials, and which itself provides sufficient evidence of safety and efficacy to be included as a Phase 3 Trial in filings with Regulatory Authorities.

"Phase 3 Trial" means a human clinical trial of a Product on a sufficient number of subjects that is designed to establish that a pharmaceutical product is safe and efficacious for its intended use, and to determine warnings, precautions and adverse reactions that are associated with such pharmaceutical product in the dosage range to be prescribed, which trial is intended to support Approval of a Product, as described in 21 C.F.R. 312.21(c) for the United States, or a similar clinical study prescribed by the Regulatory Authorities in a foreign country.

"Phase 4 Trial" means a human clinical trial for a Product commenced after receipt of Approval in the country for which such trial is being conducted and that is conducted within the parameters of the Approval for the Product. Phase 4 Trials may include, without limitation, epidemiological studies, modeling and pharmacoeconomic studies, investigator sponsored clinical trials of Product and post-marketing surveillance studies.

"Product" means any pharmaceutical product containing a Licensed Compound (alone or with other active ingredients), in all forms, presentations, formulations and dosage forms.

"Product Development Plan" has the meaning set forth in Section 5.3.

"Product Field" means (a) the treatment and/or prophylaxis of any Indication and (b) to the extent that Regulus Controls [***] the applicable Collaboration Target as [***] for [***] to the corresponding Product in the treatment and/or prophylaxis of an approved Indication for the Product.

"Product Specific Patents" means all Patents (including all claims and the entire scope of claims therein) Controlled by Regulus or its Affiliates on the Effective Date and/or at any time thereafter, in each case claiming (a) a Collaboration Target gene sequence or a portion thereof, (b) the specific compositions of matter of Licensed Compounds or Products, or (c) methods of using Licensed Compounds or Products as therapeutics; *provided however*, that:

(1) unless the Parties otherwise agree in writing, Patents that include claims that are directed to subject matter and have a scope that is applicable to microRNA Compounds in general, and not directed solely to [***] or [***] or to the [***] thereof, will be considered to be [***] Patents; and

(2) unless the Parties otherwise agree in writing, Patents that include claims that are directed to the identification or isolation of microRNAs that are not [***], or to the production, composition, or use of [***] that are not [***] or [***], will be considered to be [***] Patents.

For clarification, any Regulus Program Patent or any Joint Patent satisfying the definition above, will be considered a Product Specific Patent. The Product Specific Patents as of the Effective Date are listed in **APPENDIX 2** attached hereto.

"Program Inventions" has the meaning set forth in Section 8.1.

"Program Patents" has the meaning set forth in Section 8.1.

"Proposed Target" has the meaning set forth in Section 3.6.1.

"R&D Plan" has the meaning set forth in Section 3.2.

"Receiving Party" has the meaning set forth in Section 7.1.

"Regulatory Authority" means any governmental authority, including without limitation FDA, EMEA or Koseisho (i.e., the Japanese Ministry of Health, Labour and Welfare, or any successor agency thereto), that has responsibility for granting any licenses or approvals or granting pricing and/or reimbursement approvals necessary for the marketing and sale of a Product in any country.

"Regulatory Documentation" means all applications, registrations, licenses, authorizations and approvals (including all Approvals), all correspondence submitted to or received from Regulatory Authorities (including minutes and official contact reports relating to any communications with any Regulatory Authority), all supporting documents and all clinical studies and tests, including the manufacturing batch records, relating to the Product, and all data contained in any of the foregoing, including all regulatory drug lists, advertising and promotion documents, adverse event files and complaint files.

"Regulus Confidential Information" means any Confidential Information for which Regulus is the Disclosing Party.

"Regulus Core Technology Patents" means, subject to 6.8.3, Patents Controlled by Regulus or its Affiliates on the Effective Date and/or at any time thereafter, in each case that are useful or necessary for the Development and Commercialization of Licensed Compound and Products. Regulus Core Technology Patents will exclude the Product Specific Patents. A representative list of the Regulus Core Technology Patents as of the Effective Date is listed in **APPENDIX 3** hereto. For clarification, any Regulus Program Patent or any Joint Patent satisfying the definition above will be considered a Regulus Core Technology Patent.

"Regulus Database" has the meaning set forth in Section 3.11.

"Regulus Inventions" has the meaning set forth in Section 8.1.

"Regulus Know-How" means all Know-How Controlled by Regulus or its Affiliates as of the Effective Date and/or at any time thereafter that is useful for the Research, discovery, Development, Approval, manufacturing and Commercialization of microRNA Compounds.

"Regulus Patents" means the Regulus Core Technology Patents and the Product Specific Patents (including patents licensed to Regulus under an Existing Regulus Agreement, or under a Future Regulus Agreement in accordance with Section 6.7).

"Regulus Program Patent" has the meaning set forth in Section 8.1.

"Regulus Technology" means collectively, the Regulus Know-How and the Regulus Patents.

"Requested Target" has the meaning set forth in Section 3.6.2.

"Research" means pre-clinical research including gene function, gene expression and target validation research using cells and animals, which may include small pilot toxicology studies but excludes IND-Enabling Studies, clinical development and commercialization.

"Research Program" has the meaning set forth in Section 3.1.

"Research Results" means all data, information, trade secrets, inventions and Know-How which are discovered, made, reduced to practice, identified or developed in whole or in part by Regulus in the course of the performance of the Research Program and Development Program.

"Research Term" has the meaning set forth in Section 3.3.1.

"Royalty Term" has the meaning set forth in Section 6.11.

"Sanofi Confidential Information" means any Confidential Information for which Sanofi is the Disclosing Party.

"Sanofi Indemnitees" has the meaning set forth in Section 11.2.

"Sanofi Inventions" has the meaning set forth in Section 8.1.

"Sanofi Product Specific Patent" means any Patents (including all claims and the entire scope of claims therein) Controlled by Sanofi or its Affiliates on the Effective Date and/or at any time thereafter, in each case claiming (a) the sequence or a portion thereof corresponding to the Mir-21 or Collaboration Target gene sequence or a portion thereof, (b) the specific composition of matter of a Product, (c) methods of using a Licensed Compound or Product as a therapeutic or (d) methods of using a Licensed Compound as a therapeutic).

"Sanofi Program Patents" has the meaning set forth in Section 8.1.

"Senior Representatives" has the meaning set forth in Section 13.4.1.

"Stock Purchase Agreement" means that certain letter agreement between the Parties dated as of the Effective Date pursuant to which Sanofi is purchasing shares of Regulus' Series B preferred stock.

"Target Encumbrances" has the meaning set forth in Section 3.6.1.

"Target Field" means (a) the treatment and/or prophylaxis of any or all Indications in Fibrosis [***] and (b) to the extent that Regulus Controls [***] the applicable Collaboration Target as [***] for [***] to the corresponding Licensed Compound in the treatment and/or prophylaxis of an Indication in Fibrosis [***].

"Target Product Profile" means, with respect to each Collaboration Target, the description, as established by the JSC, of the commercially relevant range of acceptable product performance of a Collaboration Compound against key product characteristics (including but not limited to efficacy, safety, quality, side effects, tolerability, route of administration, contraindications and clinical endpoints), and which shall be used by the Parties to guide and shape the progression of and development decisions for such Licensed Compound to achieve IND approval.

"Technology Alliance Agreement" means the Non-Exclusive Technology Alliance and Option Agreement between the Parties dated as of the Effective Date.

"Term" has the meaning set forth in Section 9.1.

"Territory" means all countries and jurisdictions throughout the world.

"Third Party" means any Person other than Regulus or Sanofi or their respective Affiliates.

"Third Party Agreement" means an Existing Regulus Agreement, Future Regulus Agreement, Existing Sanofi Agreement or Future Sanofi Agreement, as applicable.

"Third Party Claims" has the meaning set forth in Section 11.1.

"Third Party Patents" means, with respect to a particular Third Party Agreement, all Necessary Patents that a Party in-licenses or acquires from the Licensor(s) under such Third Party Agreement.

"[***] Patents" means all Patents licensed under the [***] Agreement.

"Valid Claim" means a claim of any issued, unexpired patent that has not been revoked or held unenforceable or invalid by a decision of a court or governmental agency of competent jurisdiction from which no appeal can be taken, or with respect to which an appeal is not taken within the time allowed for appeal, and that has not been disclaimed or admitted to be invalid or unenforceable through reissue, disclaimer or otherwise.

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

"[***] Agreement" means the [***] Agreement by and between the [***], commissioned by [***], and Regulus dated [***].

APPENDIX 2

PRODUCT-SPECIFIC PATENTS

[***]

APPENDIX 3

REGULUS CORE TECHNOLOGY PATENTS

[***]

APPENDIX 4

CHARTER OF THE JOINT STEERING COMMITTEE

Purpose

The Joint Research Committee is established by Regulus and Sanofi to oversee the Research Program under the Agreement.

Responsibilities

1. The JSC will, using the R&D Plan initially agreed to on the Effective Date, as a basis, continue to develop and refine the R&D Plan, as needed, and will conduct a comprehensive review of the R&D Plan on at least an annual basis.

2. The JSC will be responsible for the overall planning and execution of the Research Program and the approval and oversight of the R&D Plan. The JSC will (i) evaluate the data generated by the Parties in the course of carrying out the R&D Plan, (ii) discuss and resolve any overarching issues or significant changes in the R&D Plan, (iii) recommend project prioritization within the R&D Plan, (iv) make project progression decisions and resource allocation decisions in accordance with the R&D Plan, (v) make revisions to the R&D Plan as necessary and (vi) consistent with Article 7 of the Agreement,

review and approve all public communications and disclosures, including but not limited to data presented at external meetings and journals on the joint Research Results. Except for amendments to the R&D Plan (as adopted in accordance with this charter and the Agreement), in no event will the JSC have the power or authority to amend any provision of the Agreement.

3. The JSC will have the power to delegate its authority and duties to sub-committees as it deems appropriate.

Composition

4. The JSC will initially have six members, and will at all times have an equal number of members designated by each Party. Each Party may replace its appointed JSC representatives at any time upon written notice to the other Party. The size and composition of the JSC provided herein may not be changed without the consent of both Regulus and Sanofi.

5. Each JSC member will have the requisite background, experience and training to carry out the duties and obligations of the JSC.

6. Each Party will designate one of its representatives as co-chairperson of the JSC. Each of the co-chairpersons will be responsible, on an alternating basis with the Sanofi co-chairperson having responsibility with respect to the initial meeting, for scheduling meetings, preparing and circulating an agenda in advance of each meeting, and preparing the minutes of each meeting.

Decisions

7. Each Party's JSC members will collectively have three votes, regardless of the number of its JSC members participating in any meeting. No votes will be taken unless there is at least one JSC member representing each of Regulus and Sanofi participating in such meeting. Each Party may allocate its three votes among its attending JSC members in any manner, at such Party's discretion. If only one JSC member is attending on behalf of a given Party, such JSC member may cast all the votes allocated to such Party. Unless otherwise specified herein, all actions taken by the JSC as a committee will be by majority vote. If the JSC members reach a deadlock on any vote, then the deadlock will be resolved in accordance with Paragraph 8 below. Notwithstanding anything to the contrary, no decision by the JSC will require the other Party to: (i) breach any written agreement that such other Party may have with a Third Party (except where such agreement is entered into in breach of any representation, warranty, covenant or obligation of such Party under to this Agreement); (ii) perform any activities that are outside the scope of the Objective; or (iii) violate any Applicable Law or principles of scientific integrity.

8. If the JSC is unable to decide by a majority vote on any issue within the scope of its authority and duties, then the JSC will promptly raise such issue to each Parties co-chairperson on the JSC, and such co-chairs will have 10 days to mutually agree on how to resolve such issue. If the co-chairs are unable to resolve such issue within the 10 day period, then such issue will be brought to each Party's Senior Representatives, or their designees. The Senior Representatives will have 10 days to mutually agree on how to resolve such issue. If the Senior Representatives are unable to resolve such issue within the 10-day period, then, subject to the express limitations set forth in the Agreement and in Paragraph 9 below, such issue will be finally resolved by the Senior Representative of Sanofi, and such resolution will be binding on Sanofi and Regulus.

9. Notwithstanding anything to the contrary, Sanofi will not have the final decision with respect to any dispute involving any of the following: (i) moving the performance of the Research Program [***]; (ii) changing (a) the R&D Plan to [***] (e.g., [***]), or (b) the [***] after [***] have begun, all of which changes in the aggregate would cumulatively increase Regulus' fully burdened costs of performing R&D Plan activities for a given Collaboration Target by more than a total of $[***], unless [***] in costs in excess of $[***] for such Collaboration Target; and (iii) whether to drop or replace a Collaboration Target during the first [***] months following the applicable Request Notice for such Collaboration Target.

Operations; Meetings

10. During the Research Term the JSC will initially meet once per month, unless and until the JSC determines that such meetings should occur once per Calendar Quarter (in either case, each a ***"Scheduled Meeting"***). Scheduled Meetings may be held in person or by audio or video teleconference when appropriate, but at a minimum, once each year in person (which in-person meeting will be held on an alternating basis in New York, NY and in Carlsbad, CA). In addition, any two members of the JSC may jointly call for an *ad hoc* meeting of the JSC by teleconference at any time, by giving the other members of the JSC advance written notice of at least two
Business Days (each, an "***Ad Hoc Meeting***"). An Ad Hoc Meeting may be called to address any time-sensitive matter.

11. Meetings of the JSC will be effective only if at least one JSC representative of each Party is present or participating. Each Party will be responsible for all of its own expenses of participating in the JSC meetings. The Parties will endeavor to schedule meetings of the JSC with at least 30 days advance notice.

12. Each Party may bring additional employees to each meeting as non-voting observers.

13. The co-chair responsible for each meeting (the ***"Responsible Chair"***) will, in consultation with other members of the JSC, develop and set the JSC's agenda for each Scheduled Meeting. The Responsible Chair will include on such agenda each item requested within a reasonable time in advance of such Scheduled Meeting by a JSC member. The agenda and information concerning the business to be conducted at each Scheduled Meeting will be communicated in writing to the members of the JSC within a reasonable time in advance of such Scheduled Meeting to permit meaningful review. No agenda is required for an Ad Hoc Meeting.

14. The Responsible Chair, or such person as the Responsible Chair may designate, will prepare, and distribute to all JSC members, draft committee minutes within 2 weeks following each Scheduled Meeting or Ad Hoc Meeting and such minutes will be finalized by the JSC promptly thereafter. As part of the agenda of the first Scheduled Meeting, the JSC members will agree upon a standard procedure for review and approval of such draft committee minutes by the JSC.

APPENDIX 5

EXISTING REGULUS AGREEMENTS

[***]

APPENDIX 6

COLLABORATION TARGETS

[***]

APPENDIX 7

LISTED COUNTRIES

Patent Country Code	Patent Filing Country or Jurisdiction
[***]	[***]

Appendix 7.3A

Regulus Initial Press Release

sanofi-aventis and Regulus Therapeutics Form Major Strategic Alliance on microRNA Therapeutics

- Largest microRNA therapeutics alliance to date, valued at potentially over $750 million including a $25 million upfront, a $10 million future equity investment subject to mutual agreement on company valuation, and a three-year option worth $50 million for a broader technology alliance -

- Focused on developing microRNA-based medicines toward four targets -

- Structured as multi-year collaboration intended to advance several investigational new drugs into clinical development -

Carlsbad, CA., June XX, 2010 — Regulus Therapeutics Inc. and sanofi-aventis (EURONEXT: SAN and NYSE: SNY) announced today that they have entered into a global, strategic alliance to discover, develop, and commercialize microRNA therapeutics. The alliance represents the largest microRNA partnership formed to date, valued at potentially over $750 million, and includes a $25 million upfront fee, a $10 million future equity investment subject to mutual agreement on company valuation, and annual research support for three years with the option to extend two additional years. The alliance will initially focus on the therapeutic area of fibrosis. Regulus and sanofi-aventis will collaborate on up to four microRNA targets, including Regulus' lead fibrosis program targeting microRNA-21. sanofi-aventis also receives an option for a broader technology alliance that provides Regulus certain rights to participate in development and commercialization of resulting products. If exercised, this three-year option is worth an additional $50 million to Regulus.

microRNAs are a new class of small non-coding RNAs that regulate gene expression by interfering with translation or stability of target messenger RNA transcripts. Endogenous microRNAs regulate the expression of over one-third of all human genes, and the association of microRNA dysfunction with disease phenotypes has given rise to an entirely new class of pharmaceutically relevant targets. In preclinical studies, Regulus has demonstrated that modulating microRNAs can effectively regulate disease pathways and produce therapeutically beneficial effects.

"This new partnership continues to illustrate sanofi-aventis' commitment to develop innovative therapies," declared Marc Cluzel, M.D., Ph.D, Executive Vice-President, Research & Development, sanofi-aventis. "microRNAs are believed to be extremely important in human development and physiology. Together with Regulus we will develop therapeutics which could potentially open a new paradigm in the treatment of major diseases and could offer an attractive new therapeutic approach for patients."

"Regulus is very pleased to form this landmark alliance with sanofi-aventis, a leading visionary company developing important new medicines," said Kleanthis Xanthopoulos, Ph.D., President and Chief Executive Officer of Regulus. "The significant support from sanofi-aventis

in this new alliance will strengthen our efforts as we continue to build the leading microRNA therapeutics company through our commitment to scientific excellence and advancement of our pipeline of innovative new medicines. Indeed, this landmark alliance will significantly extend our capabilities and resources to lead the discovery and development of microRNA therapeutics."

Alnylam Pharmaceuticals (Nasdaq: ALNY) and Isis Pharmaceuticals (Nasdaq: ISIS) formed Regulus in 2007, with each company currently owning approximately 50% of the preferred stock.

About the Regulus and sanofi-aventis Collaboration

Regulus and sanofi-aventis have entered into a strategic alliance on microRNA therapeutics. The alliance is initially focused on the therapeutic area of fibrosis. Regulus has granted sanofi-aventis four worldwide, exclusive licenses to discover, develop, and commercialize microRNA therapeutics, including Regulus' leading fibrosis program targeting microRNA-21. Regulus receives from sanofi-aventis an upfront fee of $25 million, a future equity investment of $10 million subject to mutual agreement on company valuation, and annual research funding for three years with the option to extend for two additional one-year periods. Regulus also could receive preclinical milestones as well as development and sales milestones for collaboration targets. In addition, Regulus is eligible to receive royalties on microRNA therapeutic products commercialized by sanofi-aventis. sanofi-aventis will support 100% of the costs of clinical development and commercialization of each program. In addition, Regulus has granted sanofi-aventis an option to enter into a technology alliance worth up to $50 million that could provide sanofi-aventis with access to Regulus' microRNA platform and a limited number of product licenses. Assuming exercise of the technology alliance option, Regulus has certain opt-in rights to participate in the development and commercialization of future sanofi-aventis clinical microRNA programs. In addition, Regulus is eligible to receive milestone payments and royalties on microRNA therapeutic products developed and commercialized under the technology alliance option.

The alliance is valued at potentially over $750 million in consideration of upfront payments, equity investment, research funding, and potential preclinical, clinical and commercial milestone payments for multiple products if all products are successfully commercialized. Regulus will pay approximately $4 million of the initial funding to its licensors, the majority of which will be to Isis and Alnylam. Isis and Alnylam could also receive additional payments based on future success-based milestone payments earned during the alliance.

About microRNAs

The discovery of microRNA in humans is one of the most exciting scientific breakthroughs in the last decade. microRNAs are small RNA molecules, typically 20 to 25 nucleotides in length that do not encode proteins but instead regulate gene expression. Nearly 700 microRNAs have been identified in the human genome, and more than one-third of all human genes are believed to be regulated by microRNAs. As a single microRNA can regulate entire networks of genes, these new molecules are considered the master regulators of the genome. microRNAs have been shown to play an integral role in numerous biological processes

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including the immune response, cell-cycle control, metabolism, viral replication, stem cell differentiation and human development. Most microRNAs are conserved across multiple species indicating the evolutionary importance of these molecules as modulators of critical biological pathways. Indeed, microRNA expression or function has been shown to be significantly altered in many disease states, including cancer, heart failure and viral infections. Targeting microRNAs with anti-miRs, antisense oligonucleotide inhibitors of microRNAs, or miR-mimics, double-stranded oligonucleotides to replace microRNA function, opens the possibility of a novel class of therapeutics and a unique approach to treating disease by modulating entire biological pathways. To learn more about microRNAs please visit http://www.regulusrx.com/microrna/microrna-explained.php.

About Regulus Therapeutics Inc.

Regulus Therapeutics is a biopharmaceutical company leading the discovery and development of innovative new medicines based on microRNAs. Regulus is targeting microRNAs as a new class of therapeutics by working with a broad network of academic collaborators and leveraging oligonucleotide drug discovery and development expertise from its founding companies Alnylam Pharmaceuticals (Nasdaq:ALNY) and Isis Pharmaceuticals (Nasdaq:ISIS). Regulus is advancing microRNA therapeutics towards the clinic in several areas including hepatitis C infection, cardiovascular disease, fibrosis, oncology, immuno-inflammatory diseases, and metabolic diseases. Regulus' intellectual property estate contains both the fundamental and core patents in the field and includes over 600 patents and more than 300 pending patent applications pertaining primarily to chemical modifications of oligonucleotides targeting microRNAs for therapeutic applications. In 2008, Regulus entered into a major alliance with GlaxoSmithKline to discover and develop microRNA therapeutics for immuno-inflammatory diseases. In 2010, Regulus entered into a new collaboration with GlaxoSmithKline to develop and commercialize microRNA therapeutics targeting microRNA-122 for the treatment of Hepatitis C Viral infection. For more information, visit http://www.regulusrx.com.

About sanofi-aventis

Sanofi-aventis, a leading global pharmaceutical company, discovers, develops and distributes therapeutic solutions to improve the lives of everyone. Sanofi-aventis is listed in Paris (EURONEXT: SAN) and in New York (NYSE: SNY). For more information, please visit: www.sanofi-aventis.com.

About Alnylam Pharmaceuticals

Alnylam is a biopharmaceutical company developing novel therapeutics based on RNA interference, or RNAi. The company is applying its therapeutic expertise in RNAi to address significant medical needs, many of which cannot effectively be addressed with small molecules or antibodies, the current major classes of drugs. Alnylam is leading the translation of RNAi as a new class of innovative medicines with peer-reviewed research efforts published in the world's top scientific journals including Nature, Nature Medicine, and Cell. The company is leveraging these capabilities to build a broad pipeline of RNAi therapeutics for the treatment of a wide range of disease areas, including respiratory syncytial virus (RSV), liver cancers, TTR-mediated amyloidosis (ATTR), hypercholesterolemia, and Huntington's disease. In addition, Alnylam

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formed Alnylam Biotherapeutics, a division of the company focused on the development of RNAi technologies for application in manufacturing processes for biotherapeutic products, including recombinant proteins and monoclonal antibodies. The company's leadership position in fundamental patents, technology, and know-how relating to RNAi has enabled it to form major alliances with leading companies including Medtronic, Novartis, Biogen Idec, Roche, Takeda, Kyowa Hakko Kirin, and Cubist. Alnylam and Isis are joint owners of Regulus Therapeutics Inc., a company focused on the discovery, development, and commercialization of microRNA-based therapeutics. Founded in 2002, Alnylam maintains headquarters in Cambridge, Massachusetts. For more information, please visit www.alnylam.com.

About Isis Pharmaceuticals, Inc.

Isis is exploiting its expertise in RNA to discover and develop novel drugs for its product pipeline and for its partners. The Company has successfully commercialized the world's first antisense drug and has 22 drugs in development. Isis' drug development programs are focused on treating cardiovascular, metabolic, and severe neurodegenerative diseases and cancer. Isis' partners are developing antisense drugs invented by Isis to treat a wide variety of diseases. Isis and Alnylam Pharmaceuticals are joint owners of Regulus Therapeutics Inc., a company focused on the discovery, development and commercialization of microRNA therapeutics. Isis also has made significant innovations beyond human therapeutics resulting in products that other companies, including Abbott, are commercializing. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of over 1,600 issued patents worldwide. Additional information about Isis is available at www.isispharm.com.

Forward-Looking Statements

This press release includes forward-looking statements regarding the future therapeutic and commercial potential of Isis', Alnylam's and Regulus' business plans, technologies and intellectual property related to microRNA therapeutics being discovered and developed by Regulus, including statements regarding expectations around the newly formed alliance between Regulus and sanofi-aventis, the therapeutic potential of targeting microRNA-21 and the potential for future payments to Isis and Alnylam under this alliance. Any statement describing Isis', Alnylam's or Regulus' goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such products. Such parties' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause their results to differ materially from those expressed or implied by such forward-looking statements. Although these forward-looking statements reflect the good faith judgment of the management of each such party, these statements are based only on facts and factors currently known by Isis, Alnylam or Regulus, as the case may be. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Regulus', Isis', and Alnylam's programs are described in additional detail in each of Isis' and Alnylam's annual report on Form 10-K for the year ended December 31, 2009 and their most recent quarterly report on Form 10-Q, which are on file with the SEC. Copies of these and other documents are available from either Isis or Alnylam.

Appendix 7.3B

Sanofi Initial Press Release

Sanofi-Aventis and Regulus Therapeutics Form Major Strategic Alliance on microRNA Therapeutics

- Collaboration starting with a specific lead in Fibrosis -

Paris, France - June XX, 2010 - Sanofi-Aventis (EURONEXT: SAN and NYSE: SNY) and Regulus Therapeutics Inc announced today that they have entered into a global strategic alliance to discover, develop, and commercialize microRNA therapeutics. The alliance will initially focus on the therapeutic area of fibrosis.

MicroRNAs (micro-RiboNucleic Acid) are a new class of small non-coding RNAs that regulate gene expression by interfering with translation or stability of target messenger RNA transcripts. Endogenous microRNAs regulate the expression of over one-third of all human genes. The association of microRNA dysfunction with disease phenotypes has given rise to an entirely new class of pharmaceutically relevant targets.

Sanofi-aventis and Regulus will collaborate on microRNA drug discovery and preclinical development for up to four microRNA targets, including the lead fibrosis program targeting microRNA-21. Sanofi-Aventis also received an option, which if exercised, provides access to the technology to develop and commercialize other micro-RNA based therapeutics, beyond the first four targets.

"Regulus is very pleased to form this new major alliance with sanofi-aventis, a leading visionary company developing important new medicines bringing value to patients," said Kleanthis G. Xanthopoulos, Ph.D., President and Chief Executive Officer of Regulus. "The significant support from sanofi-aventis in this new alliance will strengthen our efforts as we continue to build the leading micro-RNA therapeutics company based on a commitment to scientific excellence and advancement of a pipeline of innovative new medicines. Indeed, we are confident that this new alliance will significantly extend our capabilities and resources to lead the discovery and development of micro-RNA therapeutics."

"This new partnership continues to illustrate sanofi-aventis' commitment to develop innovative therapies", declared Marc Cluzel, M.D., Ph.D, Executive Vice-President, Research & Development, sanofi-aventis.

"Micro-RNAs are believed to be extremely important in human development and physiology. Together with Regulus we will develop therapeutics which could potentially open a new paradigm in the treatment of major diseases and could offer an attractive new therapeutic approach for patients".

Regulus will receive a $25 million upfront fee and a future $10 million equity investment subject to mutual agreement on company valuation. The alliance could be valued at over $750 million

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when taking into account upfront payments, equity investment, research funding, and potential near-term preclinical, clinical and commercial milestone payments for multiple products.

Regulus was formed in 2007 and is jointly owned by Alnylam Pharmaceuticals (Nasdaq: ALNY) and Isis Pharmaceuticals (Nasdaq: ISIS).

About microRNAs

The discovery of microRNA in humans is one of the most exciting scientific breakthroughs in the last decade. MicroRNAs are small RNA molecules, typically 20 to 25 nucleotides in length, that do not encode proteins but instead regulate gene expression. Nearly 700 microRNAs have been identified in the

human genome, and more than one-third of all human genes are believed to be regulated by microRNAs. As a single microRNA can regulate entire networks of genes, these new molecules are considered the master regulators of the genome. MicroRNAs have been shown to play an integral role in numerous biological processes including the immune response, cell-cycle control, metabolism, viral replication, stem cell differentiation and human development. Most microRNAs are conserved across multiple species indicating the evolutionary importance of these molecules as modulators of critical biological pathways. Indeed, microRNA expression or function has been shown to be significantly altered in many disease states, including cancer, heart failure and viral infections. Targeting microRNAs with anti-miRs, antisense oligonucleotide inhibitors of microRNAs, or miR-mimics, double-stranded oligonucleotides to replace microRNA function, opens the possibility of a novel class of therapeutics and a unique approach to treating disease by modulating entire biological pathways. To learn more about microRNAs please visit http://www.regulusrx.com/microrna/microrna-explained.php

About Regulus Therapeutics Inc.

Regulus Therapeutics is a biopharmaceutical company leading the discovery and development of innovative new medicines based on microRNAs. Regulus is targeting microRNAs as a new class of therapeutics by working with a broad network of academic collaborators and leveraging oligonucleotide drug discovery and development expertise from its founding companies Alnylam Pharmaceuticals (Nasdaq:ALNY) and Isis Pharmaceuticals (Nasdaq:ISIS). Regulus is advancing microRNA therapeutics towards the clinic in several areas including hepatitis C infection, cardiovascular disease, fibrosis, oncology, immuno-inflammatory diseases, and metabolic diseases. Regulus' intellectual property estate contains both the fundamental and core patents in the field and includes over 600 patents and more than 300 pending patent applications pertaining primarily to chemical modifications of oligonucleotides targeting microRNAs for therapeutic applications. For more information, visit http://www.regulusrx.com.

About sanofi-aventis

Sanofi-aventis, a leading global pharmaceutical company, discovers, develops and distributes therapeutic solutions to improve the lives of everyone. Sanofi-aventis is listed in Paris (EURONEXT: SAN) and in New York (NYSE: SNY). For more information, please visit: www.sanofi-aventis.com.

Forward-Looking Statement

This press release contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, as amended. Forward-looking statements are statements that are not historical facts. These statements include projections and estimates and their underlying assumptions, statements regarding plans, objectives, intentions and expectations with respect to future financial results, events, operations, services, product development and potential and statements regarding future performance. Forward-looking statements are generally identified by the words "expects," "anticipates," "believes," "intends," "estimates," "plans" and similar expressions. Although sanofi-aventis' management believes that the expectations reflected in such forward-looking statements are reasonable, investors are cautioned that forward-looking information and statements are subject to various risks and uncertainties, many of which are difficult to predict and generally beyond the control of sanofi-aventis, that could cause actual results and developments to differ materially from those expressed in, or implied or projected by, the forward-looking information and statements. These risks and uncertainties include among other things, the uncertainties inherent in research and development, future clinical data and analysis, including post marketing, decisions by regulatory authorities, such as the FDA or the EMA, regarding whether and when to approve any drug, device or biological application that may be filed for any such product candidates as well as their decisions regarding labelling and other matters that could affect the availability or commercial potential of such products candidates, the absence of guarantee that the products candidates if approved will be commercially successful, the future approval and commercial success of therapeutic alternatives, the Group's ability to benefit from external growth opportunities as well as those discussed or identified in the public filings with the SEC and the AMF made by sanofi-aventis, including those listed under "Risk Factors" and "Cautionary Statement Regarding Forward-Looking Statements" in sanofi-aventis' annual report on Form 20-F for the year ended December 31, 2009. Other than as required by applicable law, sanofi-aventis does not undertake any obligation to update or revise any forward-looking information or statements.

APPENDIX 9

Regulus Detailed Allocation of Upfront Payments

[***]

CONFIDENTIAL TREATMENT REQUESTED UNDER 17 C.F.R. §§ 200.80(B)4, AND 240.24B-2

NON-EXCLUSIVE TECHNOLOGY ALLIANCE AND OPTION AGREEMENT

between

REGULUS THERAPEUTICS INC.

and

SANOFI-AVENTIS

NON-EXCLUSIVE TECHNOLOGY ALLIANCE AND OPTION AGREEMENT

THIS NON-EXCLUSIVE TECHNOLOGY ALLIANCE AND OPTION AGREEMENT (the ***"Agreement"***) is made and entered into this June 17, 2010 (the ***"Effective Date"***), by and between **SANOFI-AVENTIS**, a French Corporation (***"Sanofi"***) having a place of business at 174 avenue de France, 75013, Paris, France and registered in the Paris Trade and Company Register under no. 395 030 844, and **REGULUS THERAPEUTICS INC.**, a Delaware Corporation (***"Regulus"***) having a place of business at 1896 Rutherford Road, Carlsbad, California 92008. Sanofi and Regulus each may be referred to herein individually as a ***"Party,"*** or collectively as the ***"Parties."***

WHEREAS, Regulus possesses certain patent rights, know-how and technology with respect to therapeutic microRNA Compounds;

WHEREAS, the Parties concurrently entered into a Collaboration and License Agreement of even date herewith (the ***"Collaboration Agreement"***);

WHEREAS, Sanofi desires to obtain from Regulus an option to obtain (i) a nonexclusive license to conduct Research on microRNA Compounds, including a technology sharing from Regulus; and (ii) an exclusive license to Develop and Commercialize a limited number of microRNA Compounds as Option Products; and

WHEREAS, Regulus desires to grant Sanofi such options, and if Sanofi exercises such options, to perform such technology sharing and grant Sanofi such licenses.

NOW, THEREFORE, in consideration of the foregoing and the mutual covenants herein contained, the Parties do hereby agree as follows.

ARTICLE 1

DEFINITIONS

The terms used in this Agreement with initial letters capitalized, whether used in the singular or the plural, will have the meaning set forth in **Appendix 1**, or if not listed in **Appendix 1**, the meaning designated in places throughout the Agreement.

ARTICLE 2

RESEARCH OPTION AND TECHNOLOGY ALLIANCE

2.1 Research Option. Subject to the terms and conditions of this Agreement, Regulus hereby grants to Sanofi the nonexclusive, nontransferable right, exercisable in accordance with this ARTICLE 2, to obtain the nonexclusive license set forth in Section 2.3 below under the terms and conditions set forth in this Agreement (the ***"Research Option"***).

2.2 Research Option Exercise. Subject to the one-time extension described in the last sentence of this Section 2.2, Sanofi may exercise the Research Option at any time prior to

5:00 PM Pacific time on the 30th day following the expiration of the third anniversary of the Effective Date (as may be adjusted per the one-time, one-year extension, the ***"Research Option Deadline"***), by (i) providing Regulus a written notice that Sanofi is exercising the Research Option prior to the Research Option Deadline; and (ii) paying Regulus the first installment of the option exercise payment set forth in Section 5.1 below. If Sanofi does not provide Regulus a written notice that Sanofi is exercising the Research Option on or before the Research Option Deadline, then the Research Option will automatically expire and become null and void. Sanofi may extend the Research Option Deadline for [***], by providing Regulus a written notice thereof and paying Regulus an irrevocable, non-creditable and nonrefundable payment of $[***] for such [***] extension, such notice must be made prior to the original Research Option Deadline, and such payment must be made no later than 10 Business Days after such notice is given. If Sanofi intends to exercise the Research Option, it will so notify Regulus in a non-binding written notice and Regulus will have [***] Business Days from its receipt of such notice (the ***"Bring Down Period"***) to deliver a schedule of exceptions (the ***"Disclosure Schedule"***) qualifying the representations and warranties (collectively, the ***"Bring Down Warranties"***) Regulus previously made in Sections 10.1 and 10.2 of this Agreement; *provided, however* that if the Research Option Deadline

would occur during the Bring Down Period and Regulus has not delivered to Sanofi the Disclosure Schedule prior to the Research Option Deadline, then the Research Option Deadline will automatically be extended to the next Business Day immediately following the expiration of the Bring Down Period. Notwithstanding anything to the contrary, if following the expiration of the Bring Down Period, Sanofi exercises its Research Option, then Regulus will be deemed to reissue, as of the end of the Bring Down Period and as qualified by the Disclosure Schedule, the Bring Down Warranties.

2.3 Research License. Effective solely upon exercise (if any) of the Research Option in accordance with Section 2.2 above (the date of such exercise, the ***"Research Option Exercise Date"***), and subject to the terms and conditions of this Agreement, Regulus hereby grants to Sanofi a worldwide, royalty-free, nonexclusive license (with the right to grant sublicenses solely to Affiliates of Sanofi) under the Regulus Platform Technology solely to Research microRNA Compounds. The license granted under this Section 2.3 will be referred to as the ***"Research License."*** For clarity, the Research License does not include the right to Develop or Commercialize microRNA Compounds, and Sanofi covenants that it will not use any Regulus Platform Technology to Develop or Commercialize microRNA Compounds except as expressly permitted by the Collaboration Agreement or in accordance with Commercial Licenses granted pursuant to this Agreement.

2.4 Technology Alliance. Commencing on the Research Option Exercise Date, Regulus and Sanofi will conduct a technology sharing program (the ***"Technology Sharing Program"***) as follows:

2.4.1 the Technology Sharing Program will begin on the Research Option Exercise Date and continue until the [***] anniversary of the Research Option Exercise Date (such period, the ***"Technology Sharing Period"***); *provided*, *however* that if Regulus does not achieve the technology sharing milestones contemplated by clauses (ii) and (iii) of Section 5.1.1 or clause (ii) of Section 5.1.2, as applicable, before sixty (60) days prior to the scheduled end of the Technology Sharing Period, then the Technology Sharing Period shall be automatically extended for additional [***] periods until the earlier of (a) the date all such technology sharing

milestones have been achieved; and (b) the [***] anniversary of the Research Option Exercise Date.

2.4.2 on a periodic basis as agreed by the Parties, and promptly following Sanofi's reasonable request from time to time, Regulus will deliver to Sanofi, for no additional consideration, all relevant Regulus Platform Technology (including Regulus Tangible Materials) that exists in recorded form (or copies thereof) and is necessary or useful for Sanofi to exercise its rights under the Research License;

2.4.3 at Sanofi's reasonable request, Regulus will collaborate with Sanofi to ensure that Sanofi can optimize Option Compounds for the Option Targets; and

2.4.4 Regulus will make its relevant scientific and technical personnel (including, but not limited to personnel from Regulus' bioinformatics, chemistry, oligonucleotide design, biology, toxicology and pharmacokinetics groups) reasonably available to Sanofi as reasonably necessary to implement the Technology Sharing Plan, and to answer any questions or provide instruction (which may include hands-on training) as reasonably requested by Sanofi concerning the items delivered pursuant to Section 2.4.2, in connection with Sanofi's Research of microRNA Compounds under the Research License.

2.5 Technology Sharing Plan.

2.5.1 Before Research Option Deadline. No later than [***] [***] prior to the Research Option Deadline, Regulus will deliver to Sanofi (i) a schedule disclosing the material terms of the Regulus Existing In-Licenses and Regulus Future In-Licenses in effect as of the date of such schedule (including any potential milestone, royalty or similar payments related to Option Compounds or Option Products under such Regulus Existing In-Licenses and Regulus Future In-Licenses) (an ***"In-License Summary"***); and (ii) a preliminary Technology Sharing Plan (consistent with the requirements of Section 2.5.2). In addition, at any time prior to the Research Option Exercise Deadline, if Sanofi is considering an exercise of the Research Option, Regulus and Sanofi will reasonably cooperate to draft a preliminary Technology Sharing Plan (consistent with the requirements of Section 2.5.2) and In-License Summary in advance of Sanofi's exercise of its Research Option, such right to be exercised no more than [***] in any [***]-month period.

2.5.2 After Research Option Exercise Date. The Parties contemplate that the bulk of the Technology Sharing Program will occur in the first [***]. Within forty-five (45) days after the Research Option Exercise Date, the Parties will update the latest technology sharing plan provided to Sanofi under Section 2.5.1, subject to mutual agreement by the Parties (the ***"Technology Sharing Plan"***). The Technology Sharing Plan will: (i) specify goals and time lines for the achievement of the technology sharing under Section 2.4; (ii) identify specific technology to be shared; (iii) specify criteria for successful achievement of the technology sharing; and (iv) assign obligations to each Party with respect to technology sharing and technical assistance. The Technology Sharing Plan may be amended from time to time through written amendments unanimously approved by both Parties' JTSC representatives.

2.6 Technology Sharing Committee. No later than thirty (30) days after the Research Option Exercise Date, the Parties will establish a Joint Technology Sharing Committee (the ***"JTSC"***) that will, during the Technology Sharing Period, oversee the activities of the Parties under the Technology Sharing Plan and facilitate the sharing of technology (and information related thereto) from Regulus to Sanofi. The JTSC will dissolve at the end of the Technology Sharing Period.

2.6.1 The JTSC will be composed of two (2) representatives designated by Regulus and two (2) representatives designated by Sanofi, *provided* that the Parties will appoint additional representatives as appropriate with respect to subject area-specific subteams. Each Party's JTSC representatives will be of the seniority and experience appropriate for service on the JTSC in light of the functions, responsibilities and authority of the JTSC. Sanofi will select from its representatives a chairperson for the JTSC. Each Party may replace any or all of its representatives on the JTSC with individual(s) of appropriate experience and seniority at any time upon written notice to the other Party. The JTSC chairperson will call a meeting of the JTSC as required by this Agreement or promptly upon the written request of either Party.

2.6.2 The JTSC will meet in person or hold video conferences once per Calendar Quarter basis until the end of the Technology Sharing Period; *provided*, that two (2) such meetings will occur in person and two (2) such meetings will occur by video conference. Meetings of the JTSC in person

will alternate between the offices of Regulus and Sanofi, or such other place as the Parties may agree, with the first such meeting for the JTSC being at Regulus' offices. The members of the JTSC also may convene or be polled or consulted from time to time by means of telecommunications, video conferences, electronic mail or correspondence, as deemed necessary or appropriate.

2.6.3 The JTSC will perform the following functions: (1) managing and overseeing the performance of the Technology Sharing Plan, (2) providing updates to the Parties regarding the Technology Sharing Plan, (3) reviewing and approving any updates, amendments or modifications to the Technology Sharing Plan, (4) developing and adopting remediation plan(s) specifically designed to address any incomplete sharing of Regulus Platform Technology, including amendments to the Technology Sharing Plan with respect to the achievement of the applicable timelines set forth therein, (5) providing an initial forum for resolving disputes arising under the Technology Sharing Plan, and (6) such other responsibilities as may be assigned to the JTSC pursuant to this Agreement or as may be mutually agreed upon by the Parties from time to time. For purposes of clarity, the JTSC will not have the authority to modify the terms of this Agreement or to take any action inconsistent with the terms of this Agreement.

2.7 End of Technology Sharing Period. Upon the expiration of the Technology Sharing Period, Regulus will not be obligated to continue to perform work under the Technology Sharing Plan.

ARTICLE 3

LIMITED OPTION TO OBTAIN COMMERCIAL LICENSE

3.1 Option Targets.

3.1.1 Designating Option Targets. At any time after the Research Option Exercise Date through the [***] anniversary of the Effective Date, Sanofi may designate a new microRNA with respect to which Sanofi would like a Commercial License (any such microRNA to which a Commercial License is granted, an ***"Option Target"***) by providing Regulus with a written notice (the ***"Request Notice"***) of the microRNA it wishes to designate as an Option Target (the ***"Proposed Target"***); *provided*, *however*, there can be no more than [***] Option Targets at any time. The Request Notice will include the microRNA name and the miRBase Accession Number and specify whether Sanofi wants to pursue such microRNA with a microRNA Antagonist or a microRNA Mimic. Within 15 Business Days of receipt of the Request Notice, Regulus will give Sanofi written notice (i) stating if any of the criteria set forth in clauses (a) through (e) below applied to such Proposed Target at the time of Regulus' receipt of the Request Notice (or otherwise confirming that such Proposed Target is available); and (ii) only if none of clauses (a) through (e) below applied to such Proposed Target at the time of Regulus' receipt of the Request Notice, disclosing all relevant Regulus In-License Agreements and prior Third Party Agreements and other potential encumbrances known by Regulus and related to the Proposed Target (***"Target Encumbrances"***). If, at such time, the Proposed Target is (a) subject to a [***]; (b) subject to [***] (and not merely an [***]) granted by Regulus to a Third Party that explicitly identifies such Proposed Target by name and prohibits Regulus from collaborating with Sanofi under this Agreement or from granting a license under Section 3.5 with respect to the Proposed Target, (c) subject to [***] has [***]; (d) identified by name and the subject of a *bona fide* [***] Regulus has [***] a Third Party [***] (*except* where Regulus has not [***] following Regulus' [***]) under [***] such Third Party either a Regulus Collaborator Exclusive Option with respect to microRNA Compounds directed to such Proposed Target, or an exclusive license to Develop and Commercialize microRNA Compounds directed to such Proposed Target, or (e) the subject of the Collaboration Agreement, then, and only then, in each case, the Proposed Target will be rejected and will not become an Option Target. If the Proposed Target is rejected, Sanofi can request another microRNA in accordance with the terms of this Section 3.1.1. If the Proposed Target is not rejected, the Proposed Target will become an Option Target; *provided*, *however*, that if the Proposed Target has any Target Encumbrances (and Regulus has disclosed such Target Encumbrances to Sanofi), before such Proposed Target can become an Option Target, Sanofi must agree in writing (within 30 days of receiving from Regulus the description of such Target Encumbrances) to assume all applicable Target Encumbrances for such Proposed Target.

3.1.2 Confidentiality. The fact that Sanofi has designated a particular microRNA an Option Target is Confidential Information of Sanofi. The fact that Regulus has rejected a particular microRNA under Section 3.1.1 and any information disclosed under an Inquiry Notice is Confidential Information of Regulus.

3.2 Commercialization Options. Subject to the terms and conditions of this Agreement, on an Option Target-by-Option Target basis, effective solely upon the Research

Option Exercise Date, Regulus hereby grants to Sanofi the nonexclusive, nontransferable right, exercisable in accordance with this ARTICLE 3, to obtain the exclusive licenses set forth in Section 3.5 below under the terms and conditions set forth in this Agreement (each a ***"Commercial Option"***). For clarity, until Regulus grants Sanofi a Commercial License with respect to a particular Option Target, Regulus may collaborate with a Third Party (including granting a license) with respect to such Option Target, and any Commercial License Regulus later grants to Sanofi with respect to such Option Target will be subject to any rights Regulus granted to such Third Party prior to Sanofi's exercise of the applicable Commercial Option. If after the Research Option Exercise Date, Sanofi reasonably believes that [***] under either the [***] or [***] fall within the definition of Regulus Platform Technology Patents and cover a Option Product being developed by Sanofi, Regulus and Sanofi will negotiate in good faith and use commercially reasonable efforts to [***] under the specific [***] that cover the Option Product solely to Research, Develop, make, have made, use, gain Approval, Commercialize, sell, offer for sale, have sold, export and import the applicable Option Compounds and Option Products.

3.3 Commercial Option Exercise. Sanofi shall be deemed to have exercised its Commercial Option with respect to any Option Target and any related Option Products when the microRNA under any Request Notice becomes an Option Target pursuant to Section 3.1.1. If Sanofi does not exercise its Commercial Option for a microRNA Antagonist or a microRNA Mimic before the [***] anniversary of the Effective Date (the ***"Commercial Option Deadline"***), then such Commercial Option will automatically expire and become null and void.

3.4 Filing of INDs. At any time, and from time to time, during the IP Period, Sanofi shall have the right to file up to a total of [***] INDs for Option Compounds (each, an "***Option IND***") that is either a microRNA Antagonist that inhibits an Option Target, or is a microRNA Mimic that mimics Option Targets. Any product which contains an Option Compound that is the subject of an Option IND shall herein be referred to as an "***Option Product***".

3.5 Commercial License. Effective solely upon exercise of the Commercial Option in accordance with Section 3.3 above, and subject to the terms and conditions of this Agreement Regulus will grant to Sanofi a worldwide, royalty-bearing, exclusive license, with the right to grant sublicenses as set forth in Section 3.7 below, under the Regulus Platform Technology to Research, Develop, make, have made, use, gain Approval, Commercialize, sell, offer for sale, have sold, export and import Option Compounds and Option Products. Each license granted under this Section 3.5 will be referred to as a ***"Commercial License."***

3.6 Term of the Commercial Licenses. Except as set forth in the immediately following sentence, each Commercial License shall automatically expire on the [***] anniversary of the Effective Date. Solely to the extent necessary to Develop and Commercialize Option Products, each Commercial License or portion thereof, shall survive beyond the [***] anniversary of the Effective Date and continue unless and until otherwise terminated pursuant to ARTICLE 8.

3.7 Sublicenses. The licenses granted to Sanofi under Section 3.5 are fully sublicensable to any Affiliate of Sanofi, and only sublicensable to a Third Party in connection with a sublicense of an Option Compound or Option Product for the continued Research,

Development and Commercialization of such Option Compound or Option Product in accordance with the terms of this Agreement. If Sanofi sublicenses any Commercial License to a Third Party, then Sanofi shall pay Regulus a non-refundable royalty of [***] of any Sanofi Licensing Revenues received by Sanofi from any Third Party. For purposes of this Agreement, ***"Sanofi Licensing Revenues"*** will mean any payments that Sanofi receives from a Third Party in consideration of a license (or sublicense) to further the Development and Commercialization of an Option Compound or Option Product, in each case including, but not limited to, upfront payments, license fees, regulatory or sales milestone payments, royalties and/or profit sharing payments, but *excluding*: (i) payments made in consideration of Sanofi's equity or debt securities (except to the extent such payments exceed the fair market value of such securities upon date of receipt), (ii) payments to reimburse Sanofi for the out-of-pocket costs and expenses of research and development, and (iii) payments to reimburse Sanofi for patent prosecution costs and expenses.

3.8 Exclusivity Covenants.

3.8.1 Regulus Exclusivity Covenant. On an Option Target-by-Option Target basis, so long as the applicable Commercial License granted to Sanofi under Section 3.5 is in effect, Regulus agrees that it will not practice the Regulus Platform Technology or inventions claimed within Sanofi Blocking Patents to work independently of this Agreement for itself or any Third Party (including the grant of any license to any Third Party under the Regulus Platform Technology or Sanofi Blocking Patents) to discover, Research, Develop and/or Commercialize (i) with respect to Option Targets that are the subject of a Commercial License under Section 3.5 where the applicable Option Product contains a microRNA Antagonist, microRNA Compounds that [***] such Option Target; and (ii) with respect to Option Targets that are the subject of a Commercial License under Section 3.5 where the applicable Option Product contains a microRNA Mimic, microRNA Compounds with a [***] as the applicable Option Target that are [***] such Option Target. Notwithstanding any other provision of this Agreement, Regulus retains the right to grant Permitted Licenses.

3.8.2 Sanofi Exclusivity Covenant. On a Regulus Target-by-Regulus Target basis, during the Technology Sharing Period and thereafter during the Term, Sanofi agrees that it will not practice the Regulus Platform Technology, Regulus Collaborator Blocking Technology or inventions claimed within Sanofi Blocking Patents or to work independently of this Agreement for itself or any Third Party (including the grant of any license to any Third Party under the Regulus Platform Technology, Regulus Collaborator Blocking Technology or Sanofi Blocking Patents) to discover, Research, Develop and/or Commercialize (i) with respect to Regulus Targets where the applicable Regulus Product contains a microRNA Antagonist, microRNA Compounds that [***] such Regulus Target; and (ii) with respect to Regulus Targets where the applicable Regulus Product contains a microRNA Mimic, microRNA Compounds with a [***] as the applicable Regulus Target that are [***] such Regulus Target. For purposes of this Agreement, ***"Regulus Product"*** means any product that contains a microRNA Compound as an active pharmaceutical ingredient, that Regulus is Developing and/or Commercializing pursuant to [***] (whether on its own or in collaboration with or under a license with a Third Party). For purposes of this Agreement, ***"Regulus Target"*** means (i) with respect to a Regulus Product that is a microRNA Antagonist, the microRNA that is inhibited by such Regulus

Product; or (ii) with respect to a Regulus Product that is a microRNA Mimic, the microRNA that is mimicked by such Regulus Product.

ARTICLE 4

LIMITATIONS ON LICENSES

4.1 License Conditions; Limitations.

4.1.1 Sanofi will use Commercially Reasonable Efforts to Develop and Commercialize the applicable Option Compound and Option Product.

4.1.2 The Research License is subject to and limited by the Prior Third Party Agreements as listed in **Appendix 5** attached hereto. From time to time, on or before the Research Option Deadline, Regulus shall be free to enter into license and/or collaboration agreements with Third Parties with respect to Regulus Platform Technology on a product-by-product or target-by-target basis; *provided, however,* that Regulus shall not grant to any Third Party any [***] (such as [***]) with respect to Regulus Platform Technology, unless either (a) such [***] on or before the Research Option Deadline, or (b) the Research License, each Commercial License, and subject to Section 3.1.1, Sanofi's right to obtain Commercial Licenses are excluded from Regulus' [***]. From time to time, on or before the Research Option Deadline, Regulus may update **Appendix 5** to include any license and/or collaboration agreement entered into by Regulus and any Third Party as permitted by this Section 4.1.2, by providing written notice to Sanofi.

4.1.3 Each Commercial License and the exclusivity covenants under Section 3.8.1 are subject to and limited by the Prior Third Party Agreements listed in **Appendix 6** attached hereto. From time to time during the Term, Regulus shall be free to enter into license and/or collaboration agreements with Third Parties with respect to Regulus Platform Technology on a product-by-product or target-by-target basis; *provided, however,* that Regulus shall not grant to any Third Party any [***] (such as [***]) with respect to Regulus Platform Technology, unless either (a) such [***] on or before

the Research Option Deadline, or (b) the Research License, each Commercial License, and subject to Section 3.1.1, Sanofi's right to obtain Commercial Licenses are excluded from Regulus' [***]. From time to time on or before the Commercial Option Deadline, Regulus may update **Appendix 6** to include any license and/or collaboration agreement entered into by Regulus and any Third Party as permitted by this Section 4.1.3 by providing written notice to Sanofi.

4.1.4 Without limiting this Article 4, Regulus' ability to grant Sanofi the Research License or any Commercial License with respect to [***] is limited by, and subject to, the terms of the Founding Company License Agreement solely to the extent Regulus has, prior to the Effective Date, provided Sanofi the provisions of such agreements in unredacted form. Regulus will use commercially reasonable efforts (and will exercise its rights under the Founding Company License Agreement) to secure the right to grant Sanofi the Research License or any Commercial License with respect to Option Compounds that are [***] to the fullest extent contemplated by this Agreement.

4.1.5 Notwithstanding Section 3.5 and Section 3.8.1, Regulus retains the right to grant Permitted Licenses.

4.1.6 Certain of the Regulus Platform Technology that may be licensed to Sanofi under Section 2.3 or 3.5 will have been in-licensed or acquired by Regulus under the Regulus Future In-License Agreements (such Regulus Platform Technology, the ***"Regulus Future In-Licensed Technology"***), and certain milestone and/or royalty payments may become payable by Regulus to such Third Parties under such license or purchase agreements based on the Research, Development and/or Commercialization of an Option Compound and/or Option Product by Sanofi under this Agreement. The Parties acknowledge that whether a milestone and/or royalty payment becomes payable by Regulus to such Third Party licensor depends on the terms and conditions of the Regulus Future In-License Agreement. If Sanofi wishes to include any Regulus Future In-Licensed Technology as part of the licenses granted by Regulus under Section 2.3 or 3.5, Sanofi will notify Regulus of its desire to do so and the Parties will [***] upfront payments or ongoing payment obligations [***] and [***] that are [***] and other Regulus licensees, if appropriate. As part of this [***], Regulus will share with Sanofi, in reasonable detail, the [***] Regulus used to [***]. [***] does not [***]to Option Compound and Option Products, and to be responsible for the [***] of any [***] to Option Compound and Option Products, then the applicable Regulus Future In-licensed Patents will [***].

4.1.7 After the Effective Date, Regulus will not enter into any Regulus Future In-License Agreements that (i) treat Sanofi differently than Regulus' other partners who are Developing and Commercializing microRNA compounds under license from, or in collaboration with, Regulus; or (ii) contain obligations that would have a material adverse effect on Option Compounds or Option Products and that are [***] that are in effect on the Effective Date.

ARTICLE 5

FINANCIAL PROVISIONS.

5.1 Research Option Exercise. In partial consideration for the licenses and other rights granted under this Agreement, as a condition to exercise of the Research Option, Sanofi will pay Regulus an irrevocable, non-creditable and nonrefundable option exercise fee as follows:

5.1.1 If Sanofi exercises the Research Option before 5:00 PM Pacific time on the 30th day following the expiration of the third anniversary of the Effective Date, the option exercise fee will be $[***], which will be payable in installments as follows: (i) $[***] of such fee is payable within ten Business Days following the Research Option Exercise Date; (ii) subject to the successful achievement of the relevant technology sharing milestones as set forth in the Technology Sharing Plan, $[***] of such fee is payable within ten (10) Business Days of the first anniversary of the Research Option Exercise Date; and (iii) subject to the successful achievement of the relevant technology sharing milestones as set forth in the Technology Sharing Plan, the remaining $[***] of such fee is payable within ten (10) Business Days of the second anniversary of the Research Option Exercise Date; or

5.1.2 If, in compliance with 2.2, Sanofi exercises the Research Option after 5:00 PM Pacific time on the 30th day following the expiration of the third anniversary of the Effective Date, the option exercise fee will be $[***], which will be payable in installments as follows: (i) $[***] of such fee is payable within ten Business Days following the Research Option Exercise Date; and (ii) subject to the successful achievement of the relevant technology sharing milestones as set forth in the Technology Sharing Plan, $[***] of such fee is payable within ten (10) Business Days of the first anniversary of the Research Option Exercise Date.

5.2 Royalties. Subject to the other provisions of this Agreement, Sanofi will pay to Regulus a royalty of [***]% (as adjusted per Section 5.3, the ***"Royalty Rate"***) on Net Sales of each Option Product during the applicable Royalty Term. Royalties payable under this Section 5.2 will be payable for each Option Product on an Option Product-by-Option Product and country-by-country basis until the date that is the [***] of (i) [***] years after the First Commercial Sale of the Option Product in such country or (ii) the expiration of the last to expire Valid Claim within the Regulus Platform Technology Patents which would be infringed by the sale of the applicable Option Product in the applicable country by an unauthorized party. In addition, to the extent Sanofi has [***] (collectively, the ***"[***]"***), Sanofi will pay Regulus such financial obligations in addition to the royalties set forth in this Section 5.2. Such period during which royalties are payable with respect to an Option Product in a country, including giving effect to any cessation due to Generic Products as described in Section 5.3, is referred to herein as the "***Royalty Term***" for such Option Product in such country; *provided however* that Sanofi will be required to pay any Sanofi Supported Obligations to the extent such Sanofi Supported Obligations extend past the Royalty Term. Regulus will be solely responsible for [***]% of any payments due under the Regulus Existing In-Licenses in relation to the Development and Commercialization of Option Products by Sanofi under this Agreement.

5.3 Generic Competition. Notwithstanding anything to the contrary, if a Generic Product corresponding to an Option Product is launched in a particular country and the Percentage Reduction of Net Sales is greater than [***] for any given Calendar Quarter, then the Royalty Rate will be reduced to [***]. As used herein, the "***Percentage Reduction of Net Sales***" for any particular Calendar Quarter means the quotient (expressed as a percentage) obtained by dividing (A) the difference obtained by subtracting [***] such applicable Calendar Quarter from the [***] by (B) the [***]. Notwithstanding the foregoing, to the extent that, after the [***] to the extent so [***].

5.4 [***] Milestone. On an Option Product-by-Option Product basis, Sanofi will give Regulus written notice within thirty (30) days of receiving the [***]. After receiving such written notice Regulus shall submit an invoice to Sanofi for $[***], and Sanofi will pay Regulus such amount within ten (10) Business Days after receipt of such invoice from Regulus. For each Option Product such $[***] milestone payment by Sanofi to Regulus will only be triggered by the first [***] by Sanofi, its sublicensees or their respective Affiliates by each Option Product.

5.5 Royalty Report and Payment. During the Royalty Term following the First Commercial Sale of any Option Product, within [***] after the end of each Calendar Quarter,

Sanofi will provide Regulus with a royalty report for such Quarter showing, on an Option Product-by-Option Product and country-by-country basis:

(a) the Net Sales of Option Products sold by Sanofi, its sublicensees and their respective Affiliates during such Calendar Quarter reporting period;

(b) the royalties which will have accrued hereunder with respect to such Net Sales;

(c) any adjustment for Generic Products under Section 5.3; and

(d) any other information related to the calculation of Net Sales of Option Products reasonably requested by Regulus that (i) is contained in a report and format that is regularly generated by Sanofi's accounting department in its normal course of business and (ii) is reasonably necessary for Regulus to comply with a Regulus Existing In-License Agreement or Regulus Future In-License Agreement.

Sanofi will keep, and will require its sublicensees and their respective Affiliates to keep, complete, true and accurate books of account and records for the purpose of determining the payments to be made under this Agreement. Upon reasonable request by Regulus (but no more frequently than [***] in any [***]-month period), Sanofi will report to Regulus the quantity of Option Product not subject to royalties distributed by Sanofi, its Affiliates or sublicensees as part of an expanded access program to include compassionate use, named patients or other similar use or as part of Phase 4 Trials or as bona fide samples. All information disclosed by Sanofi to Regulus under this Section 5.5 will be Sanofi Confidential Information.

5.6 Manner of Payment and Exchange Rate. Except as otherwise provided in this Agreement, Regulus shall invoice Sanofi for all milestone, royalty and other payments hereunder and Sanofi shall pay all such milestone, royalty and other payments that are due within ten (10) Business Days after the receipt of the applicable invoice. All payments to be made by Sanofi to Regulus hereunder will be made by deposit of U.S. Dollars by wire transfer in immediately available funds in the requisite amount to such bank account Regulus may from time to time designate by notice to Sanofi. For sales that were made in a currency other than U.S. Dollars, such amounts will be converted into U.S. Dollars using the average exchange rates as calculated and utilized by Sanofi's group reporting system and published accounts for the applicable royalty period. All invoices to be provided by Regulus to Sanofi under this Agreement shall include a breakdown of the goods, services and/or activities for which payment is due, as well is payment instructions and shall be sent by express courier service to:

Sanofi-Aventis
Direction Comptable Holding
174 avenue de France
75013 Paris
France

5.7 Audits, including Audits of Royalty Reports.

5.7.1 Audits of Royalty Reports. Upon the written request of Regulus and not more than once in each Calendar Year, Sanofi will permit an independent certified public accounting firm of nationally recognized standing selected by Regulus and reasonably acceptable to Sanofi, at Regulus' expense to have access during normal business hours to such records of Sanofi and/or its Affiliates as may be reasonably necessary to verify the accuracy of the royalty reports hereunder for any Calendar Year ending not more than [***] months prior to the date of such request. These audit rights (but not any obligation to pay unpaid royalties for such periods) with respect to any Calendar Year will terminate [***] years after the end of such Calendar Year. Regulus will provide Sanofi with a copy of the accounting firm's written report within 30 days of completion of such report.

5.7.2 If such accounting firm concludes that an overpayment or underpayment was made, then the owing Party will pay the amount due within 30 days of the date Regulus delivers to Sanofi such accounting firm's written report so correctly concluding. Regulus will bear the full cost of such audit unless such audit correctly discloses that the additional payment payable by Sanofi for the audited period is more than 5% of the amount of the royalties paid for that audited period, in which case Sanofi will pay the reasonable fees and expenses charged by the accounting firm.

5.7.3 Sanofi will use commercially reasonable efforts to include in each sublicense granted by it to any sublicensee a provision requiring the sublicensee to maintain records of sales made pursuant to such license and to grant access to such records by Sanofi's independent accountant to the same extent and under substantially similar obligations as required of Sanofi under this Agreement. Sanofi will advise Regulus in advance of each audit of any sublicensee with respect to Product sales. Sanofi will provide Regulus with a summary of the results received from the audit and, if Regulus so requests, a copy of the audit report with respect to Product sales. Sanofi will pay the reasonable fees and expenses charged by the accounting firm, except that Regulus will pay for all additional services requested exclusively by Regulus from Sanofi's independent accountant unless the audit discloses that the additional payments payable to Regulus for the audited period differ by more than 5% from the amount of the royalties otherwise paid.

5.7.4 All financial information subject to review under this Section or under any license agreement with a sublicensee will be Sanofi Confidential Information and will be treated in accordance with the confidentiality provisions of this Agreement. As a condition precedent to Regulus' audit rights under this Section, Regulus' accounting firm will enter into a confidentiality agreement with Sanofi obligating it to treat all such financial information in confidence pursuant to such confidentiality agreement. Regulus may provide Third Parties to which Regulus owes royalties on Products information in

such audit report that are relevant and required to comply with such Third Party's audit rights under the applicable license agreement between Regulus and such Third Party, *provided* that such Third Party agrees in writing to keep such information confidential under terms no less restrictive than Regulus' obligations of confidentiality under this Agreement.

5.8 Interest. If Sanofi fails to make any payment due to Regulus under this Agreement, then interest will accrue on a daily basis at the greater of an annual rate equal to the 1 month LIBOR Rate plus 1% (or such lower interest rate to the extent necessary to comply with Applicable Law).

5.9 Taxes.

5.9.1 Sanofi will make all payments to Regulus under this Agreement without deduction or withholding for taxes except to the extent that any such deduction or withholding is required by Applicable Law in effect at the time of payment.

5.9.2 Sanofi will promptly pay on behalf of Regulus any tax required to be withheld on amounts payable under this Agreement to the appropriate governmental authority, and Sanofi will furnish Regulus with proof of payment of such tax. Any such tax required to be withheld will be an expense of and borne by Regulus.

5.9.3 Sanofi and Regulus will cooperate with respect to all documentation required by any taxing authority or reasonably requested by Sanofi to secure a reduction in the rate of applicable withholding taxes.

ARTICLE 6

CONFIDENTIALITY; PRESS RELEASES & PUBLICATIONS

6.1 Confidentiality; Exceptions. Except to the extent expressly authorized by this Agreement or otherwise agreed in writing, the Parties agree that, during the Term and for five (5) 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 Know-How or other confidential and proprietary information and materials, patentable or otherwise, in any form (written, oral, photographic, electronic, magnetic, or otherwise) which is disclosed to it by the other Party (the ***"Disclosing Party"***) or its Affiliates or otherwise received or accessed by a Receiving Party in the course of performing its obligations or exercising its rights under this Agreement, including, but not limited to, 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 (collectively, ***"Confidential Information"***), except to the extent that it can be established by the Receiving Party that such Confidential Information:

6.1.1 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;

6.1.2 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;

6.1.3 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

6.1.4 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.

6.2 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) with respect to any such disclosure of Confidential Information, under confidentiality provisions no less restrictive than those in this Agreement, and solely in connection with the performance of its obligations or exercise of rights granted or reserved in this Agreement (including, without limitation, the rights to Develop and Commercialize Option Compounds and/or Option Products under Section 3.3, and to grant licenses and sublicenses hereunder), *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 with such Receiving Party if such Receiving Party has used reasonable efforts to impose such requirement without success and disclosure to such governmental entity or agency is necessary for the performance of the Receiving Party's obligations hereunder; (ii) to the extent such disclosure is reasonably necessary in filing or prosecuting patent, copyright and trademark applications, complying with applicable governmental regulations, obtaining Approvals, conducting clinical trials, marketing Option Products, 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, for example, but without limitation, in the event of a medical emergency, 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, arm's length financial 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 and only to the extent that 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) to prosecute or defend litigation as permitted by this Agreement or (vi) to the extent mutually agreed to in writing by the Parties.

6.3 Press Release; Disclosure of Agreement. The Parties agree that the public announcement of the execution of this Agreement will be made by individual press releases issued by each Party and will not be made in a joint press release. Except to the extent required to comply with applicable law, regulation, rule or legal process or as otherwise permitted in accordance with this Section 6.3, neither Party nor such Party's Affiliates will make any public

announcements, press releases or other public disclosures concerning this Agreement or the terms or the subject matter hereof without the prior written consent of the other, which will not be unreasonably withheld. Each Party will give the other Party a reasonable opportunity (to the

extent consistent with law) 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, including without limitation the provisions of this Agreement for which confidential treatment should be sought.

6.4 Remedies. Each Party will be entitled to seek, in addition to any other right or remedy it may have, at law or in equity, a temporary injunction, without the posting of any bond or other security, enjoining or restraining the other Party from any violation or threatened violation of this Article 6.

6.5 Acknowledgment. Unless otherwise agreed upon in writing by the Parties, each Party will acknowledge in any press release, public presentation or publication regarding an Option Target, Option Compound and/or Option Product, the other Party's role in discovering and developing the Option Target, Option Compound or Option Product, as applicable, and that such Option Targets, Option Compounds or Option Products are under license from Regulus (including, if requested by Regulus, Regulus' stock ticker) and otherwise acknowledge the contributions from the other Party.

ARTICLE 7

PATENTS

7.1 CREATE Act. Notwithstanding anything to the contrary in this Article 7, neither Party will have the right to make an election under the Cooperative Research and Technology Enhancement Act of 2004, 35 U.S.C. § 103(c)(2)-(c)(3) (the ***"CREATE Act"***) when exercising its rights under this Article 7 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.

7.2 Filing, Prosecution and Maintenance of Patents. Except as otherwise may be agreed pursuant to any written agreement between the Parties, each Party will have the sole right, at its cost and expense and at its sole discretion, to prepare, file, prosecute (including, without limitation, to control any interferences, reissue proceedings, oppositions and reexaminations), maintain, enforce and defend throughout the world any Patents solely owned or Controlled by such Party, including, with respect to Regulus, the Regulus Platform Technology Patents, provided however, that Sanofi will have the right to prepare, file, prosecute (including, without limitation, to control any interferences, reissue proceedings, oppositions and reexaminations), maintain, enforce and defend throughout the world the Regulus Platform Technology Patents, solely to the extent that Sanofi possesses such rights pursuant to the Collaboration Agreement.

7.3 No Challenge. As a material inducement for entering into this Agreement, Sanofi covenants to Regulus that during the Term, solely with respect to claims within the Regulus Platform Technology Patents that are included in the options or license granted to Sanofi under Article 2 or Article 3, Sanofi, its Affiliates or sublicensees will not (a) commence or otherwise voluntarily determine to participate in (other than as may be necessary or reasonably required to

respond to a court request or order or administrative law request or order) any action or proceeding, challenging or denying the validity of any claim within an issued patent or patent application within the Regulus Platform Technology Patents, or (b) direct, support or actively assist any other Person (other than as may be necessary or reasonably required 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 the Regulus Platform Technology Patents. For purposes of clarification, any breach of this Section 7.3 will be a material breach of this Agreement and will be grounds for termination by Regulus of this Agreement under Section 8.3.

7.4 Unblocking License.

7.4.1 Subject to Section 7.4.2, Sanofi hereby grants Regulus a worldwide, royalty-free, nonexclusive license, with the right to grant sublicenses, under any Sanofi Blocking Patent to Research, Develop, make, have made, use, gain Approval, Commercialize, sell, offer for sale, have sold, export and import microRNA Compounds that are neither Licensed Compounds under the Collaboration Agreement nor Option Compounds being Developed or Commercialized by Sanofi under this Agreement (***"Regulus Collaborator Compounds"***). The license granted pursuant to this Section 7.4.1 is hereinafter referred to as the ***"Unblocking License"***.

7.4.2 The sublicense of any Unblocking License to any Regulus Collaborator will be [***] if (i) Regulus' sublicense agreement with such Regulus Collaborator would permit [***] to Sanofi of any of such Regulus Collaborator's Regulus Collaborator Blocking Technology [***] and otherwise under substantially similar terms and conditions in all material respects as the Unblocking License granted by Sanofi under this Agreement, (ii) Regulus remains responsible to Sanofi for the performance of Regulus' obligations with respect to the Sanofi Blocking Patents under this Agreement (either directly by Regulus or by the Regulus Collaborator), and (iii) Regulus provides to Sanofi a copy of such sublicense (and/or the applicable license agreement with such Regulus Collaborator) solely to the extent reasonably necessary to demonstrate the satisfaction of the condition in subsection (i) above and a written confirmation by the Regulus Collaborator that it agrees to be bound by the terms and conditions of this Agreement that are applicable to the Sanofi Blocking Patents.

7.4.3 If the sublicense of any Unblocking License does not meet the requirements of Section 7.4.2, then Regulus will pay to Sanofi a [***] royalty on annual worldwide Calendar Year Net Sales by such Regulus Collaborator or its Affiliates or sublicensees of products containing any Regulus Collaborator Compound the sale of which is covered by the Sanofi Blocking Patents (***"Regulus Collaborator Products"***). Royalties payable under this Section 7.4.3 will be payable for each Regulus Collaborator Product on a product-by-product and country-by-country basis until the date that is the later of (i) [***] years after the first commercial sale of such product in such country and (ii) the expiration of the last to expire Valid Claim within the Sanofi

Blocking Patents which would be infringed by the sale of such product in the applicable country by an unauthorized party; in each case, in accordance with the terms of Sections 5.3 through 5.8, *mutatis mutandis*.

ARTICLE 8

TERM AND TERMINATION

8.1 Term. The term of this Agreement (the ***"Term"***) commences upon the Effective Date and, unless earlier terminated in accordance with the provisions of this Article 8, this Agreement will continue until: (a) the Research Option Deadline, unless Sanofi exercises the Research Option prior to the Research Option Deadline; or (b) if Sanofi exercises the Research Option prior to the Research Option Deadline, the later of the expiration of all Sanofi payment obligations to Regulus or Regulus payment obligations to Sanofi.

8.2 Sanofi Right to Terminate. Sanofi may terminate this Agreement (including its license rights under this Agreement) in full, or on an Option Product-by-Option Product basis, effective upon 30 calendar days prior written notice.

8.3 Material Breach.

(a) If either Party believes that the other is in material breach of this Agreement, then the non-breaching Party may deliver notice of such breach to the other Party. In such notice the non-breaching Party will identify the actions or conduct that it wishes such Party to take for an acceptable and prompt cure of such breach (or will otherwise state its good faith belief that such breach is incurable); *provided* that such identified actions or conduct will not be binding upon the other Party with respect to the actions that it may need to take to cure such breach. If the breach is curable, the allegedly breaching Party will have [***] days to either cure such breach (except to the extent such breach involves the failure to make a payment when due, which breach must be cured within thirty (30) days following such notice) or, if a cure cannot be reasonably effected within such [***] day period, to deliver to the non-breaching Party a plan for curing such breach which is reasonably sufficient to effect a cure within a reasonable period. If the breaching Party fails to (i) cure such breach within the [***] day period (or 30 day as applicable) or (ii) use Commercially Reasonable Efforts to carry out the plan and cure the breach, the non-breaching Party may terminate this Agreement on an Option Target-by-Option Target basis or Option Product-by-Option Product basis by providing written notice to the breaching Party.

(b) Notwithstanding the foregoing, if the allegedly breaching Party 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 (the ***"Other Party"***) of such dispute within such [***] day period, the Other Party will not have the right to terminate this Agreement in accordance with this Section 8.3 unless and until it has been determined in accordance with Section 11.4 that this Agreement was materially breached by the allegedly breaching Party and that Party fails to cure such breach within [***] days following such determination. It is understood and acknowledged that during the pendency of such a dispute, all of the terms and conditions of this Agreement will remain in effect and the Parties will continue to perform all of their respective obligations hereunder.

(c) Using the same procedures set forth in paragraphs (a) and (b) of this Section 8.3, Regulus may terminate this Agreement if Regulus exercises its termination right

under the Collaboration Agreement for Sanofi's uncured material breach of the Collaboration Agreement.

8.4 Consequences of Termination.

8.4.1 Options and Licenses. Upon termination of this Agreement in its entirety (or in part with respect to an Option Product) by either Party pursuant to this Article 8, the options and licenses granted by Regulus to Sanofi hereunder with respect to the Option Products that were the subject of such termination will terminate. Upon termination of this Agreement with respect to an Option Target or an Option Product pursuant to this Article 8, the options and licenses granted by Regulus to Sanofi hereunder with respect to such Option Targets, associated Option Compounds and Option Products will terminate.

8.4.2 Return of Information and Materials. Upon termination of this Agreement in its entirety (or on an Option Target or Option Product basis) by either Party pursuant to this Article 8, 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 that is related to the Option Target(s) or Option Product(s) that were the subject of such termination. Notwithstanding the foregoing, the Parties will be permitted to retain one copy of such data, files, records, and other materials for archival purposes.

8.5 Accrued Rights; Surviving Obligations.

8.5.1 Accrued Rights. Termination or expiration 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 or expiration. Such termination or expiration will not relieve a Party from obligations that are expressly indicated to survive the termination or expiration of this Agreement. For clarification, if Sanofi exercises the Research Option under Article 2, Sanofi's obligation to pay the full $[***] option exercise fee under Section 5.1 will have accrued as of the Research Option Exercise Date, and no termination under this Agreement after the Research Option Exercise Date will relieve Sanofi of its obligation to pay the full $[***] option exercise fee under Section 5.1.

8.5.2 Survival. Articles 6, 9, and 11 and Sections 5.7, 5.8, 7.4, 8.4, 8.5, 8.6, 8.7, 8.8 and 10.4 of this Agreement will survive expiration or termination of this Agreement for any reason.

8.6 Rights in Bankruptcy. All rights, options, and licenses granted under or pursuant to this Agreement by Regulus or Sanofi are, and will otherwise be deemed to be, for purposes of Section 365(n) of the U.S. Bankruptcy Code (*i.e.*, Title 11 of the U.S. Code) or analogous provisions of

Applicable Law outside the United States, licenses of rights to "intellectual property" as defined under Section 101 of the U.S. Bankruptcy Code or analogous provisions of Applicable Law outside the United States. The Parties agree that each Party, as licensee of such rights under this Agreement, will retain and may fully exercise all of its rights and elections under the U.S. Bankruptcy Code or any other provisions of Applicable Law outside the United States that provide similar protection for 'intellectual property.' The Parties further agree that, in the event of the commencement of a bankruptcy proceeding by or against a Party

under the U.S. Bankruptcy Code or analogous provisions of Applicable Law outside the United States, the Party that is not subject to such proceeding will be entitled to a complete duplicate of (or complete access to, as appropriate) such intellectual property and all embodiments of such intellectual property, which, if not already in the non subject Party's possession, will be promptly delivered to it upon the non subject Party's written request therefor. Any agreements supplemental hereto will be deemed to be "agreements supplementary to" this Agreement for purposes of Section 365(n) of the U.S. Bankruptcy Code.

8.7 Regulus Opt-In Rights.

8.7.1 If Sanofi terminates the Agreement under Section 8.2, Regulus may continue to Develop and Commercialize any Option Compound or Option Product that is the subject of such termination (a ***"Discontinued Product"***). If Regulus provides a notice in writing to Sanofi within 90 days of such termination (an ***"Election Notice"***) that Regulus is exercising its rights under this Section 8.7.1, Sanofi will, subject to Regulus' payment obligations in Section 8.7.2: (i) grant to Regulus a sublicensable, worldwide license or sublicense, as the case may be, to all [***] Controlled by Sanofi as of the date of the Election Notice solely as they are necessary to make, have made, use, sell, offer for sale, have sold and import Discontinued Products, (ii) transfer to Regulus, for Regulus' use with respect to the Development and Commercialization of the Discontinued Products, any data, results, regulatory information and files in the possession of Sanofi as of the date of the Election Notice that relate to such Discontinued Products, and (iii) [***] and [***] to Regulus [***] with respect to such Discontinued Product (including but not limited to [***] for Regulus, and [***] Regulus to [***], any [***] with a [***] related to such Discontinued Product).

8.7.2 Regulus Payment Obligations for Opt-In Rights. If Regulus provides an Election Notice for any Discontinued Product which has [***], then Regulus shall pay to Sanofi a non-refundable royalty of (i) [***] of any Regulus Licensing Revenues received by Regulus from a Third Party in consideration for licensing such Discontinued Product to such Third Party; or (ii) if Regulus is Developing and Commercializing such Discontinued Product on its own or through an Affiliate, a royalty equal to [***]% of the Net Sales of such Discontinued Product made through Regulus or any of its Affiliates with the provisions of Section 5.3 through 5.8 applying *mutatis mutandis*. For purposes of this Agreement, ***"Regulus Licensing Revenues"*** will mean any payments that Regulus receives from a Third Party in consideration of a license (or sublicense) to further the Development and Commercialization of a Discontinued Product, in each case including, but not limited to, upfront payments, license fees, regulatory or sales milestone payments, royalties and/or profit sharing payments, but excluding: (i) payments made in consideration of Regulus' equity or debt securities (except to the extent such payments exceed the fair market value of such securities upon date of receipt), (ii) payments to reimburse Regulus for the out-of-pocket costs and expenses of research and development, and (iii) payments to reimburse Regulus for patent prosecution costs and expenses.

8.8 Regulus Right of First Negotiation. If Sanofi has a good-faith desire to grant any Third any right to Develop or Commercializing an Option Compound or Option Product, then Sanofi will promptly (but in any case within thirty (30) days) provide written notice to Regulus, and Sanofi will promptly deliver to Regulus evaluation materials reasonably relevant to the Option Compound or Option Product and no less than those materials provided to applicable

Third Parties. Regulus will then have forty-five (45) days to notify Sanofi in writing whether Regulus desires to take a license from Sanofi to Develop and Commercialize the applicable Option Compound and Option Product. If Regulus provides Sanofi with timely written notice that Regulus desires to take a license from Sanofi to Develop and Commercialize the applicable Option Compound and Option Product, then Regulus and Sanofi will, in good faith, use commercially reasonable efforts to conclude a written collaboration and license agreement within one hundred twenty (120) days. If Regulus fails to timely notify Sanofi that Regulus desires to take a license from Sanofi to Develop and Commercialize the applicable Option Compound and Option Product, or if despite good-faith commercially reasonable efforts Regulus and Sanofi are unable to reach an agreement within one hundred twenty (120) days after Regulus' receipt of such notice from Sanofi, then Sanofi may enter into a collaboration and license agreement with any Third Party with respect to the applicable Option Compound and Option Product on economic terms which, when taken as a whole, are no more favorable to any such Third Party than the terms last offered under this right of first negotiation by Sanofi to Regulus.

ARTICLE 9

INDEMNIFICATION, INSURANCE AND LIMITATION OF LIABILITY

9.1 Indemnification of Regulus. Sanofi agrees to defend Regulus, its Affiliates and their respective directors, officers, stockholders, employees and agents, and their respective successors, heirs and assigns (collectively, the ***"Regulus Indemnitees"***), and will indemnify and hold harmless the Regulus 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 Regulus Indemnitee and resulting from or occurring as a result of: (a) the Development, manufacture, use, handling, storage, sale or other Commercialization or disposition of any Option Compound or Option Product in the Territory by Sanofi or its Affiliates, sublicensees or contractors, (b) any breach by Sanofi of any of its representations, warranties or covenants pursuant to this Agreement or (c) the negligence or willful misconduct of Sanofi or any Sanofi Affiliate or sublicensee in connection with this Agreement; *except* in any such case to the extent such Losses result from: (i) the negligence or willful misconduct of any Regulus Indemnitee, (ii) any breach by Regulus of any of its representations, warranties, covenants or obligations pursuant to this Agreement, or (iii) any breach of Applicable Law by any Regulus Indemnitee.

9.2 Indemnification of Sanofi. Regulus agrees to defend Sanofi, its Affiliates and their respective directors, officers, stockholders, employees and agents, and their respective successors, heirs and assigns (collectively, the ***"Sanofi Indemnitees"***), and will indemnify and hold harmless the Sanofi Indemnitees, from and against any Losses and Third Party Claims brought against any Sanofi Indemnitee and resulting from or occurring as a result of: (a) any activities conducted by a Regulus employee, consultant or (sub)contractor in effecting a Sanofi request pursuant to Section 2.4.3; (b) any breach by

Regulus of any of its representations, warranties or covenants pursuant to this Agreement; or (c) the negligence or willful misconduct of any Regulus Indemnitee or any (sub)contractor of Sanofi in connection with this Agreement; *except* in any such case to the extent such Losses result from: (i) the negligence or willful

misconduct of any Sanofi Indemnitee, (ii) any breach by Sanofi of any of its representations, warranties, covenants or obligations pursuant to this Agreement, or (iii) any breach of Applicable Law by any Sanofi Indemnitee.

9.3 Notice of Claim. All indemnification claims provided for in Sections 9.1 and 9.2 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 9.1 or 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 calendar 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 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 (i) the employment thereof has been specifically authorized by the indemnifying Party in writing, (ii) 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 (iii) 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 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 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 Regulus' Insurance Obligations. Regulus shall 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 clinical trials and 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, provided, that, at a minimum, Regulus shall maintain, in force at its sole cost, a general liability insurance policy providing coverage of at least $[***] per claim and $[***] annual aggregate, provided that such coverage is increased to at least $[***] at least thirty (30) days before Regulus initiates the First Commercial Sale of any Discontinued Product hereunder. Regulus shall furnish to Sanofi evidence of such insurance, upon request.

9.5.2 Sanofi's Insurance Obligations. Sanofi hereby represents and warrants to Regulus that it is self-insured against liability and other risks associated with its activities and obligations under this Agreement 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 Sanofi under this Agreement. Sanofi shall furnish to Regulus evidence of such self-insurance, upon request.

ARTICLE 10

REPRESENTATIONS AND WARRANTIES

10.1 Representations and Warranties. Each Party hereby represents and warrants as of the Effective Date 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; and

10.1.4 the execution and delivery of this Agreement and the performance of such Party's obligations hereunder (i) 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 (ii) 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.

10.2 Regulus Representations and Warranties. Regulus hereby represents and warrants to Sanofi as of the Effective Date that:

10.2.1 Regulus is the owner of, or otherwise has the right to grant all rights and licenses it purports to grant to Sanofi with respect to the Regulus Platform Technology Patents under this Agreement;

10.2.2 No written claims have been made against Regulus alleging that (i) any of the Regulus Platform Technology Patents are invalid or unenforceable or (ii) Regulus has infringed any intellectual property rights of a Third Party.

10.2.3 The licenses granted to Regulus under the Existing Regulus In-Licenses, the Regulus Future In-Licenses and the Regulus In-License Agreements are in full force and effect and Regulus has not received any written notice, and is not aware, of any breach by any party to such agreements.

10.3 Sanofi Nonsolicitation Covenant. During the period from the date hereof to and including the [***] anniversary of the Effective Date (the ***"Nonsolicitation Period"***), Sanofi shall not and shall not permit any of their respective representatives to directly or indirectly, (i) without the prior written consent of Regulus, induce or attempt to induce any employee of Regulus to leave the employ of Regulus, or in any way interfere with the relationship between Regulus and any employee of Regulus, or known consultant or independent contractor thereof. For purposes of this Section 10.3, "induce" shall not be deemed to mean (i) circumstances where an employee, consultant or independent contractor or former employee, consultant or independent contractor initiates contact with a Party with regard to possible employment, or (ii) general solicitations of employment not specifically targeted at specific employees of a Party, including responses to general advertisements.

10.4 DISCLAIMER OF WARRANTY. EXCEPT FOR THE EXPRESS WARRANTIES SET FORTH IN THIS **ARTICLE 10**, SANOFI AND REGULUS MAKE NO REPRESENTATIONS AND GRANT NO WARRANTIES, EXPRESS OR IMPLIED, EITHER IN FACT OR BY OPERATION OF LAW, BY STATUTE OR OTHERWISE, AND SANOFI AND REGULUS 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 PATENTS OR THE NON-INFRINGEMENT OF ANY INTELLECTUAL PROPERTY RIGHTS OF THIRD PARTIES.

ARTICLE 11

MISCELLANEOUS

11.1 Assignment; Sanofi Affiliates. Except as expressly set forth in this Agreement, without the prior written consent of the other Party hereto, neither Party will sell, transfer, assign, delegate, pledge or otherwise dispose of, whether voluntarily, involuntarily, by operation of law or otherwise, this Agreement or any of its rights or duties hereunder. Any purported assignment or transfer in violation of this Section 11.1 will be void *ab initio* and of no force or effect. Notwithstanding the foregoing:

11.1.1 Sanofi may, without Regulus' consent, assign this Agreement and its rights and obligations hereunder to an Affiliate of Sanofi, *provided that* such Affiliate agrees to be bound by the terms and conditions of this Agreement and that no such assignment to an Affiliate will relieve Sanofi of its obligations hereunder;

11.1.2 Regulus may assign or transfer this Agreement or any of its rights or obligations hereunder without Sanofi's consent to any Third Party with which it has merged or consolidated, or to which it has transferred all or substantially all of its assets or stock of the business to which this Agreement relates, if in any such event the Third Party assignee or surviving entity assumes in writing all of Regulus' obligations under this Agreement; *provided further* that in the event of such a sale or transfer (whether this Agreement is actually assigned or is assumed by the acquiring party by operation of law (*e.g.*, in the context of a reverse triangular merger)), intellectual property rights of the acquiring party in such sale or transfer (if other than one of the Parties) shall not be included in the technology licensed hereunder or otherwise subject to this Agreement; and

11.1.3 Regulus may assign or transfer its rights under Article 5 (but no liabilities) to a Third Party in connection with a royalty factoring transaction.

11.2 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.

11.3 Governing Law; Jurisdiction. 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.

11.4 Dispute Resolution.

11.4.1 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 which is outside the JTSC's decision-making authority will be promptly presented to each Party's respective co-chair of the JTSC for resolution, and if the co-chairs of the JTSC are unable to resolve such dispute, such dispute will then be presented to the Executive Vice President of R&D of Sanofi and the Executive Vice President of Regulus (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 JTSC's decision-making authority will not be subject to arbitration.

11.4.2 Arbitration. If after negotiating in good faith pursuant to Section 11.4.1, 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 this Section 11.4.2 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.

(a) 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 Sections 11.4.2 will be resolved by final and binding arbitration conducted in accordance with the terms of this Section 11.4.2. 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 (3) 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 be instructed not to award any punitive or special damages and will render a written decision no later than twelve (12) months following the selection of the arbitrator, including a basis for any damages awarded and a statement of how the damages were calculated. Any award will be promptly paid in Euros free of any tax, deduction or offset. Each Party agrees to abide by the award rendered in any arbitration conducted pursuant to this Section 11. 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. By entering into this agreement to arbitrate, the Parties expressly waive any claim for punitive or exemplary damages. 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.

(c) EXCEPT FOR LOSSES COVERED BY THE INDEMNITIES PROVIDED UNDER ARTICLE 9, AND ANY BREACH OF THE CONFIDENTIALITY RESTRICTIONS UNDER ARTICLE 6, EACH PARTY HERETO WAIVES (1) ANY CLAIM TO PUNITIVE, EXEMPLARY OR MULTIPLIED DAMAGES FROM THE OTHER; AND (2) ANY CLAIM OF CONSEQUENTIAL, INDIRECT OR INCIDENTAL DAMAGES FROM THE OTHER.

11.4.3 Disputes Regarding Material Breach. If the Parties are in dispute as to whether one Party is in material breach of this Agreement, then the arbitrator will first determine if material breach has in fact occurred, and if so, will grant the defaulting Party the cure period provided pursuant to Section 8.3. If the material breach is not cured within the time period provided pursuant to Section 8.3, the arbitration will continue and the arbitrator will, as part of the same arbitration, award actual direct damages to the non-defaulting Party.

11.4.4 Court Actions. Nothing contained in this Agreement shall 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 shall be subject to arbitration pursuant to Section 11.4.

11.5 Notices. Except as otherwise provided for in this Agreement, all notices or other communications that are required or permitted hereunder will be in the English language and in writing and delivered personally with acknowledgement of receipt, sent by facsimile (and promptly confirmed by personal delivery, registered or certified mail or overnight courier as provided herein), sent by nationally-recognized overnight courier or sent by registered or certified mail, postage prepaid, return receipt requested, addressed as follows:

If to Sanofi, to:

Sanofi-Aventis
174, avenue de France
75013 Paris, France
Attention: General Counsel
Facsimile No.: +33 1 53 77 43 03

If to Regulus, to:

Regulus Therapeutics Inc.
1896 Rutherford Road,
Carlsbad, California 92008
USA
Attention: Executive Vice President
Facsimile: +1(760) 268-6868

With a copy to:

Attention: General Counsel
Facsimile: +1 (760) 268-4922

With a copy to:

Attention: Thomas Coll
Cooley LLP
4401 Eastgate Mall
San Diego, CA 92121
USA
Facsimile: +1 (858) 550-6420

or to such other address as the Party to whom notice is to be given may have furnished to the other Party in writing in accordance herewith. Any such communication will be deemed to have been given (i) when delivered, if personally delivered or sent by facsimile on a Business Day, (ii) on the Business Day after dispatch, if sent by nationally-recognized overnight courier, and

(iii) on the third Business Day following the date of mailing, if sent by mail. It is understood and agreed that this Section 10.5 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.

11.6 Entire Agreement; Modifications. This Agreement (including the attached Appendices, and the Technology Sharing Plan, if any), together with the Collaboration Agreement and the Stock Purchase Agreement (as such term is defined in the Collaboration Agreement), 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; *provided* nothing in this Agreement will be deemed to amend or modify the Collaboration Agreement and as such the Collaboration Agreement remains in full force and effect in accordance with its terms. 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.

11.7 Headings. The headings of Articles and Sections of this Agreement are for ease of reference only and will not affect the meaning or interpretation of this Agreement in any way.

11.8 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.

11.9 Waiver. Any term or condition of this Agreement may be waived at any time by the Party that is entitled to the benefit thereof, but no such waiver will be effective unless set forth in a written instrument duly executed by or on behalf of the Party waiving such term or condition. Any such waiver will not be deemed a waiver of any other right or breach hereunder.

11.10 Counterparts. This Agreement may be executed in two or more counterparts, each of which will be deemed an original, but all of which together will constitute one and the same instrument.

11.11 No Benefit to Third Parties. The representations, warranties, covenants and agreements set forth in this Agreement are for the sole benefit of the Parties hereto and their successors and permitted assigns, and they will not be construed as conferring any rights on any other parties.

11.12 Further Assurances. Each Party will duly execute and deliver, or cause to be duly executed and delivered, such further instruments and do and cause to be done such further acts and things, including the filing of such assignments, agreements, documents and instruments, as may be necessary to carry out the provisions and purposes of this Agreement.

11.13 Force Majeure. Neither Party will be charged with any liability for delay in performance of an obligation under this Agreement to the extent such delay is due to a cause beyond the reasonable control of the affected Party, such as war, riots, labor disturbances, fire, explosion, earthquake, and compliance in good faith with any governmental Law, regulation or

order. The Party affected will give prompt written notice to the other Party of any material delay due to such causes.

11.14 Interpretation.

11.14.1 Each of the Parties acknowledges and agrees that this Agreement has been diligently reviewed by and negotiated by and between them, that in such negotiations each of them has been represented by competent counsel and that the final agreement contained herein, including the language whereby it has been expressed, represents the joint efforts of the Parties hereto and their counsel. Accordingly, in the event an ambiguity or a question of intent or interpretation arises, this Agreement will be construed as if drafted jointly by the Parties and no presumption or burden of proof will arise favoring or disfavoring any Party by virtue of the authorship of any provisions of this Agreement. This Agreement has been prepared in the English language and the English language shall control its interpretation.

11.14.2 The definitions of the terms herein will apply equally to the singular and plural forms of the terms defined. Whenever the context may require, any pronoun will include the corresponding masculine, feminine and neuter forms. The words “include”, “includes” and “including” will be deemed to be followed by the phrase “without limitation”. The word “will” will be construed to have the same meaning and effect as the word “will”. The word “any” will mean “any and all” unless otherwise clearly indicated by context.

11.14.3 Unless the context requires otherwise, (i) any definition of or reference to any agreement, instrument or other document herein will be construed as referring to such agreement, instrument or other document as from time to time amended, supplemented or otherwise modified (subject to any restrictions on such amendments, supplements or modifications set forth herein or therein), (ii) any reference to any Applicable Laws herein will be construed as referring to such Applicable Laws as from time to time enacted, repealed or amended, (iii) any reference herein to any person will be construed to include the person’s successors and assigns, (iv) the words “herein”, “hereof” and “hereunder”, and words of similar import, will be construed to refer to this Agreement in its entirety and not to any particular provision hereof, and (v) all references herein to Articles, Sections or Appendices, unless otherwise specifically provided, will be construed to refer to Articles, Sections and Appendices of this Agreement.

11.14.4 References to sections of the Code of Federal Regulations and to the United States Code will mean the cited sections, as these may be amended from time to time.

[SIGNATURE PAGE FOLLOWS]

IN WITNESS WHEREOF, the Parties hereto have caused this Agreement to be executed by their duly authorized representatives as of the date first above written.

REGULUS THERAPEUTICS INC.:

By: /s/ Kleanthis G. Xanthopoulos

Title: President and CEO

SANOFI-AVENTIS:

By: /s/ Philippe GOUPIT

Title: VP Corporate Licenses

List of Appendices

Appendix 1: Definitions

Appendix 2: Reserved

Appendix 3: Reserved

Appendix 4: Regulus Platform Technology Patents

Appendix 5: Certain Regulus Prior 3rd Party Agreements

Appendix 6: Certain Regulus Prior 3rd Party Agreements

Appendix 7: Option Targets

APPENDIX 1

DEFINITIONS

"Affiliate" means any Person, whether *de jure or de facto*, which directly or indirectly through one (1) or more intermediaries controls, is controlled by or is under common control with another Person. A Person will be deemed to "control" another Person if it (a) owns, directly or indirectly, beneficially or legally, at least fifty percent (50%) of the outstanding voting securities or capital stock (or such lesser percentage which is the maximum allowed to be owned by a Person in a particular jurisdiction) of such other Person, or has other comparable ownership interest with respect to any Person other than a corporation; or (b) has the power, whether pursuant to contract, ownership of securities or otherwise, to direct the management and policies of the Person. Notwithstanding the above, neither of the Founding Companies of Regulus will be deemed an Affiliate of Regulus for the purposes of this Agreement under any circumstances.

"Agreement" means this Nonexclusive Technology Alliance and Option Agreement, together with all Appendices attached hereto, and the Technology Sharing Plan, as the same may be amended or supplemented from time to time in accordance with the terms of this Agreement.

"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 but not limited to any applicable rules, regulations, guidelines, or other requirements of the Regulatory Authorities that may be in effect from time to time, but excluding patent laws.

"Approval" means, with respect to any Product in any regulatory jurisdiction, approval from the applicable Regulatory Authority sufficient for the manufacture, distribution, use and sale of the Product in such jurisdiction in accordance with Applicable Laws.

"Business Day" means a day on which banking institutions in New York, New York, United States and Paris, France are both open for business.

"Calendar Quarter" means the respective periods of three consecutive calendar months ending on March 31, June 30, September 30 and December 31.

"Collaboration Agreement" has the meaning set in the second recital of this Agreement

"Commercialize", ***"Commercializing"*** and ***"Commercialization"*** means activities directed to manufacturing, obtaining pricing and reimbursement approvals, for, marketing, promoting, distributing, importing or selling a product, including, without limitation, 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.

"Commercially Reasonable Efforts" means, with respect to an Option Compound and product, the carrying out of discovery, research, Development or Commercialization activities using the efforts that the applicable Party would reasonably devote to a compound or product of

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similar market potential at a similar stage in development or product life resulting from its own research efforts, taking into account strategic considerations such as product profile, the competitive landscape and other relevant scientific, technical and commercial factors.

"Commercial Option Deadline" has the meaning set forth in Section 3.3.

"Confidential Information" has the meaning set forth in Section 6.1.

"Control" means, with respect to any Know-How, Patent or other intellectual property right, possession by a Party (including its Affiliates) of the right (whether by ownership, license or otherwise) to grant to the other Party ownership, a license, sublicense and/or other right to practice under such Know-How, Patent or other intellectual property right as provided for herein without violating the terms of any agreement or other arrangement with any Third Party. Notwithstanding anything to the contrary under this Agreement, with respect to any Third Party acquirer that later becomes an Affiliate of Regulus after the Effective Date, no intellectual property of such Third Party acquirer will be included in the licenses granted hereunder by virtue of such Third Party becoming an Affiliate of Regulus.

"Development" means IND-enabling toxicology studies and production of GMP quality product and clinical development activities reasonably related to the development and submission of information to a Regulatory Authority with respect to an Option Compound or product, including, without

limitation, clinical toxicology, clinical pharmacology, test method development and stability testing, manufacturing process development, formulation development, delivery system development, quality assurance and quality control development, manufacturing, statistical analysis, and clinical studies. When used as a verb, **"Develop"** means to engage in Development.

"Disclosing Party" has the meaning set forth in Section 6.1.

"Dollars" or ***"$"*** means the lawful currency of the United States.

"Effective Date" has the meaning set forth in the opening paragraph of this Agreement.

"EMEA" means the European Regulatory Authority known as the European Medicines Agency and any successor agency thereto.

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

"Founding Company" means individually, either Isis Pharmaceuticals, Inc. or Alnylam Pharmaceuticals, Inc.; and collectively, both Isis Pharmaceuticals, Inc. and Alnylam Pharmaceuticals, Inc.

"Founding Company License Agreement" means the Amended and Restated License and Collaboration Agreement among Regulus and the Founding Companies dated January 1, 2009, as amended as of the Effective Date.

"***Good Manufacturing Practice(s)***" or "***GMP***" will mean the regulatory requirements for current good manufacturing practices promulgated in the United States Code of Federal Regulations including those rules promulgated by the United States Food and Drug Administration under the U.S. Food, Drug and Cosmetic Act, 21 C.F.R. § 210 et seq. ("FD&C Act") and ICH Guidelines and applicable regulations, as the same may be amended from time to time.

"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 Studies" means the pharmacokinetic and toxicology studies required to meet the regulations for filing an IND.

"Indemnified Party" has the meaning set forth in Section 9.3.

"Indemnification Claim Notice" has the meaning set forth in Section 9.3.

"***Indication***" means mean any human or animal disease or condition, or sign or symptom of a human or animal disease or condition.

"***IP Period***" means the period of time commencing on the Research Option Exercise Date and continuing until the [***] anniversary of the Effective Date.

"JTSC" has the meaning set forth in Section 2.6.

"Know-How" means technical information and materials, including without limitation, technology, software, instrumentation, devices, data, biological materials, assays, constructs, compounds, inventions, practices, methods, knowledge, know-how, trade secrets, skill and experience.

"Losses" has the meaning set forth in Section 9.1.

"microRNA" means a structurally defined functional RNA molecule usually between 21 and 25 nucleotides in length, which is derived from genetically-encoded non-coding RNA which is predicted to be processed into a hairpin RNA structure that is a substrate for the double-stranded RNA-specific ribonuclease Drosha and subsequently is predicted to serve as a substrate for the enzyme Dicer, a member of the RNase III enzyme family; including, without limitation, those microRNAs exemplified in miRBase (http://microrna.sanger.ac.uk/). To the extent that scientific developments after the Effective Date would lead experts in the field of microRNA to expand this definition of microRNA, the Parties agree to discuss redefining microRNA for purposes of this Agreement; *provided*, *however*, that nothing contained herein will require any Party hereto to expand this definition.

"microRNA Antagonist" means a single-stranded oligonucleotide (or a single stranded analog thereof) that is designed to interfere with or inhibit a particular microRNA. For purposes of clarity, the definition of "microRNA Antagonist" is not intended to include oligonucleotides that function predominantly through the RNAi mechanism of action or the RNase H mechanism of action.

"microRNA Compound" means a compound consisting of (a) a microRNA Antagonist, or (b) a microRNA Mimic.

"microRNA Mimic" means a double-stranded or single-stranded oligonucleotide or analog thereof with a substantially similar base composition as a particular microRNA and which is designed to mimic the activity of such microRNA.

"Net Sales" means, with respect to an Option Product or, for the purposes of Section 7.4.2, in the case of a product containing a microRNA Compound, the gross invoice price of all units of such products sold by Sanofi, its Affiliates and/or their sublicensees to any Third Party or, for the purposes of Section 7.4.2, in the case of a Third Party sublicense of Regulus, or its Affiliate, to any other Third Party, less the following items: (a) trade discounts, credits or allowances, (b) credits or allowances additionally granted upon returns, rejections or recalls, (c) freight, shipping and insurance charges, (d) taxes, duties or other governmental tariffs (other than income taxes), (e) government-mandated rebates, and (f) a reasonable reserve for bad debts. "Net Sales" under the following circumstances will mean the fair market value of such Product: (i) Products which are used by Sanofi, its Affiliates or sublicensees for any commercial purpose without charge or provision of invoice, (ii) Products which are sold or disposed of in whole or in part for non cash consideration, or

(iii) Products which are provided to a Third Party by Sanofi, its Affiliates or sublicensees without charge or provision of invoice and used by such Third Party except in the cases of Products used to conduct clinical trials, reasonable amounts of Products used as marketing samples and Product provided without charge for compassionate or similar uses.

Net Sales will not include any transfer between or among Sanofi and any of its Affiliates or sublicensees for resale.

In the event a Product is sold as part of a Combination Product, the Net Sales from the Combination 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 average sale price of the Product when sold separately in finished form and B is the average sale price of the other therapeutically active pharmaceutical compound(s) included in the Combination Product when sold separately in finished form, 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 which sales of all occurred. In the event that such average sale price cannot be determined for both the Product and all other therapeutically active pharmaceutical compounds included in the Combination Product, Net Sales for the purposes of determining royalty payments will be calculated as above, but the average sales price in the above equation will be replaced by a good faith estimate of the fair market value of the compound(s) for which no such price exists.

"Option Compound" means either (i) with respect to Option Targets for which Sanofi has selected a microRNA Antagonist under Section 3.1 above, any microRNA Antagonist discovered by Sanofi or its Affiliates that modulates the expression of such Option Target where its primary mechanism of action is [***] to such Option Target, or (ii) with respect to Option Targets for which Sanofi has selected a microRNA Mimic under Section 3.1 above, a microRNA

Mimic discovered by Sanofi or its Affiliates with a [***] as the applicable Option Target and which is [***] of such Option Target.

"Option Target" has the meaning set forth in Section 3.1.

"Option Product" has the meaning set forth in Section 3.3 of this Agreement.

"Party(ies)" has the meaning set forth in the opening paragraph of this Agreement.

"Patents" means (a) patents and patent applications in any country or jurisdiction, (b) all priority applications, divisionals, continuations, and continuations-in-part of any of the foregoing, and (c) all patents issuing on any of the foregoing patent applications, together with all registrations, reissues, renewals, re-examinations, confirmations, supplementary protection certificates, and extensions of any of (a), (b) or (c).

"Permitted License" means a license granted by Regulus to a Third Party (i) under the Regulus Platform Technology to [***] (or [***] to [***]) solely to [***], or (ii) under the Regulus Platform Technology to enable such Third Party to [***] or [***] microRNA Compounds, where such Third Party is [***] and is not [***].

"Person" means any individual, firm, corporation, partnership, limited liability company, trust, business trust, joint venture company, governmental authority, association or other entity.

"Prior Third Party Agreements" means certain licenses granted by Regulus to Third Parties under a Patent Controlled by Regulus under an agreement included in the agreements listed in **Appendix 5** or **Appendix 6**.

"Proposed Target" has the meaning set forth in Section 3.7.1.

"Receiving Party" has the meaning set forth in Section 6.1.

"Regulatory Authority" means any governmental authority, including without limitation FDA, EMEA or Koseisho (i.e., the Japanese Ministry of Health, Labour and Welfare, or any successor agency thereto), that has responsibility for granting any licenses or approvals or granting pricing and/or reimbursement approvals necessary for the marketing and sale of an Option Product in any country.

"***Regulus Collaborator***" means any Third Party developing or commercializing a miRNA Compound product alone or in collaboration with Regulus under a license to Regulus Platform Technology Patents.

"***Regulus Collaborator Blocking Patents***" means Patents Controlled by a Regulus Collaborator that claim:

(i) any invention that is conceived or reduced to practice during the [***] years following Regulus' grant of a sublicense under the Sanofi Blocking Patents to such Regulus Collaborator by one or more employees of such Regulus Collaborator or any of its Affiliates who (A) have participated in any collaboration activities with Regulus pursuant to a license from

Regulus under the Regulus Platform Technology or (B) have otherwise received Regulus Platform Technology (excluding any Regulus Platform Know-How that, at the time of initial access by any such employee, was not confidential information of Regulus); and

(ii) either:

(a) microRNA Compounds in general;

(b) chemistry or delivery technology useful in connection with microRNA Compounds;

(c) general mechanisms of action by which a microRNA Compound modulates microRNA; or

(d) general methods of treating or preventing an Indication by modulating one or more microRNAs;

provided, however, that in each case, Regulus Collaborator Blocking Patents exclude Patents Controlled by the applicable Regulus Collaborator (in each, case other than as a result of the sublicense granted by Regulus) to the extent that such Patents claim:

(1) a microRNA sequence or a portion thereof;

(2) the specific compositions of matter of any microRNA Compound; or

(3) methods of using as a therapeutic any microRNA Compound.

"Regulus Collaborator Exclusive Option" means, with respect to a particular Proposed Target, an exclusive option granted by Regulus to a Third Party under a written agreement that (i) identifies such Proposed Target by name; (ii) grants such Third Party the right to obtain an exclusive license to Develop and Commercialize microRNA Compounds directed to such Proposed Target; (iii) obligates Regulus to [***] (or otherwise obligates Regulus to perform activities that will [***]) Researching and/or Developing microRNA Compounds for such Proposed Target, where such Third Party [***], whether in the form of [***] or in [***], that Regulus will use, in whole or in part, to [***]; and (iv) prohibits Regulus from collaborating with Sanofi or any other Third Party with respect to such Proposed Target or from granting Sanofi or any other Third Party a license to Research, Develop or Commercialize microRNA Compounds directed to such Proposed Target.

"Regulus Existing In-Licenses" means an agreement between Regulus and a Third Party as in effect on the Effective Date, pursuant to which Regulus has Control over a piece of the Regulus Platform Technology.

"Regulus Future In-Licenses" means an agreement between Regulus and a Third Party entered after the Effective Date, pursuant to which Regulus has Control over a piece of the Regulus Platform Technology.

"Regulus In-License Agreements" means those agreements listed on **Appendix 5** or **Appendix 6**.

"Regulus Platform Know-How" means, subject to Section 4.1.6, all Know-How Controlled by Regulus on the Effective Date or during the IP Period and related to (a) microRNA Compounds in general, (b) chemistry or delivery technology useful in connection with microRNA Compounds, (c) general mechanisms of action by which a microRNA Compounds modulate microRNA, or (d) general methods of treating an Indication by modulating one or more microRNAs; *provided, however*, that in each case, Regulus Platform Know-How will not include Know-How related specifically to (i) a microRNA sequence or a portion thereof; (ii) the specific composition of matter of any microRNA Compounds; or (iii) methods of using as a therapeutic any microRNA Compound.

"Regulus Platform Technology Patents" means, subject to Section 4.1.6, (A) all Patents Controlled by Regulus on the Effective Date and listed on **Appendix 4**, and (B) all Patents Controlled by Regulus during the IP Period that claim (a) microRNA Compounds in general, (b) chemistry or delivery technology useful technology useful in connection with microRNA Compounds, (c) general mechanisms of action by which a microRNA Compound modulates microRNAs, or (d) general methods of treating or preventing an Indication by modulating one or more microRNAs; *provided, however*, that in each case, Regulus Platform Technology Patents do not include (1) any Patents Controlled by Regulus or its Affiliates to the extent that such Patents claim (a) the sequence or a portion thereof corresponding to a specific microRNA sequence or a portion thereof, (b) the specific composition of matter of any microRNA Compound, (c) methods of using as a therapeutic any microRNA Compound; (2) the Tuschl 3 Patents; and (3) the Rockefeller Patents.

"Regulus Platform Technology" means the Regulus Platform Know How and the Regulus Platform Technology Patents.

"Regulus Tangible Materials" means any tangible documentation, whether written or electronic, existing as of the Effective Date or during the IP Period, that is Controlled by Regulus, and embodying or relating to the Regulus Platform Technology.

"Research" means chemical synthesis, manufacturing microRNA Compounds for research purposes, pre-clinical research with respect to microRNA Compounds including gene function, gene expression and target validation research using cells and animals, which may include small pilot toxicology studies but excludes IND-Enabling Studies, clinical development and commercialization.

"Research License" has the meaning set forth in Section 2.3.

"Research Option" has the meaning set forth in Section 2.1.

"Research Option Deadline" has the meaning set forth in Section 2.2.

"Research Option Exercise Date" has the meaning set forth in Section 2.3.

"[***] Patents" means the Patents in-licensed by Regulus pursuant to the Non-Exclusive License Agreement between [***] and [***] dated [***] and assigned to Regulus June 30, 2008.

"Sanofi Blocking Patents" means Patents Controlled by Sanofi or its Affiliates (in each, case other than as a result of the licenses granted by Regulus to Sanofi hereunder) that claim:

(i) [***]; and

(ii) either:

(a) microRNA Compounds in general;

(b) chemistry or delivery technology useful in connection with microRNA Compounds;

(c) general mechanisms of action by which a microRNA Compound modulates microRNA; or

(d) general methods of treating or preventing an Indication by modulating one or more microRNAs;

provided, however, that in each case, Sanofi Blocking Patents exclude Patents Controlled by Sanofi or its Affiliates (in each, case other than as a result of the licenses granted by Regulus to Sanofi hereunder) to the extent that such Patents claim:

(1) a microRNA sequence or a portion thereof;

(2) the specific compositions of matter of any microRNA Compound being developed by Sanofi, its Affiliate or any Third Party under license from Sanofi; or

(3) methods of using as a therapeutic any microRNA Compound being developed by Sanofi, its Affiliate or any Third Party under license from Sanofi.

"Sanofi Indemnitees" has the meaning set forth in Section 9.2.

"Senior Representatives" has the meaning set forth in Section 11.4.1

"Target Encumbrances" has the meaning set forth in Section 3.7.1.

"Technology Sharing Period" has the meaning set forth in Section 2.4.1.

"Technology Sharing Program" has the meaning set forth in Section 2.4.

"Technology Sharing Plan" has the meaning set forth in Section 2.5.

"Term" has the meaning set forth in Section 8.1.

"Territory" means all countries and jurisdictions throughout the world.

"Third Party" means any Person other than Regulus or Sanofi or their respective Affiliates.

"Third Party Claims" has the meaning set forth in Section 9.1.

"Tuschl 3 Patents" means the Patents in-licensed by Regulus pursuant to the License Agreement among Garching Innovation GmbH, Isis Pharmaceuticals, Inc. and Alnylam Pharmaceuticals, Inc. dated October 18, 2004

"Valid Claim" means a claim of any issued, unexpired patent that has not been revoked or held unenforceable or invalid by a decision of a court or governmental agency of competent jurisdiction from which no appeal can be taken, or with respect to which an appeal is not taken within the time allowed for appeal, and that has not been disclaimed or admitted to be invalid or unenforceable through reissue, disclaimer or otherwise.

APPENDIX 2

[reserved]

APPENDIX 3

[reserved]

APPENDIX 4

REGULUS PLATFORM TECHNOLOGY PATENTS

APPENDIX 5

REGULUS IN-LICENSE AGREEMENTS
AND
PRIOR THIRD PARTY AGREEMENTS

[***]

APPENDIX 6

REGULUS IN-LICENSE AGREEMENTS
AND
PRIOR THIRD PARTY AGREEMENTS

[***]

Exhibit 10.3

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R §§ 200.80(b)4, AND 240.24b-2

AMENDMENT NUMBER ONE
TO THE
AMENDED AND RESTATED
LICENSE AND COLLABORATION AGREEMENT

This Amendment Number One (the "***Amendment***") to the Amended and Restated License and Collaboration Agreement is entered into as of the 10th day of June, 2010 (the "***Effective Date***") by and among **ALNYLAM PHARMACEUTICALS, INC.**, a Delaware corporation, with its principal place of business at 300 Third Street, Cambridge, Massachusetts 02142 ("***Alnylam***"), **ISIS PHARMACEUTICALS, INC.**, a Delaware corporation, with its principal place of business at 1896 Rutherford Road, Carlsbad, California 92008 ("***Isis***", and each of Alnylam and Isis, a "***Licensor***" and together, the "***Licensors***"), and **REGULUS THERAPEUTICS INC.** (formerly Regulus Therapeutics LLC), a Delaware corporation, with its principal place of business at 1896 Rutherford Road, Carlsbad, California 92008 ("***Regulus***").

RECITALS

WHEREAS, Isis and Alnylam each granted a license to Regulus in accordance with that certain License and Collaboration Agreement dated September 6, 2007 (the "***Original License Agreement***"), which Original License Agreement was amended and restated on January 1, 2009 (the "***Amended License Agreement***");

WHEREAS, Isis, Alnylam, and Regulus now desire to amend the Amended License Agreement as provided herein.

AGREEMENT

NOW, THEREFORE, in consideration of the mutual covenants contained herein, and other good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, Isis, Alnylam and Regulus each agrees as follows:

1. DEFINITIONS

Capitalized terms used herein and not defined elsewhere herein have the meanings set forth in the Amended License Agreement.

2. PAYMENTS

2.1 The following bullet point shall be added as a new second bullet point in the definition of "Exclusivity Period" in the Amended License Agreement:

"· with respect to a Royalty-Bearing Product being Commercialized by a Collaborator of Regulus (other than Alnylam or Isis), the Exclusivity Period shall expire at such time as such Collaborator is no longer required to pay Regulus any royalty (not including any amounts

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paid by Collaborator to Regulus arising from payment obligations to Third Parties) with respect to such Royalty-Bearing Product; or"

2.2 Section 5.2 of the Amended License Agreement shall be deleted and replaced in its entirety by the following:

"5.2 Continued Development by Regulus of Development Projects.

(a) Diligence. If Regulus notifies Licensors pursuant to Section 5.1 that Regulus will continue to pursue the Development and Commercialization of such Development Project (on its own or with a Collaborator, as defined below), then, without limiting the generality of Section 4.1, Regulus will use Commercially Reasonable Efforts to Develop and Commercialize the relevant Development Compounds and Development Therapeutics in the Field.

(b) Third Party Payments. Regulus will be responsible for all milestones, royalties and other payments payable to Third Parties in respect of the Development, Manufacture and Commercialization of Development Therapeutics in the Field, by Regulus, its Affiliates and Sublicensees, including any amounts payable by either Licensor to Third Parties under the Third Party Rights. The Parties will use reasonable efforts to [***].

(c) Net Sales by Regulus. Regulus will pay to each Licensor a royalty of [***]% of Net Sales of Development Therapeutics which are Royalty-Bearing Products which Net Sales are generated by Regulus rather than a Collaborator, during the relevant Royalty Term (provided, however, that, for the remainder of the relevant Royalty Term following the end of the relevant Exclusivity Period, the royalty rate will be [***]%). Regulus agrees that the royalty described in Section 5.2(c) is payable to each Licensor, regardless of whether a particular Royalty-Bearing Product is covered by such Licensor's Licensed IP.

(d) Net Sales by a Collaborator of Regulus. With respect to Net Sales by a Collaborator of Regulus (other than Alnylam or Isis), Regulus will pay to each Licensor a royalty of [***]% of Net Sales of such Development Therapeutics which are Royalty-Bearing Products; provided, that (i) the agreement with such Collaborator requires such Collaborator to make royalty payments to Regulus of at least [***]% of Net Sales (after any payments required to be made by Regulus to Third Parties) and (ii) the length of the Exclusivity Period with respect to such Collaborator is no shorter than the Exclusivity Period which would apply to Net Sales by Regulus under Section 5.2(c) above ((i) and (ii) being collectively referred to as "***Consistent Sublicense Terms***"). Notwithstanding the foregoing, if the agreement with such Collaborator does not contain Consistent Sublicense Terms or if Regulus chooses at the time of, or prior to, entering into such agreement to have this sentence apply in lieu of the first sentence of this Section 5.2(d), such choice to be delivered in writing to Alnylam and Isis within thirty (30) days of entering into such sublicense agreement (a "***Sublicense Income Agreement***"), then (x)

Isis, Alnylam and Regulus will each receive the [***] of (I) [***]% of [***] (A) [***] received by Regulus on the basis of such [***] pursuant to such Sublicense Income Agreement, and (B) [***] made to Third Parties as described in [***], and (II) [***]%

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of Net Sales of such Development Therapeutics, and (y) Alnylam and Isis will be entitled to receive additional payments from Regulus in accordance with Section 5.2(e) below. "***Collaborator***" means a Third Party sublicensee or other partner of Regulus which partner receives from Regulus a sublicense, participates with Regulus in a collaboration, receives from Regulus a technology transfer or otherwise obtains from Regulus rights related to Develop or Commercialize miRNA Compounds, miRNA Therapeutics, or miRNA Antagonists. A "Collaborator" will be considered a "Sublicensee" for purposes of this Agreement.

(e) Sublicense Income. With respect to each Sublicense Income Agreement, Regulus shall pay [***] of Sublicense Income received by Regulus to Alnylam and [***] of Sublicense Income received by Regulus to Isis. "***Sublicense Income***" means all fees and other payments received by Regulus from a Collaborator in connection with a Sublicense Income Agreement, but *excluding* (i) debt, credit or lease financing (provided, however, that (x) any discount to market will not be excluded from the definition of Sublicense Income and (y) in the event that any portion of such debt, credit or lease is forgiven, such debt, credit, or lease will be deemed Sublicense Income in the amount of such forgiveness), (ii) the fair market value of any equity investments in Regulus, (iii) the bona fide reimbursement of future research and development funding by a third party (as specified in the Sublicense Income Agreement) at direct cost, (iv) the bona fide reimbursement of future out-of-pocket costs of patent filing, prosecution and maintenance, and patent defense, and (v) royalties for which compensation is paid to Alnylam and Isis pursuant to Section 5.2(d). For purposes of clarity, payments for specific events associated with sales such as net sales-based milestones or unit-based milestones will not be excluded from Sublicense Income. Notwithstanding the foregoing, the $[***] [***] payments to Regulus from [***] pursuant to [***] research collaboration will not be considered Sublicense Income.

(f) Full Consideration. Regulus agrees that the royalties described in Sections 5.2(c) and 5.2(d) and the Sublicense Income provisions contained in Section 5.2(e) are payable to each Licensor, regardless of whether a particular Royalty-Bearing Product is covered by such Licensor's Licensed IP. Each Party agrees and acknowledges that such royalty structure (i) is freely entered into by such Party, (ii) is a fair reflection of the value received by Regulus from the licenses granted by the Licensors, and (iii) is a reasonable allocation of the value received by Regulus from each Licensor, due to the difficulty of determining the extent to which Licensor's Licensed IP covers or has enabled each Royalty-Bearing Product."

3. BUY OUT

3.1 Buy-Out. Any and all references in the Amended License Agreement to the term "Buy-Out" are null and void.

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4. MISCELLANEOUS

4.1 Other Terms. All other terms and conditions of the Amended License Agreement shall remain in full force and effect. The Amendment Number One to the Amended and Restated License and Collaboration Agreement entered into among Regulus and the Licensors on June 7, 2010 is superseded and replaced by this Amendment and is deemed void *ab initio*.

4.2 Counterparts. This Agreement may be executed in any number of counterparts, each of which will be deemed an original, and all of which together will constitute one and the same instrument.

[Remainder of Page Intentionally Left Blank]

IN WITNESS WHEREOF, the Parties hereby execute this Amendment Number One to the Amended and Restated License and Collaboration Agreement as of the date first written above.

ALNYLAM PHARMACEUTICALS, INC.

By: /s/ Barry Greene
Name: Barry Greene
Title: President and Chief Operating Officer

ISIS PHARMACEUTICALS, INC.

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

REGULUS THERAPEUTICS INC.

By: /s/ Kleanthis G. Xanthopoulos
Name: Kleanthis G. Xanthopoulos, Ph.D.
Title: President and Chief Executive Officer

AMENDMENT NUMBER ONE
TO THE
FOUNDING INVESTOR RIGHTS AGREEMENT

This Amendment Number One (the "***Amendment***") to the Founding Investor Rights Agreement dated January 1, 2009 (the "***Investor Rights Agreement***") is entered into as of the 7th day of June, 2010 (the "***Effective Date***") by and among **ALNYLAM PHARMACEUTICALS, INC.**, a Delaware corporation, with its principal place of business at 300 Third Street, Cambridge, Massachusetts 02142 ("***Alnylam***"), **ISIS PHARMACEUTICALS, INC.**, a Delaware corporation, with its principal place of business at 1896 Rutherford Road, Carlsbad, California 92008 ("***Isis***", and each of Alnylam and Isis, a "***Licensor***" and together, the "***Licensors***"), and **REGULUS THERAPEUTICS INC.** (formerly Regulus Therapeutics LLC), a Delaware corporation, with its principal place of business at 1896 Rutherford Road, Carlsbad, California 92008 ("***Regulus***").

RECITALS

WHEREAS, Regulus, Isis and Alnylam entered into the Investor Rights Agreement;

WHEREAS, Isis, Alnylam, and Regulus now desire to amend the Investor Rights Agreement as provided herein.

AGREEMENT

NOW, THEREFORE, in consideration of the mutual covenants contained herein, and other good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, Isis, Alnylam and Regulus each agrees as follows:

1. DEFINITIONS

Capitalized terms used herein and not defined elsewhere herein have the meanings set forth in the Investor Rights Agreement.

2. DELETION OF BUY-OUT PROVISION

2.1 Elimination of Buy-Out Provision. Section 4 of the Investor Rights Agreement shall be deleted in its entirety and replaced with the following: "[Deliberately Omitted]"

2.2 Elimination of Exhibit D. Exhibit D of the Investor Rights Agreement shall be deleted in its entirety and replaced with the following: "[Deliberately Omitted]"

3. MISCELLANEOUS

3.1 Other Terms. All other terms and conditions of the Investor Rights Agreement shall remain in full force and effect.

3.2 Counterparts. This Agreement may be executed in any number of counterparts, each of which will be deemed an original, and all of which together will constitute one and the same instrument.

[Remainder of Page Intentionally Left Blank]

IN WITNESS WHEREOF, the Parties hereby execute this Amendment Number One to the Founding Investor Rights Agreement as of the Effective Date.

ALNYLAM PHARMACEUTICALS, INC.

By: /s/ Barry Greene
Name: Barry Greene
Title: President and Chief Operating Officer

ISIS PHARMACEUTICALS, INC.

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

REGULUS THERAPEUTICS INC.

By: /s/ Kleanthis G. Xanthopoulos

Name: Kleanthis G. Xanthopoulos, Ph.D.
Title: President and Chief Executive Officer

EXHIBIT 31.1

CERTIFICATION

I, Stanley T. Crooke, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Isis 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: August 9, 2010

/s/ Stanley T. Crooke

Stanley T. Crooke, M.D., Ph.D.
Chief Executive Officer

EXHIBIT 31.2

CERTIFICATION

I, B. Lynne Parshall, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Isis 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: August 9, 2010

/s/ B. Lynne Parshall

B. Lynne Parshall, J.D.
Chief Financial Officer

Exhibit 32.1

CERTIFICATION

Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, Stanley T. Crooke, the Chief Executive Officer of Isis Pharmaceuticals, Inc., (the "Company"), and B. Lynne Parshall, 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, 2010, 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: August 9, 2010

/s/ Stanley T. Crooke	/s/ B. Lynne Parshall
Stanley T. Crooke, M.D., Ph.D.	B. Lynne Parshall, J.D.
Chief Executive Officer	Chief Financial Officer

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